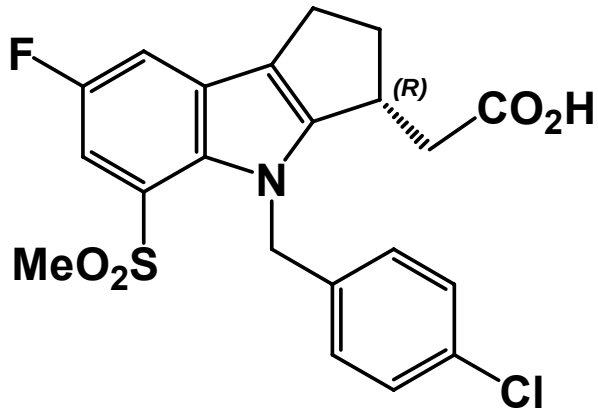
MK-524: A Study in Modern Chemical Development

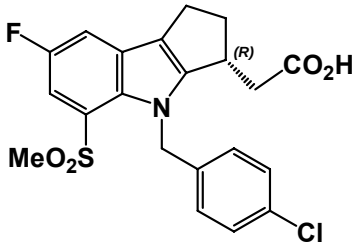


Edward J.J. Grabowski
VP Retired
Merck Research Labs

For an updated slide set see:
http://members.bellatlantic.net/~edjjg/SCI-Grabowski.ppt

Modern Chemical Development

- Determine key ‘GO-NO GO’ decision points for the overall development program
- Do minimum amount of chemical development necessary to reach these decision points
  - The probability that the compound will die is ~95%
- Deliver bulk drug as quickly as possible to get to the ‘GO-NO GO’ decision points
  - Make the most of existing chemistry
  - Live with the horrors of the medicinal route if at all possible
  - Outsource when it makes sense
- Be prepared with ‘real’ chemistry should the candidate be a ‘GO’
  - Do not leave the program hanging with no viable chemistry



MK-524A & MK-524B
Niacin & Zocor Combinations

Merck has completed Phase III clinical trials for both MK-524A and MK-524B, investigational therapies for lipid/cholesterol management. MK-524A represents a novel approach to lowering LDL-C, raising HDL-C and lowering triglycerides. MK-524B combines MK-524A with the proven benefits of simvastatin to potentially reduce the risk of coronary heart disease beyond what statins provide alone.

Web Update

4:34PM Merck: Investigational extended-release Niacin/Laropiprant coadministered with Simvastatin had significant additive effects on LDL-C, HDL-C and triglycerides in phase III study (MRK) 55.93 -0.11 : Extended-release niacin/laropiprant coadministered with simvastatin had significant additive effects on reducing LDL-cholesterol, increasing HDL-cholesterol and reducing triglyceride levels in a Phase III study with patients with primary hypercholesterolemia or mixed dyslipidemia.

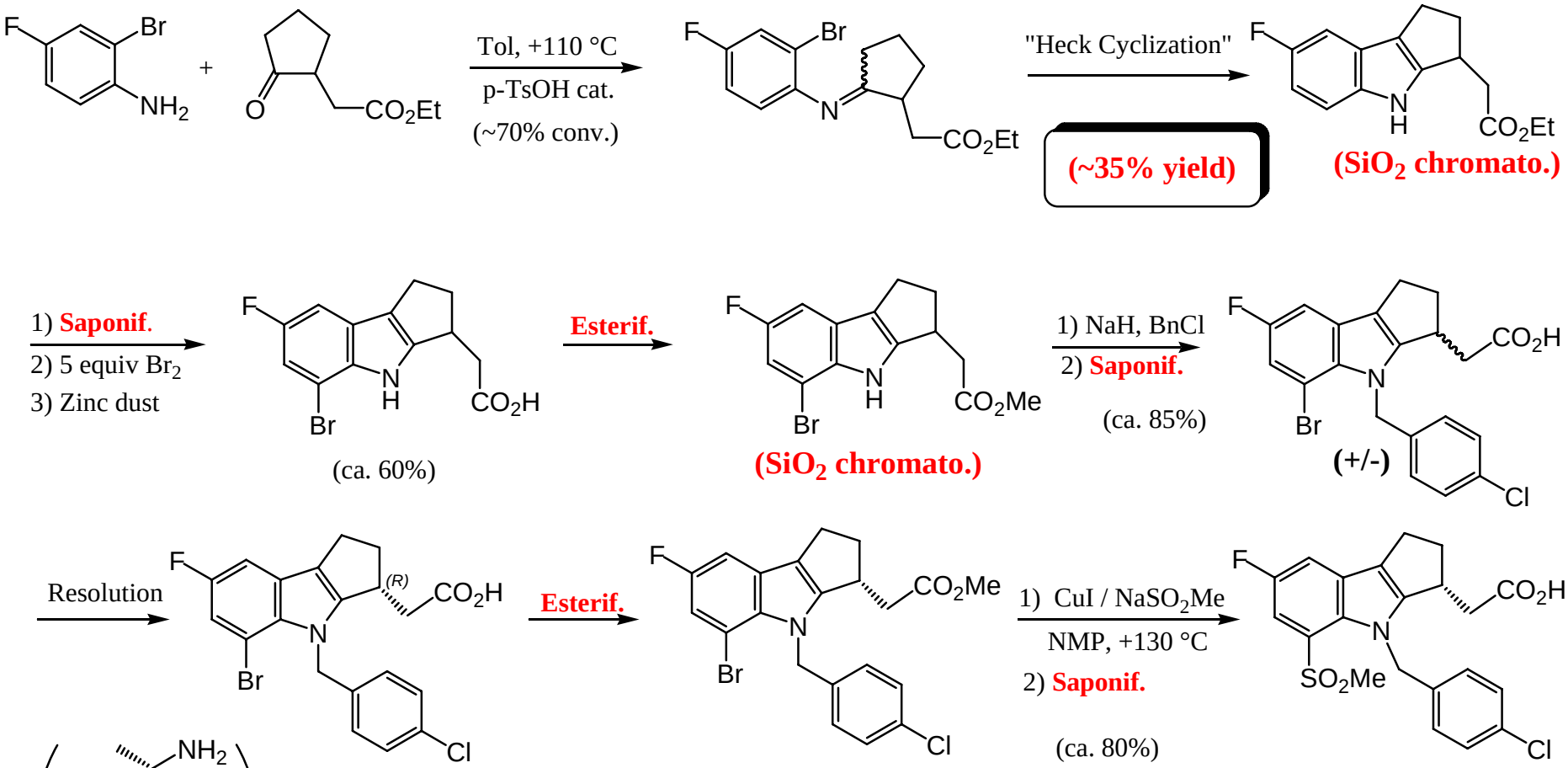
NDA sbmitted August 2007.

Development of an Ultimate Process
(Crawling before walking before running)

- Initial synthesis based on Medicinal Chemistry route ‘bulled’ through to make the first 600 g in a joint Process Research – Medicinal Chemistry effort
  - This supported early safety studies, minimal Pharm R&D work and Phase I clinical studies
- Developed version with a new resolution permitted running in the prep lab to make kgs and in the Pilot Plant to make 10 x kgs
  - This supported subsequent safety studies, Phase II studies and more extensive Pharm R&D work
- Above allowed time for exploration of a new route that has all of the attributes of a manufacturing process
- New process demonstrated in a second Pilot Plant campaign and provided Phase III materials
- This approach required a significant manpower commitment by management

Humphrey, et. al. Chem. Rev., **2006,** *106,* 2875-2911.

MEDICINAL CHEMISTRY "RACEMIC SYNTHESIS"



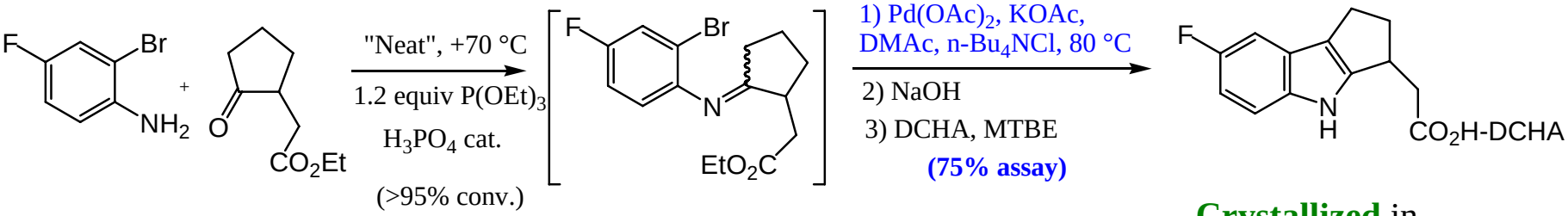
Use of the Medicinal Chemistry Synthesis

- At >3% overall yield and with numerous problematic steps, this route was not considered satisfactory for the preparation of the first delivery of 600 g
- Minimal development was undertaken to make it viable
- Two chemists from Medicinal Chemistry joined in this preliminary effort
- A tight program timeline was set for development and preparative work, and the first delivery was on-target

IMPROVED MED CHEM - FIRST GENERATION PROCESS

IMINE/HECK

ISSUES :
1) Low overall yield **(35%)**
2) Heck Cyclization non-optimized (DMF, +110 °C, **ca. 50% assay**)
3) Column chromatography

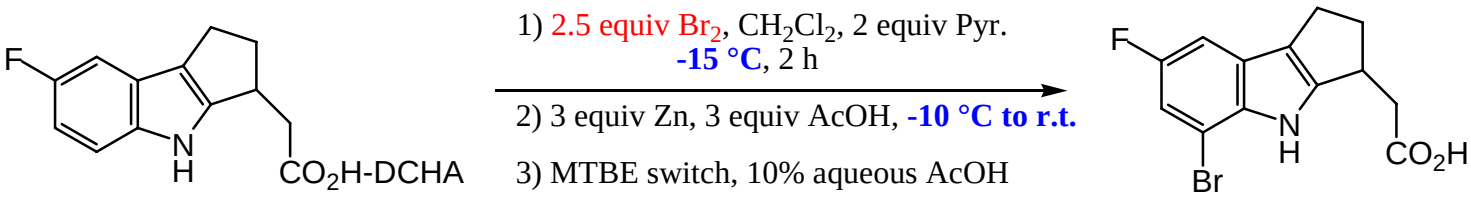


("Dean-Stark" : scaleup issue. Stalled at 85% conversion on Kg scale)

Crystallized in
65% isolated yield

BROMINATION

ISSUES :
1) Large excess of Bromine (5 equiv)
2) Low temperature (-78 °C)
3) Column chromatography

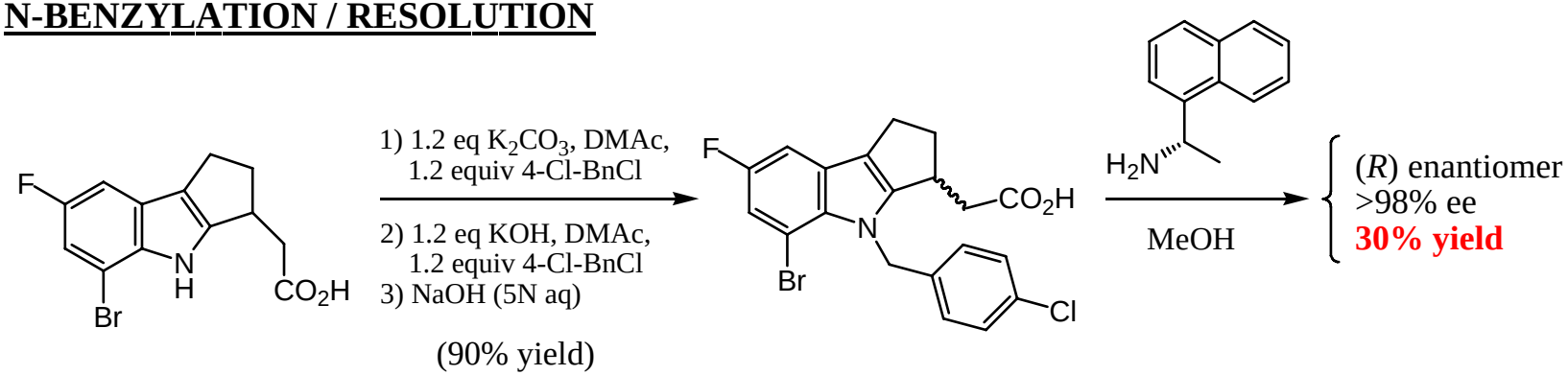


(85% isolated yield)

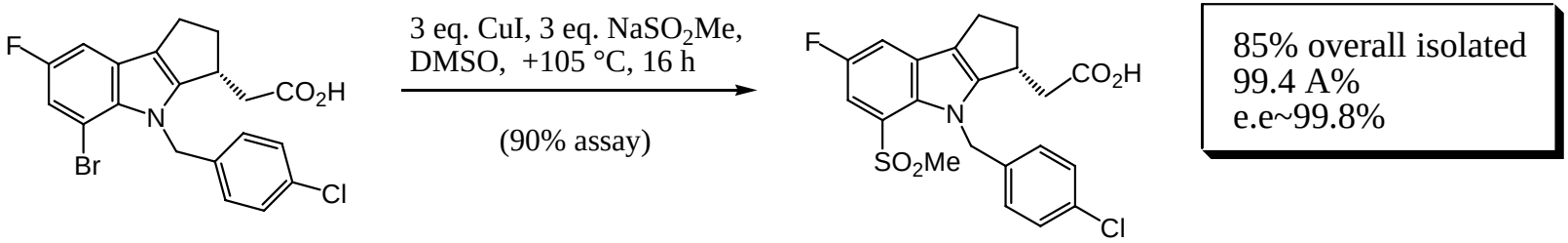
(Crystallized from IPA/Water)

IMPROVED MED CHEM - FIRST GENERATION PROCESS

N-BENZYLATION / RESOLUTION



LAST STEP - SULFONYLATION



11 steps, <3% overall yield ⟹ 6 steps, ~10% overall yield

This synthesis used for first 600 g delivery.

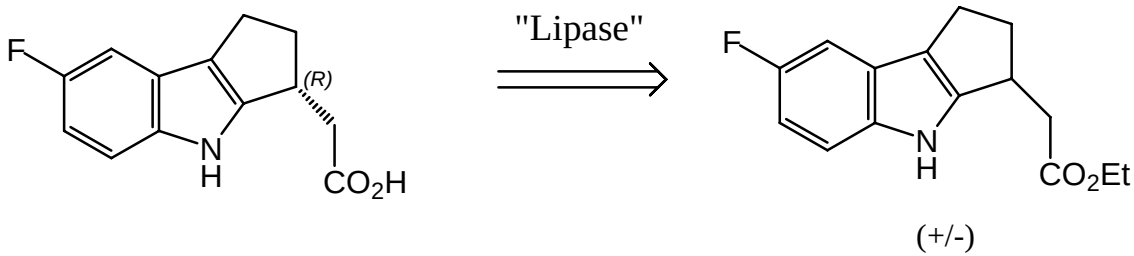
SECOND GENERATION PROCESS "ENZYMATIC RESOLUTION"

The improved Med Chem synthesis is a good **racemic** approach of the drug.

The **MAJOR DRAWBACK** is the **late**, **inefficient** (30%, "No racemization") chemical resolution.

THE IDEA : RESOLVING THE INDOLE AT THE EARLIEST STAGE (IMINE/HECK).

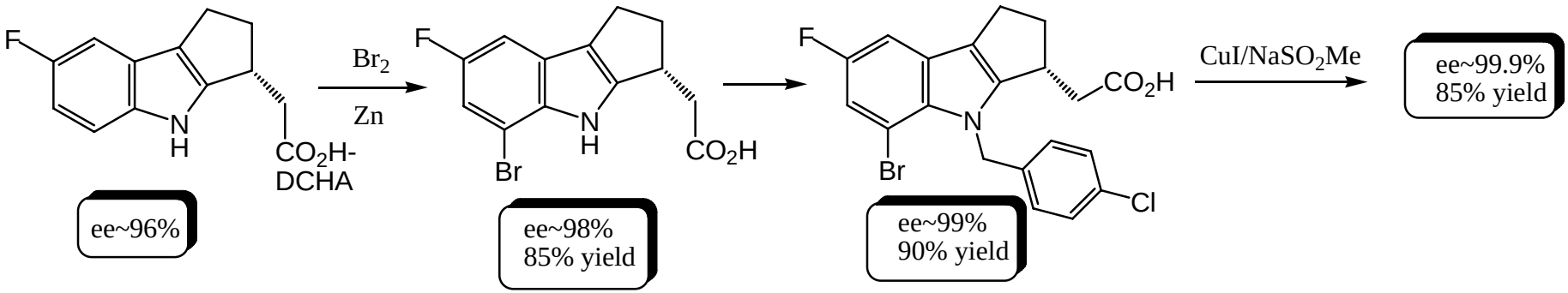
COULD THE INDOLE **ESTER** BE SELECTIVELY HYDROLYZED BY AN ENZYME?
COULD THE WRONG ENANTIOMER BE RACEMIZED, AND RECYCLED?



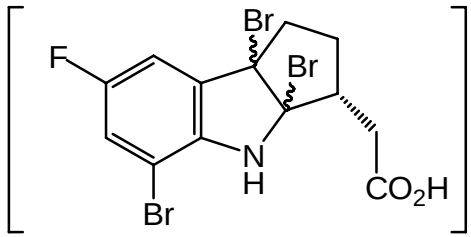
Screening of enzymes : "*Pseudomonas Fluorescens*" highly selective

SECOND GENERATION PROCESS "ENZYMATIC RESOLUTION"

WILL THE STEREOGENIC CENTER "SURVIVE" THE REST OF THE CHEMISTRY?



We have evidence that the intermediate in the bromination is:



NO ENAMINE OBSERVED

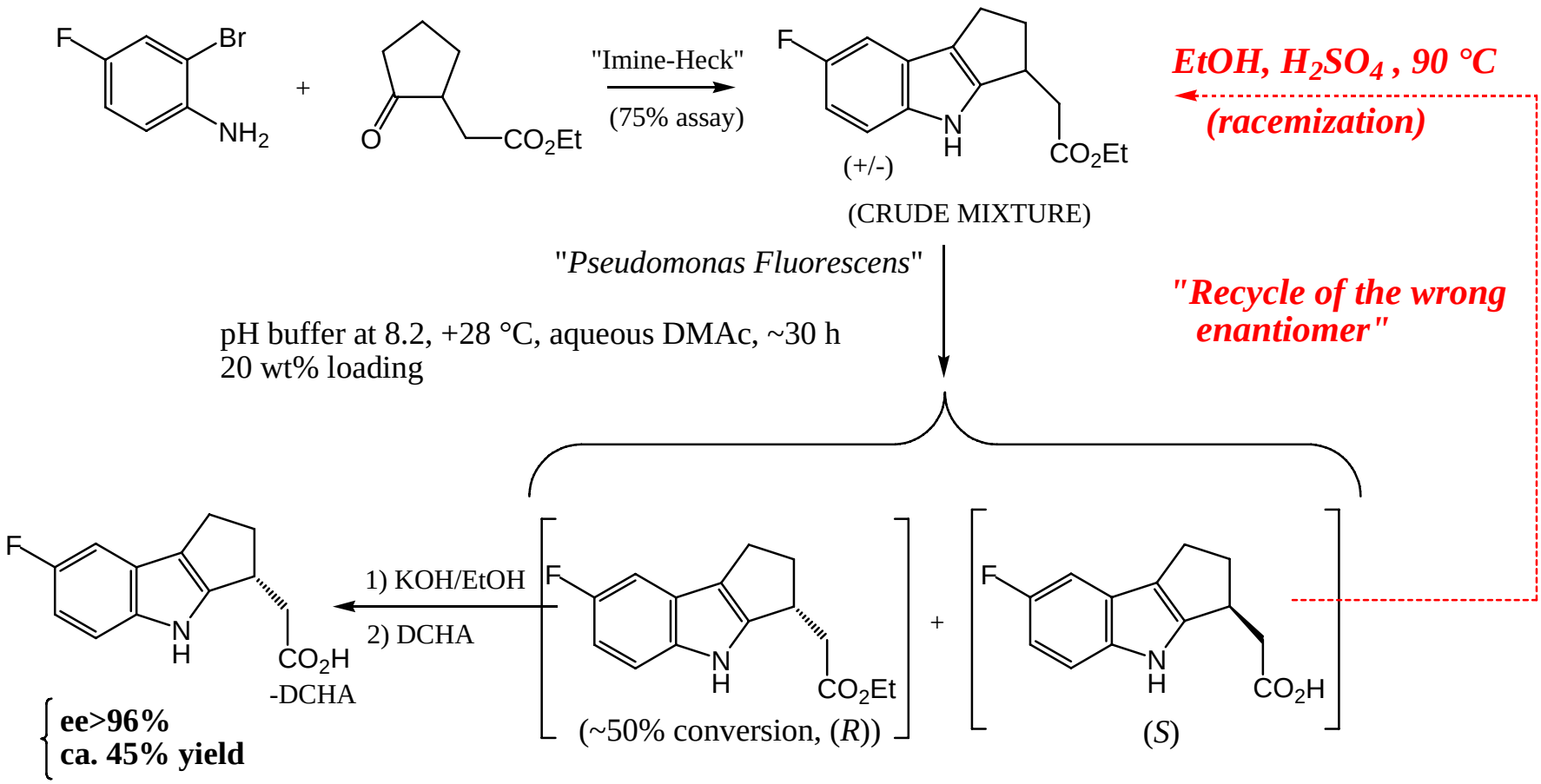
⟹

3 step process (from DCHA salt) : 63% overall yield

Retention (slight upgrade due to crystallizations) of configuration

SECOND GENERATION PROCESS "ENZYMATIC RESOLUTION"

ENZYMATIC RESOLUTION OF THE ESTER INDOLE INTERMEDIATE

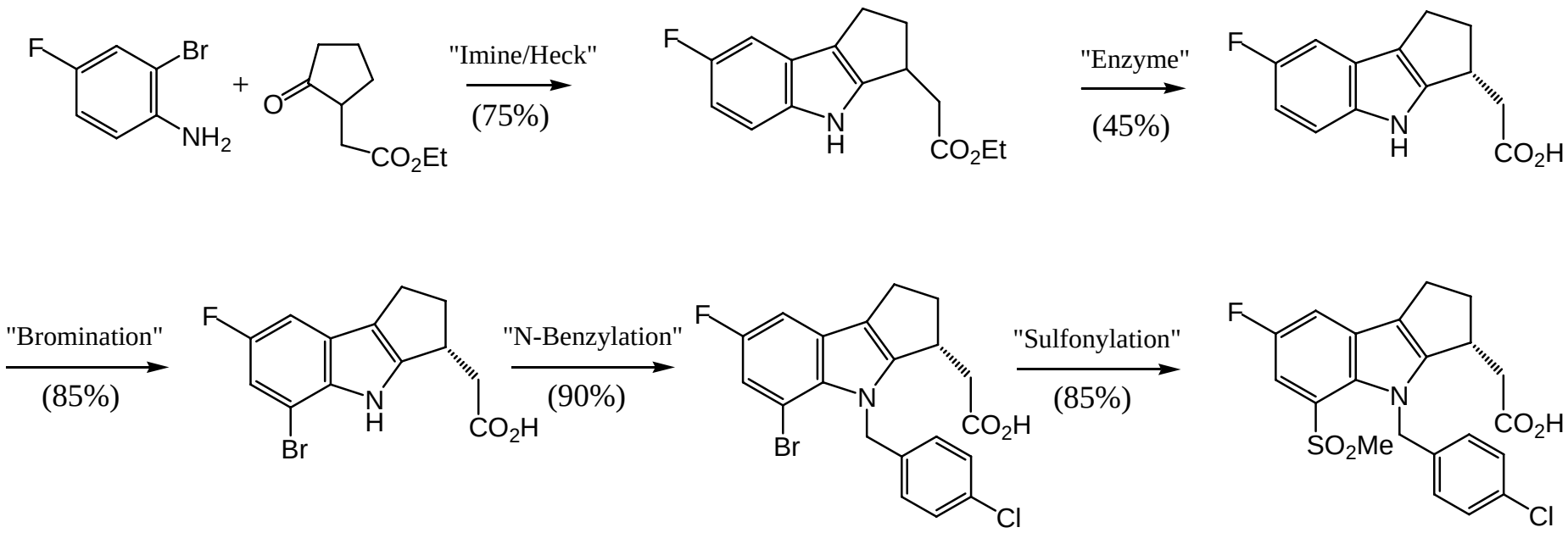


How to Sell the Team on an Enzyme Resolution

- Show slide of resolution proceeding in 45% isolated yield (10g in 4.5 g out) of the desired isomer
  - Good start, but not completely convincing
- Run 40 assay grams of racemate through the resolution and show:
  - 27 g of the DCHA salt of the desired isomer in a bottle as a pure, white and crystalline product crystalline in 45% yield
  - Racemize the unwanted isomer and show 18g of the pure, crystalline racemic ester in 45% yield
  - That is a 90% material balance on a lab demonstration run using crude, unisolated ester in its production solvent, and immediately sold us on the enzyme approach

SECOND GENERATION PROCESS "ENZYMATIC RESOLUTION"

SUMMARY OF THE SYNTHESIS (W/O RACEMIZATION)

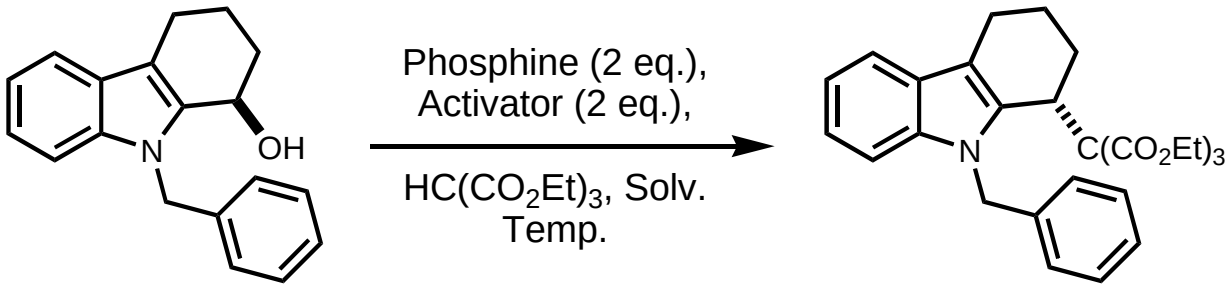


Six-step process with 22% overall yield. Projected 30-35% overall yield with further development and recycle. Synthesis used to make 26 kg of drug in the Pilot Plant.

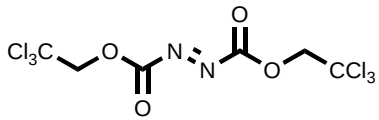
Should we stop here?

- With a projected 30-35% overall yield should we stop development at this point and transfer the process to manufacturing?
  - Many companies would say, “Yes!”
- Still early in the program and dose levels and impact of API cost on product cost were uncertain
- Decided to continue chemical development and search for the ultimate process
  - Three different approaches studied

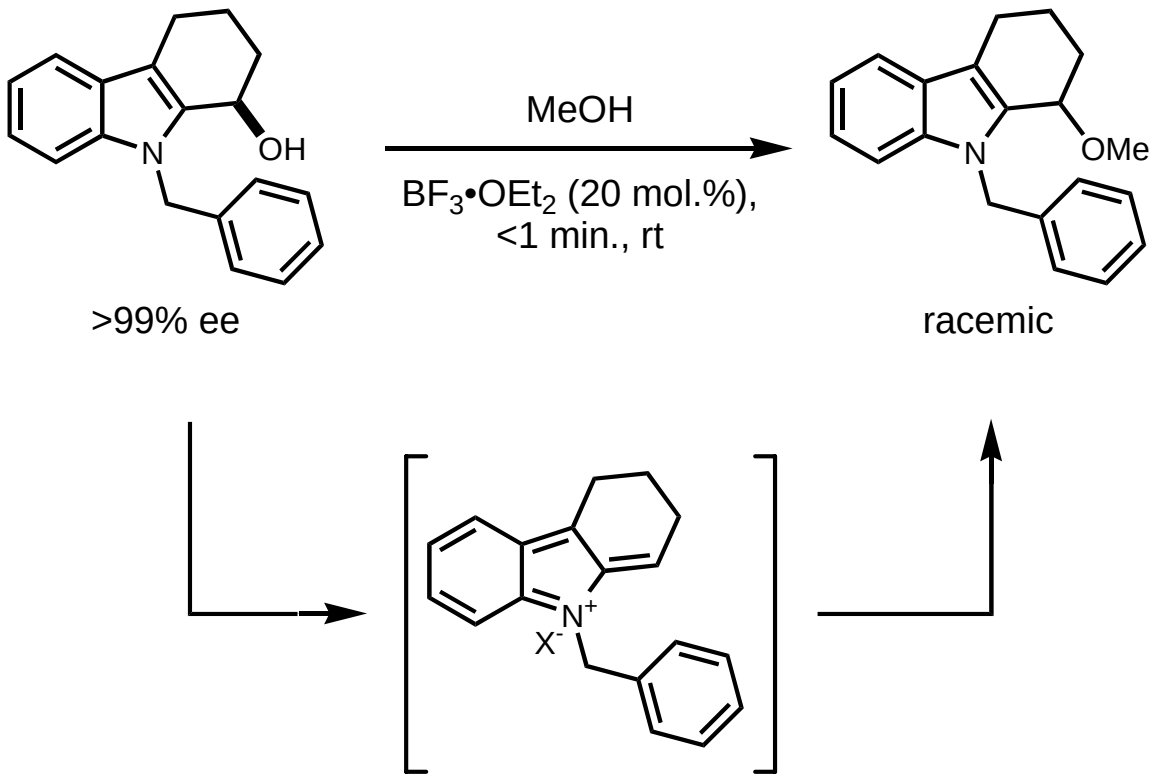
Mitsunobu Displacement



Phosphine	Activator	Solv.	Temp.	Yield, %	ee,%
PPh_3	DEAD	THF	-78 ºC to rt	nr	nr
PBu_3	"	"	"	89	38
PMe_3	"	"	"	>95	50
PMe_3	"	toluene	-18	>95	63
PMe_3	"	"	-78 ºC to rt	>95	67
"	TCEAD	"	"	>95	84

TCEAD = 

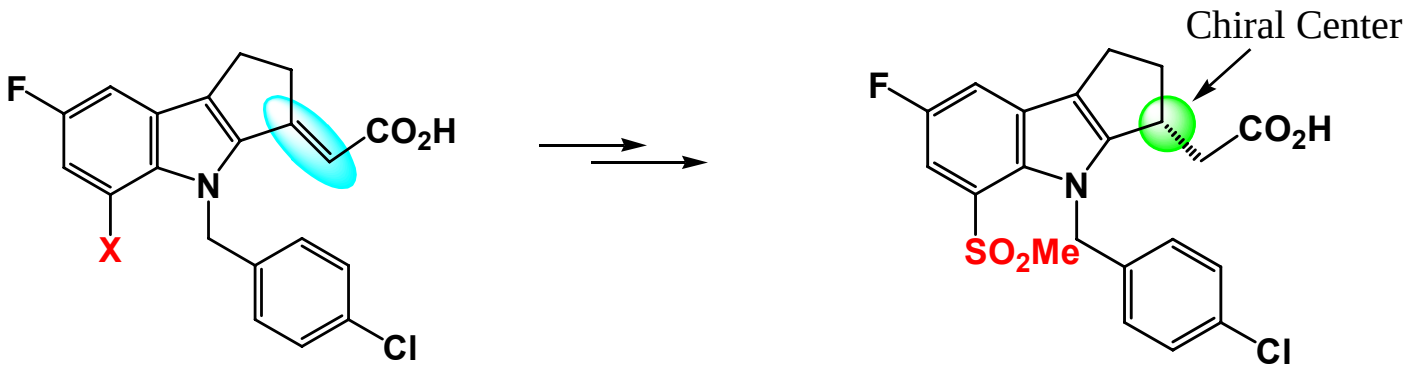
Stability of Chiral Alcohol



-Alcohol is Stable for >3 Months in MeOH with No Acid

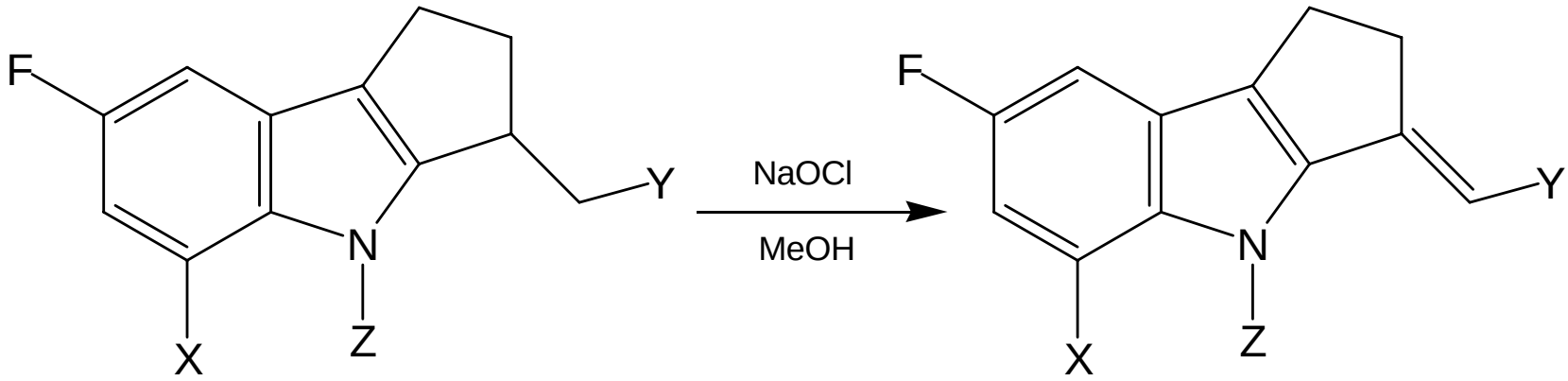
THIRD GENERATION PROCESS "ASYMMETRIC SYNTHESIS"

Ultimate goal : Asymmetric (convergent) synthesis of the DP Receptor



- **Accessible via enantioselective hydrogenation with a homogeneous catalyst?**
- **Substituent at the 7-position (X)?**

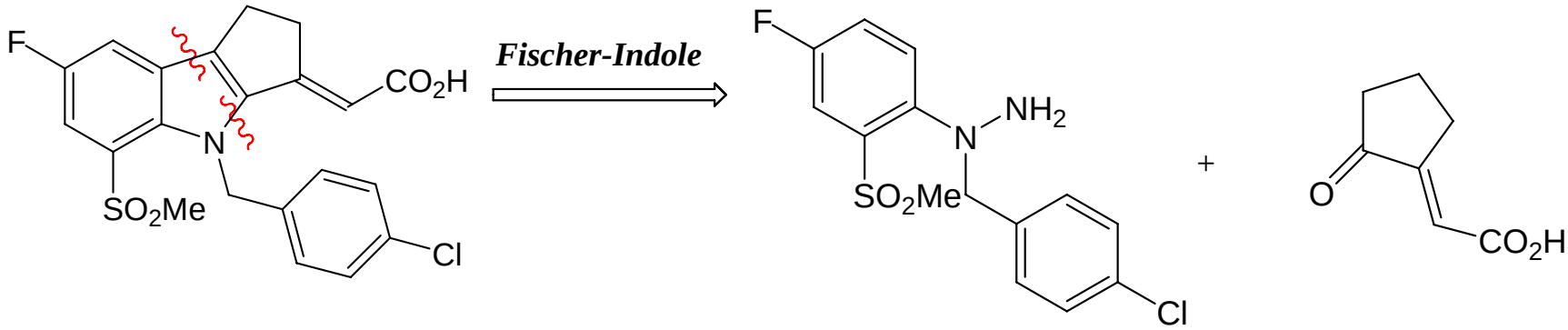
A General Oxidation Reaction in Cycloalkylindole Chemistry



We actually took 125g of final product (X = SO_2CH_3, Z = p-Cl-Benzyl and Y = CO_2H) prepared by a variant of the medicinal chemistry synthesis and oxidized it back to 100 g of substrate for AH.This was chromatographed and crystallized to provide ~50g of super pure substrate for asymmetric hydrogenation studies.

This was a key development in the program as it allowed development of a new synthesis of the penultimate intermediate and study of the asymmetric hydrogenation to proceed in parallel

Convergent Synthesis of the "Ene-Acid" Penultimate: The Fischer-Indole Approach



Ene-acid **Benzylhydrazine** **Oxo-ene Acid**

? ?

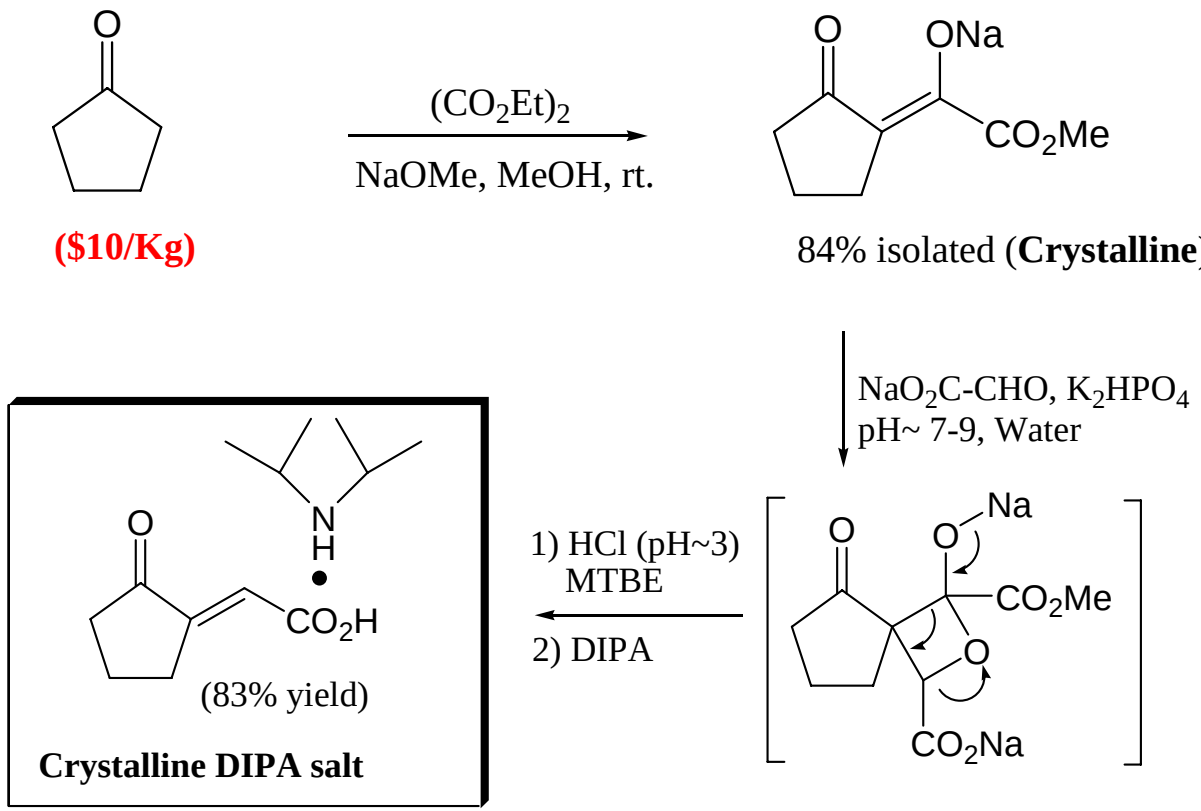
<u>PROS</u> : **- Convergent synthesis of ene-acid.**

- No regioselectivity issue in Fischer-Indole.

<u>QUESTIONS</u>: **- Unprecedented Fischer-Indole w/ such an "oxo-ene" Acid?**

- How to synthesize the hydrazine, and the "oxo-ene" Acid?

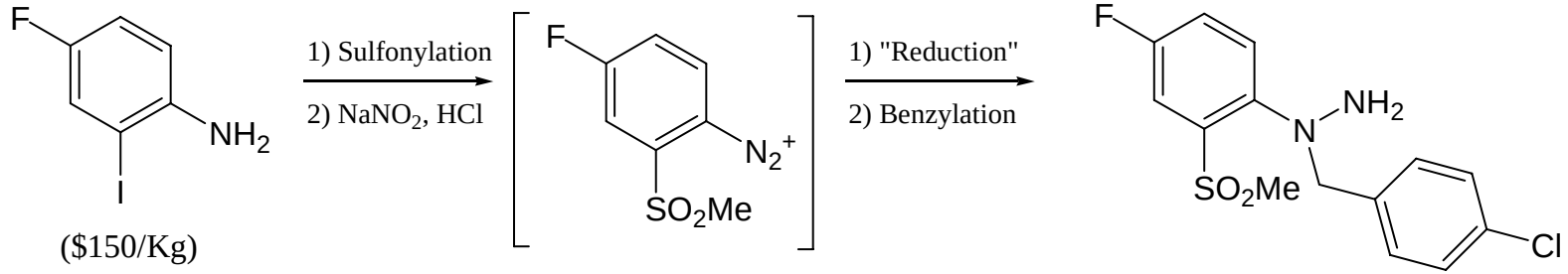
Oxo-ene Acid Synthesis



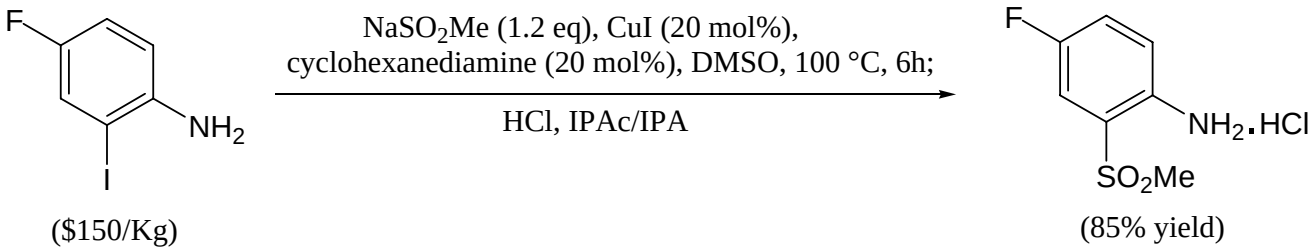
- **Readily available, inexpensive starting materials.**
- **Isolated as either free-acid (MTBE solution) or as crystalline diisopropylamine salt.**

Bonadies and Scarpati *Gazetta Chimica Italiana* **1983**, *113*, 421.

Synthesis of the Benzylhydrazine
"The Diazonium Approach"

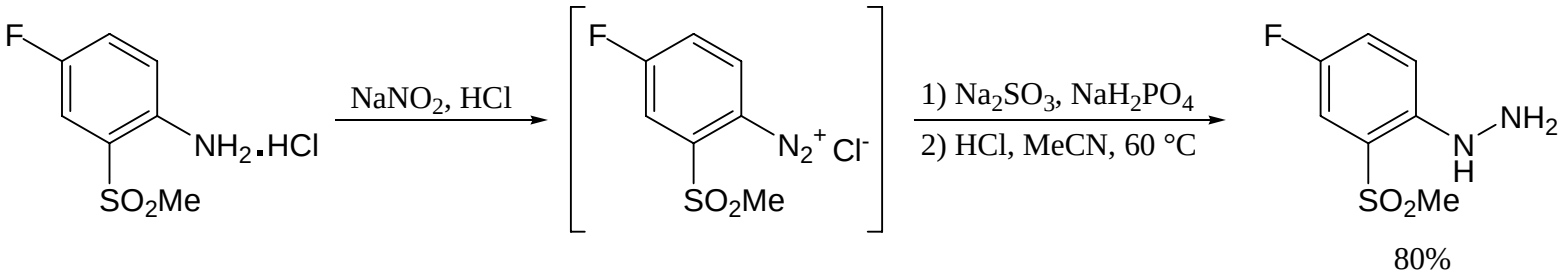


First step : Sulfonylation.



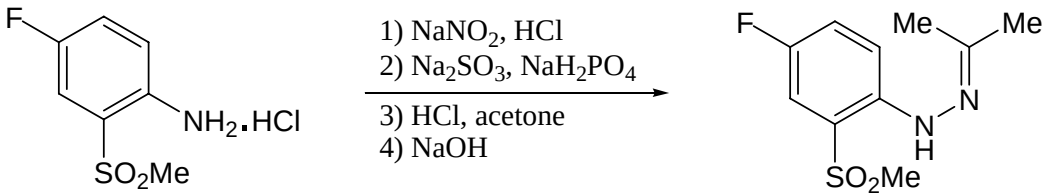
Similar to the last step of the "First and Second Generation Process" (experience) but iodide more reactive than bromide: Use of catalytic copper.

Tin-Free Hydrazine Formation and Acetone Hydrazone Isolation



80%

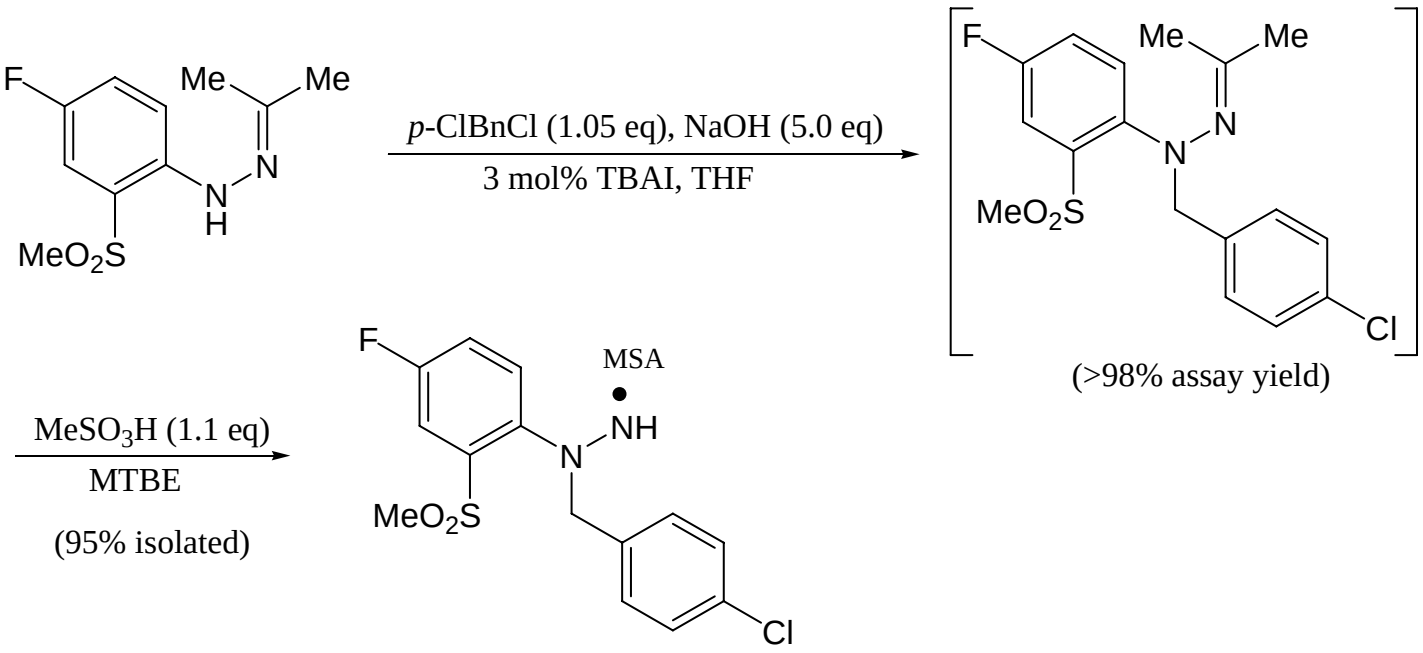
- **Sodium sulfite reduction of diazonium salt (*vs* $SnCl_2$) : Mild, Reproducible, No tin waste.**
- **Isolation issue: Mother liquor loss (-10%), Hydrazine not stable under basic conditions.**



(90% yield)

- **Acetone hydrazone directly crystallized from reaction mixture (ML loss < 1%).**

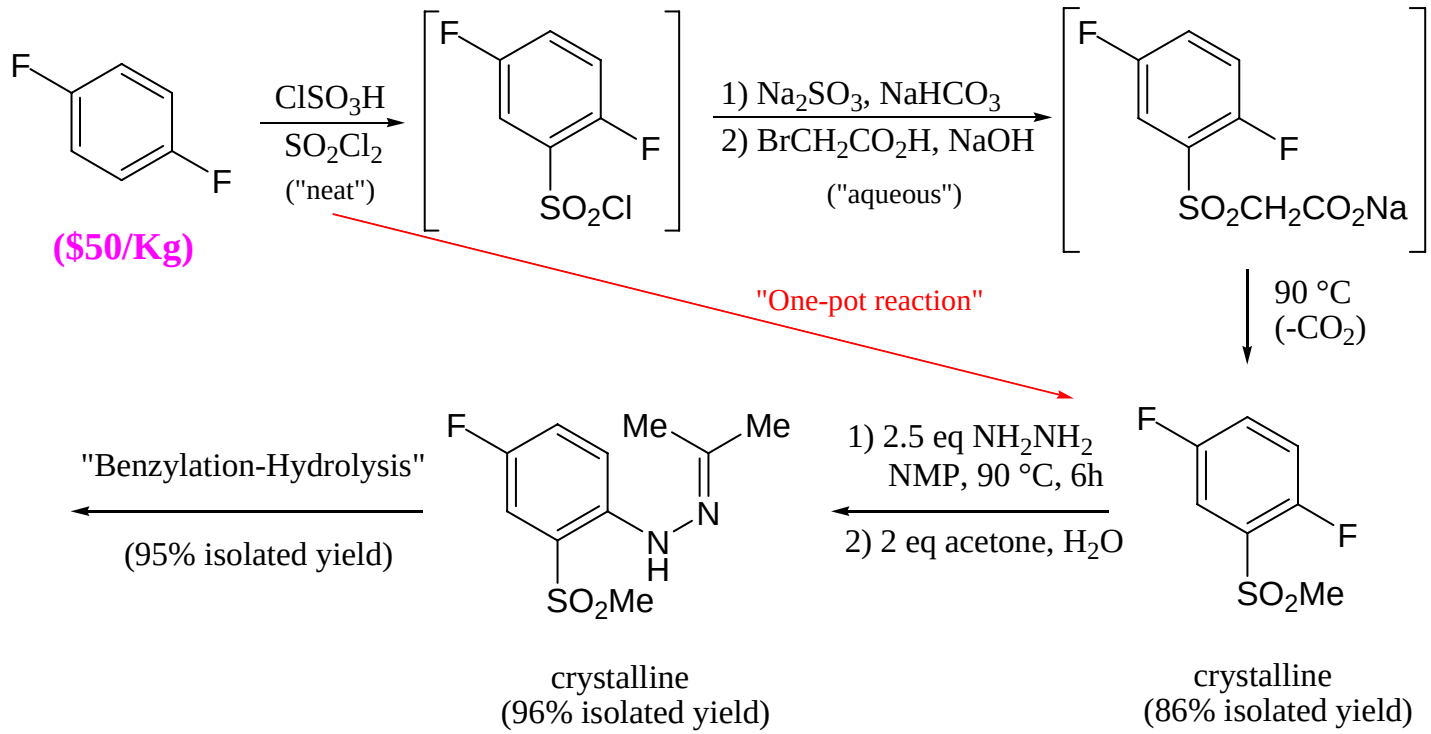
Benzylation and Hydrolysis



- **100% selective : benzylation of the free hydrazine gave 5A% of bis-benzylated product.**
- **Hydrolysis of the hydrazone *in-situ* with MSA. direct crystallization of the MSA salt from the reaction mixture.**
- **4 step process (72% overall yield).**

BUT, can we further improve the synthesis of the benzylhydrazine?
$NaSO_2Me$ (sulfonylation) $600/Kg (prep scale), copper waste etc…

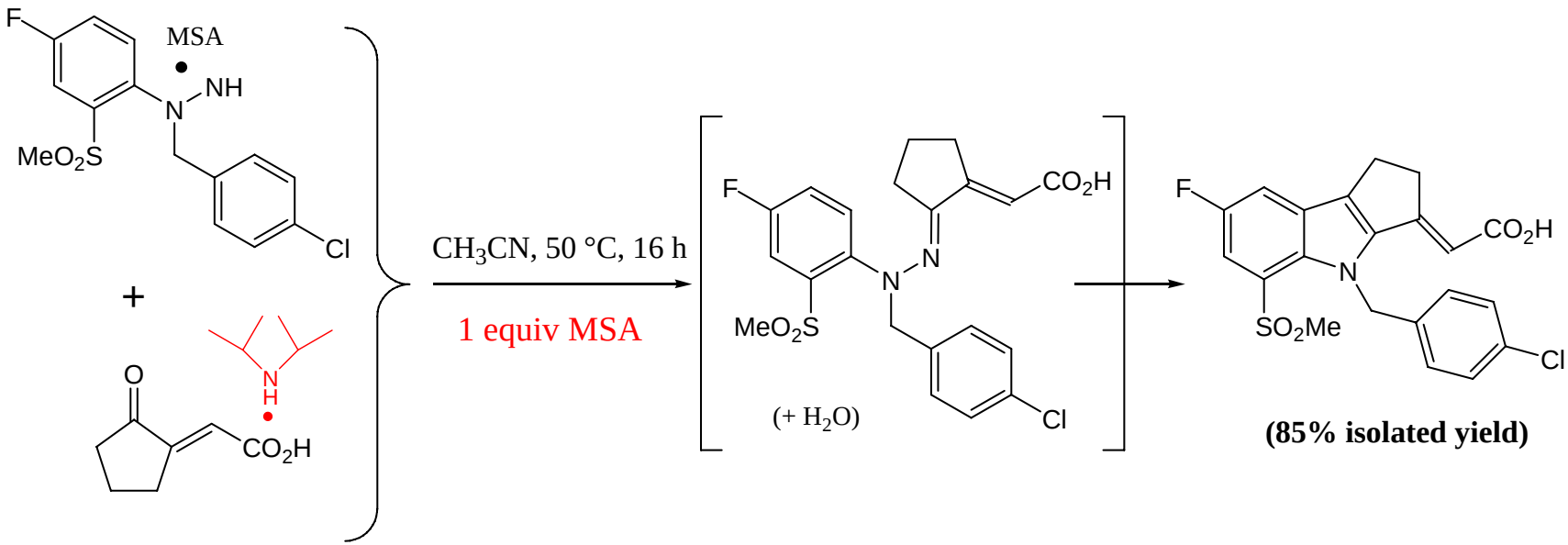
Synthesis of the Benzylhydrazine "The Fluorine Displacement Approach"



- **High yield, copper free, no extractions : Intermediates directly crystallized from the reaction mixture.**

- **"Preferred" process : "3 step process" 78% overall yield.**

Fischer-Indole : Synthesis of the "*Ene-Acid*"

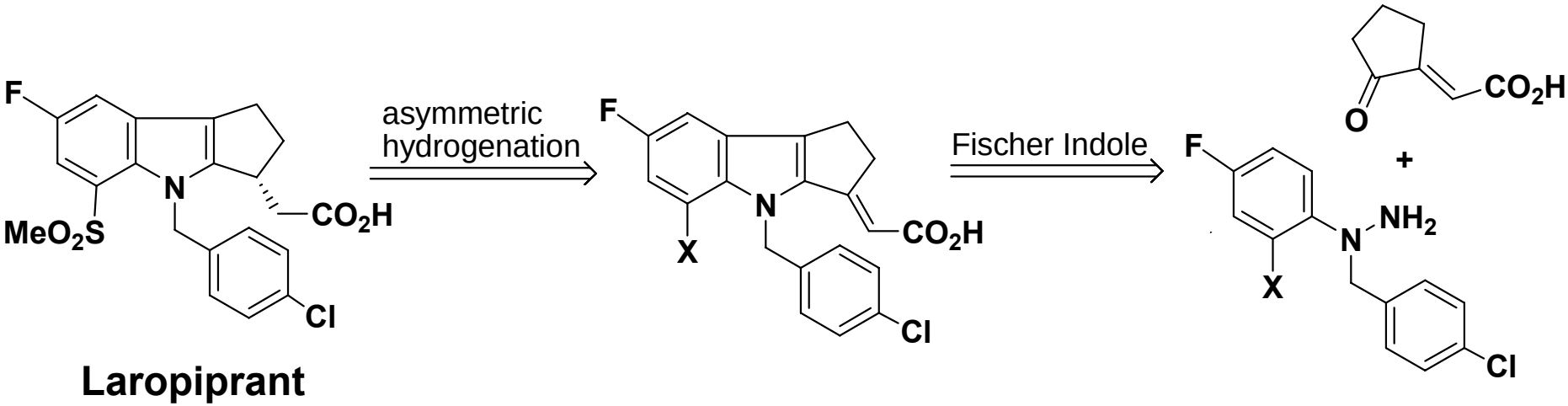


- **No need to add more acid to the reaction : MSA from hydrazine salt allows the Fischer-Indole to proceed. 1 equiv of MSA added to salt break (in situ) the DIPA salt.**

- **No isolation of the hydrazone ("barely" seen by HPLC). No need to remove water.**

- **Ene-Acid crystallizes out of the acetonitrile solution as it forms (highly insoluble).**

Homogeneous α,β-Unsaturated Ene Acid Hydrogenation - Conclusions



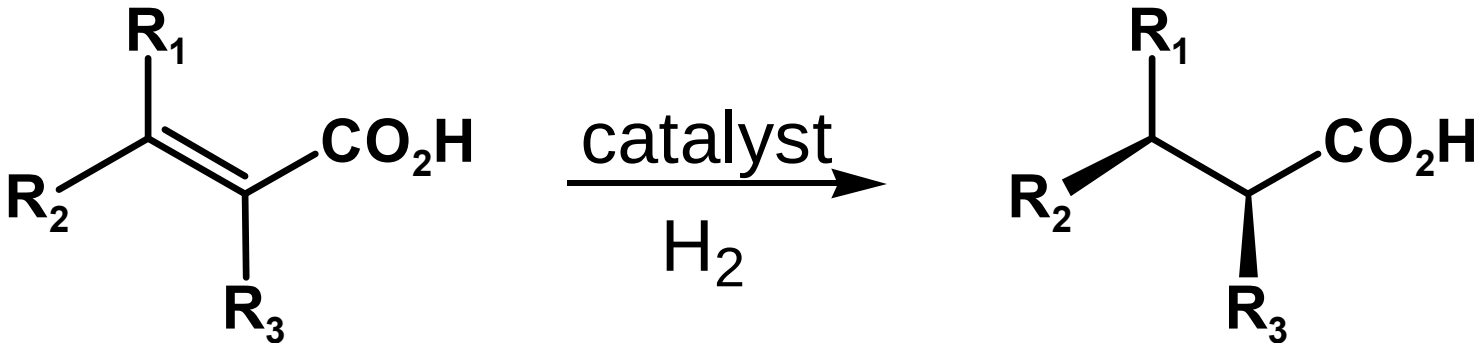
Laropiprant

J. Am. Chem. Soc. **2006**, *128*, 17063-17073

US Pat. Application 2005222428, 2005

Ene Acid Hydrogenations

- **Ene Acid Hydrogenation Background**

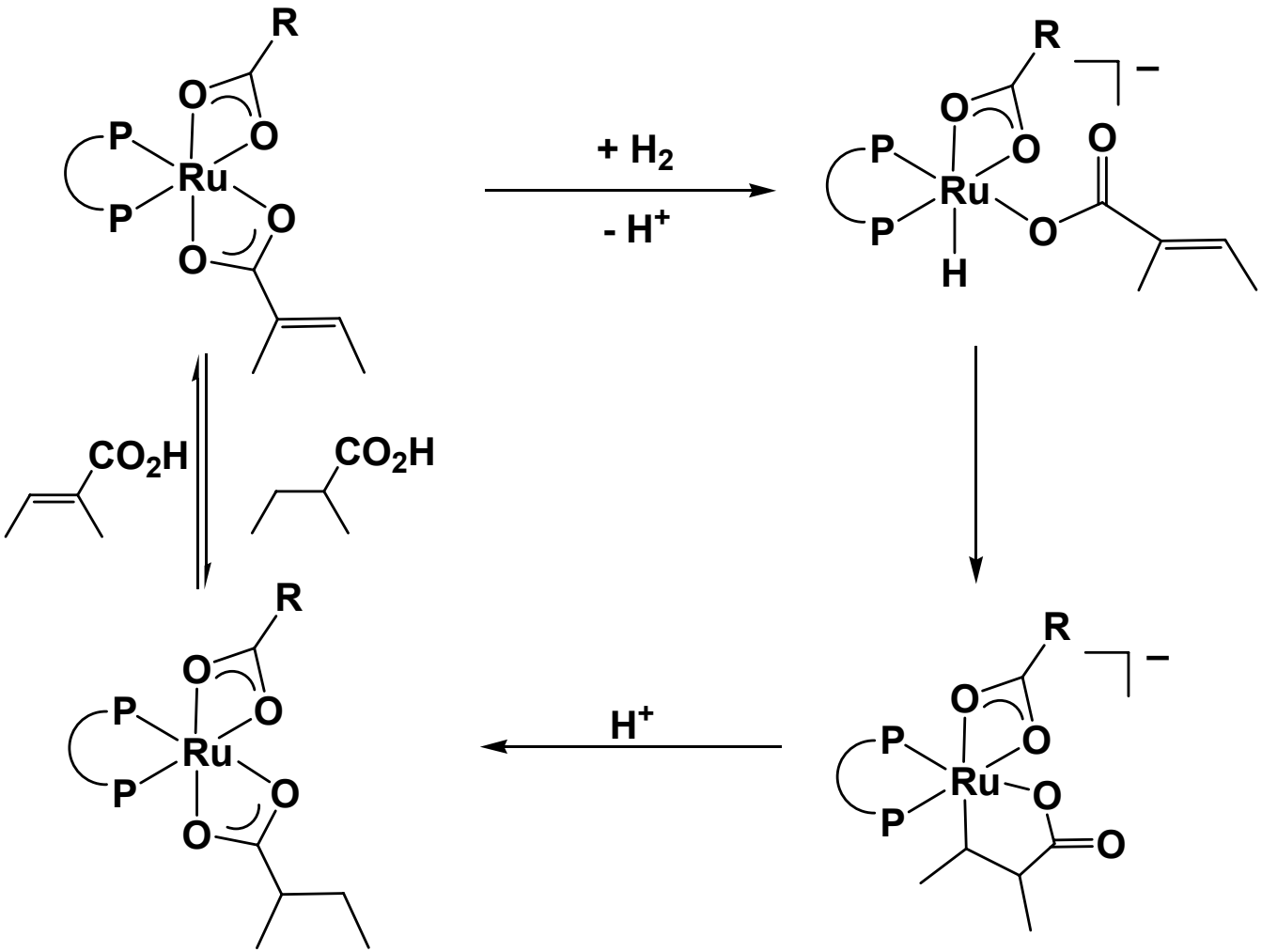


- **Typically ruthenium based with BINAP-type ligand**
- **May Exhibit Pressure Dependence**
- **Acids are typically much more reactive than ester counterpart**
- **No precedence for Laropiprant-type hydrogenation**

Tang, W.; Zhang, X. *Chem. Rev.* **2003**, 1*03*, 3029-3069

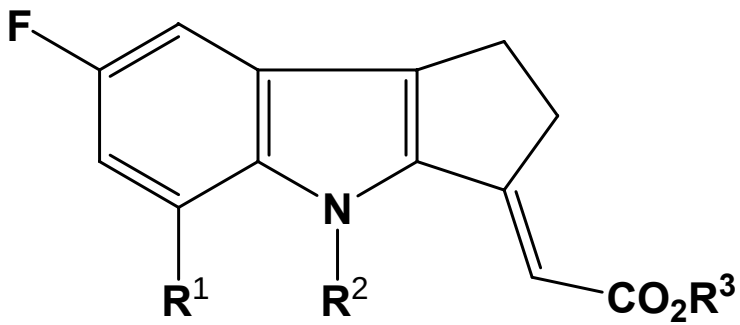
Ashby, M. T.; Halpern, J. J. Am. Chem. Soc. **1991**, 113, 589

Ene Acid Hydrogenations: Mechanism



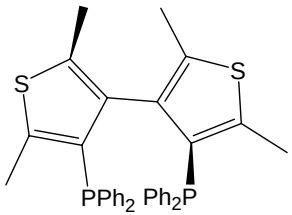
Ashby, M. T.; Halpern, J. J. Am. Chem. Soc. 1991, 113, 589

Multiple Hydrogenation Candidates Evaluated

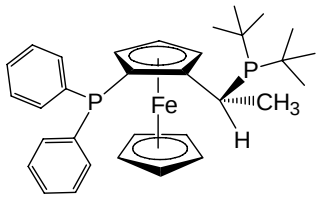


$R^1 = SO_2Me$, Br, H
R^2 = H, BnCl
R^3 = Et, H

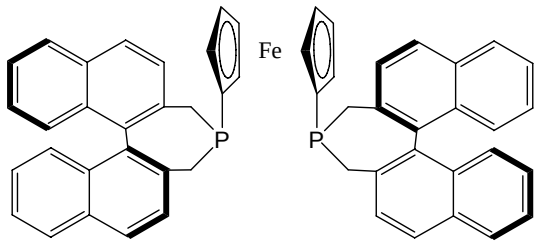
- Asymmetric hydrogenation development occurs "Real Time"
- Screened library of Rh and Ru catalysts, identified 10 hits (six Rh and four Ru) giving >80% ee



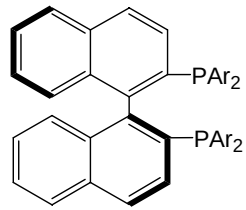
TMBTP
89% ee



Josiphos
82-89% ee



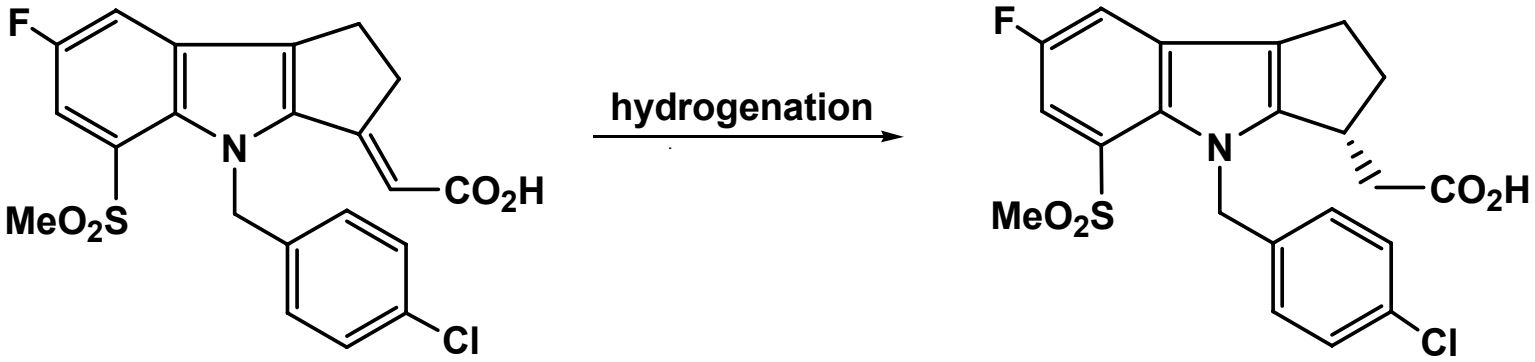
f-Binaphane
85% ee



BINAP
85-92% ee

Demonstrates viability of approach

Hydrogenation of the Penultimate



Ene Acid

"E-Isomer"

Target

Advantages

- Sets chiral center last
- avoids loss of expensive chiral intermediates
- Supports/facilitates convergent synthesis

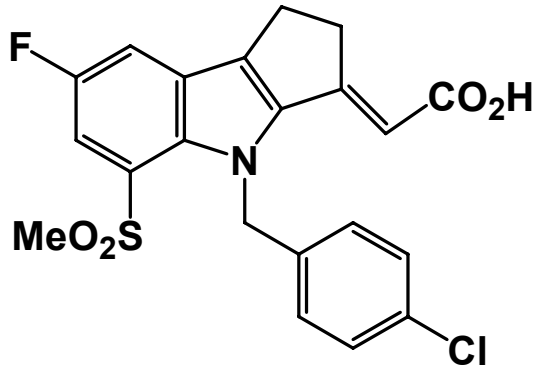
Disadvantages

- upgrade
- metal removal
- substrate purity and catalyst loading

Hydrogenation Base/Solvent Selection

- Ene Acid Exhibits Poor Solubility in "Practical" Hydrogenation Solvents

solvent	mg/mL	Solvent	mg/mL
MeOH	0.019	Toluene	0.008
EtOH	0.016	acetonitrile	0.02
DMAC	20.2	EtOAc	0.06
DMF	9.7	DMSO	19.4
THF	0.09	Acetone	0.11

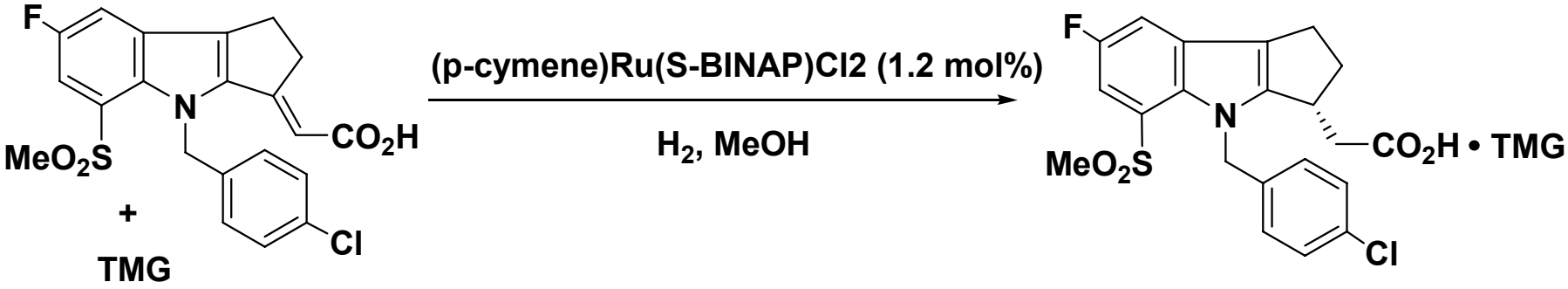


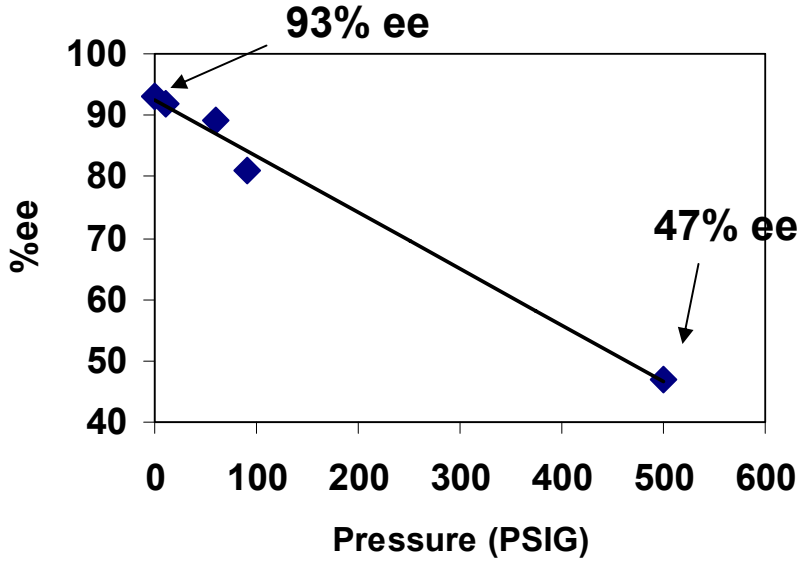
- Salt formation greatly increases ene acid solubility in MeOH (28 bases examined)

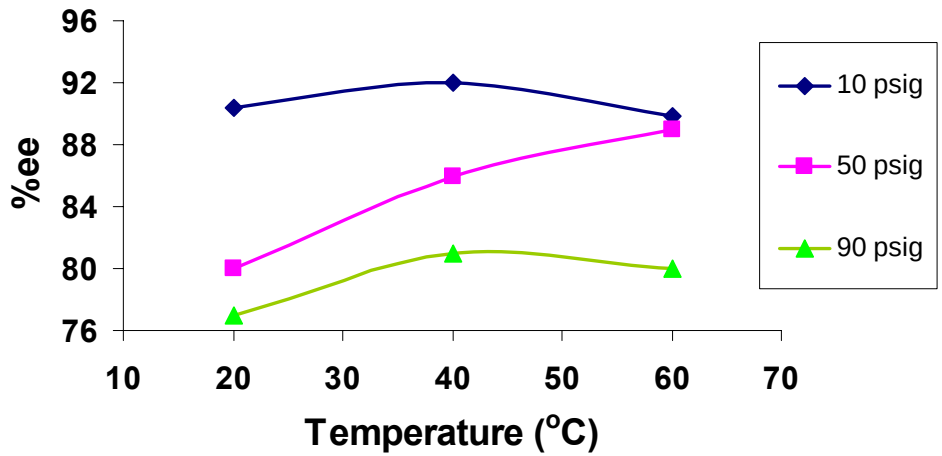
base	mg/mL
Et_3N	7.8
Cs_2CO_3	>300
KOtBu	>200
tetramethylguanidine	183

Substantial solubility enhancement and ee upgrade available

Effect of Temperature and Pressure on Enantioselectivity

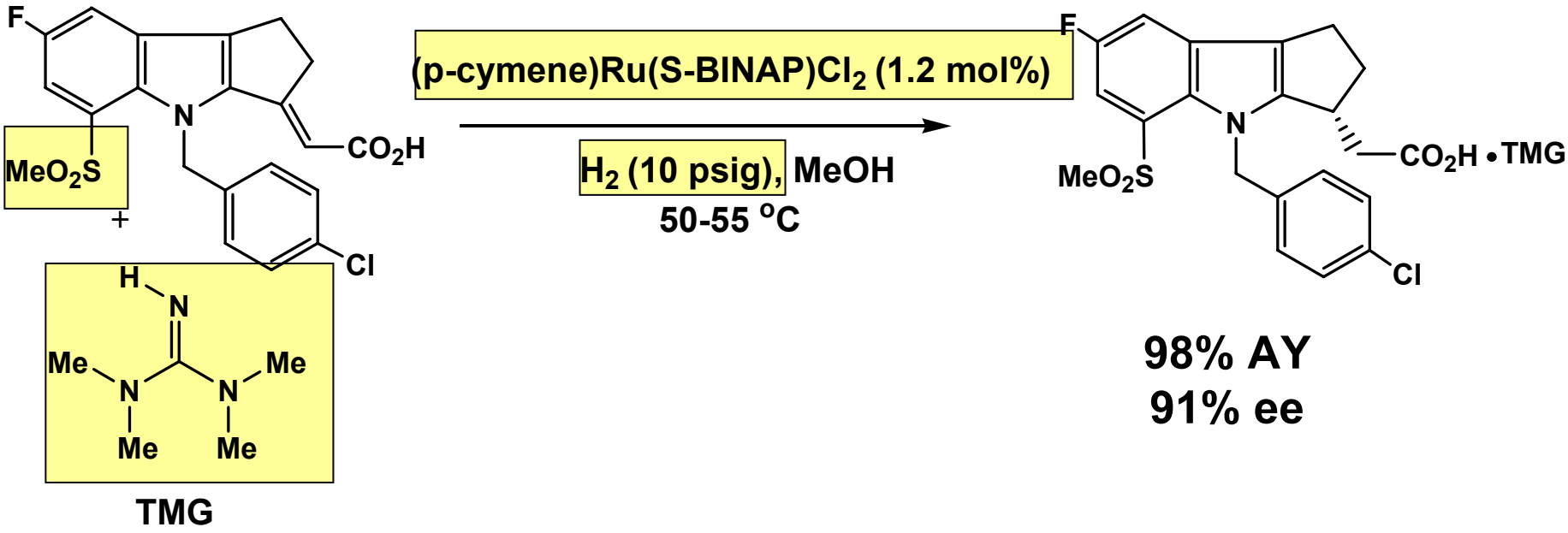






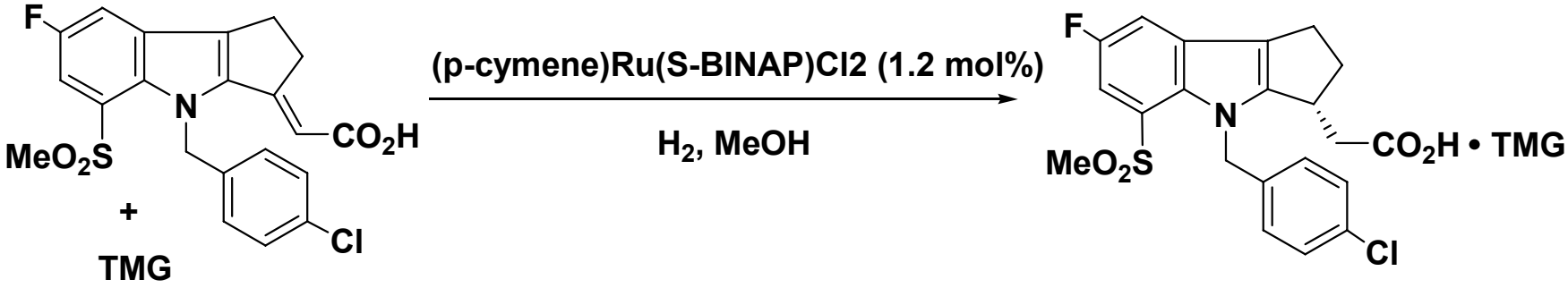
- Increasing Pressure Has a Negative Impact on Enantioselectivity
- Temperature has a sweet spot: 40 °C gives best ee

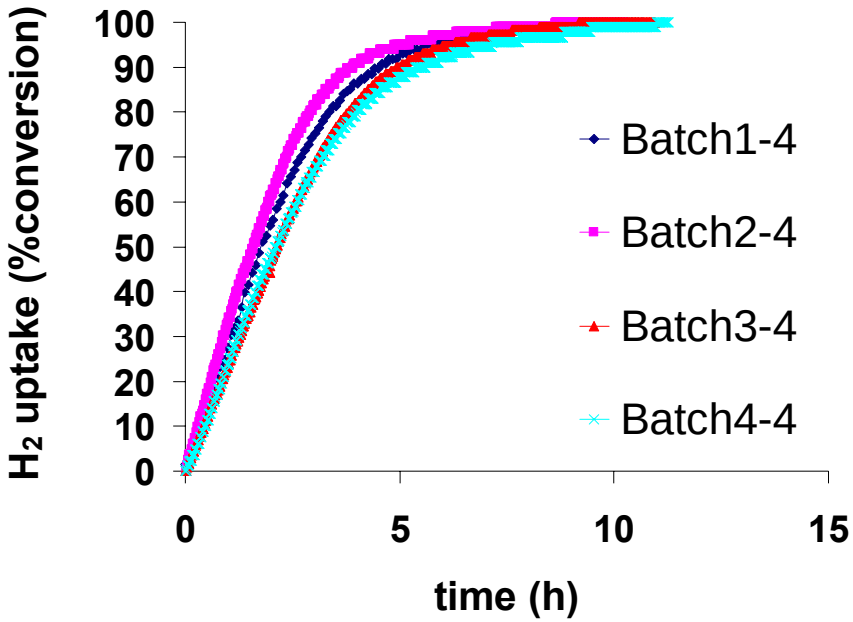
Optimized Process: Hydrogenation of Penultimate



- Chiral center installed as last step (hydrogenation of sulfone ene acid)
- Catalyst prepared in-situ tetramethylguanidine (TMG) used as base for rate and EE upgrade
- Low hydrogen pressure crucial for good enantioselectivity

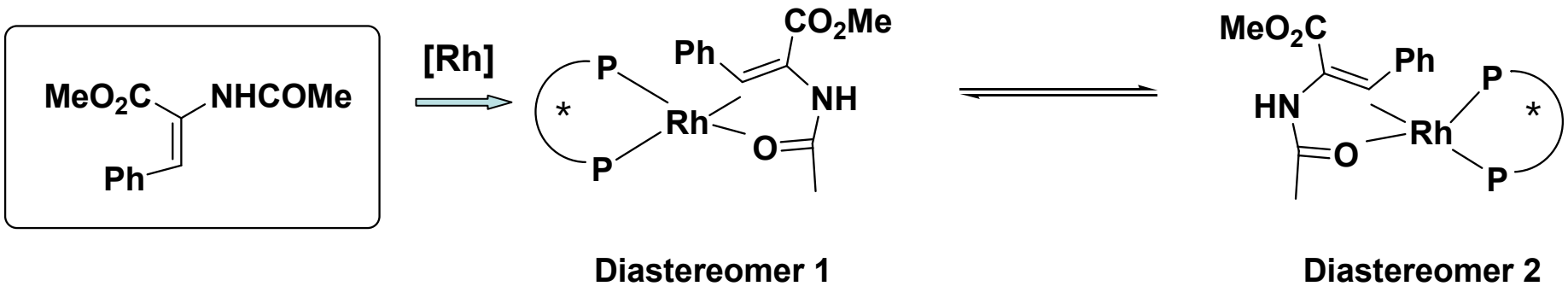
Results from First Pilot Plant Campaign





Next: Attempt to rationalize/understand enantioselectivity pressure dependence

Published Rational for Pressure Dependent Hydrogenations



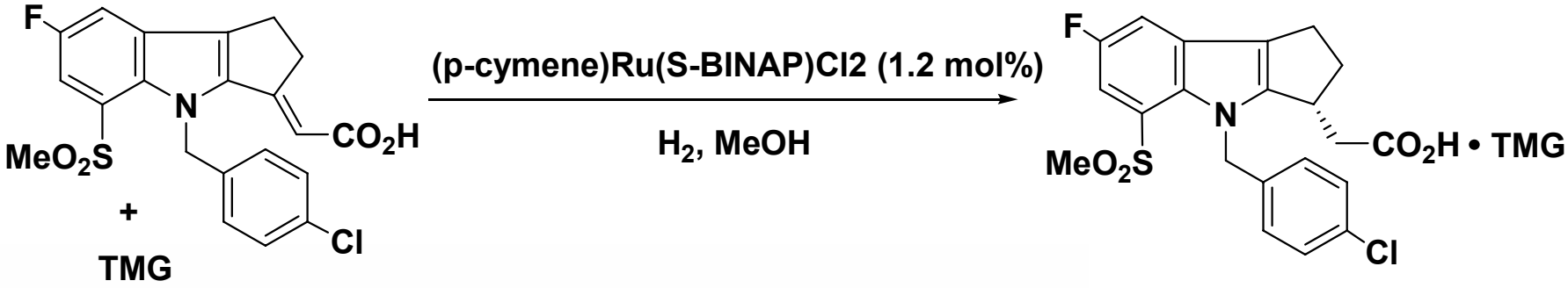
Diastereomer 1 Diastereomer 2

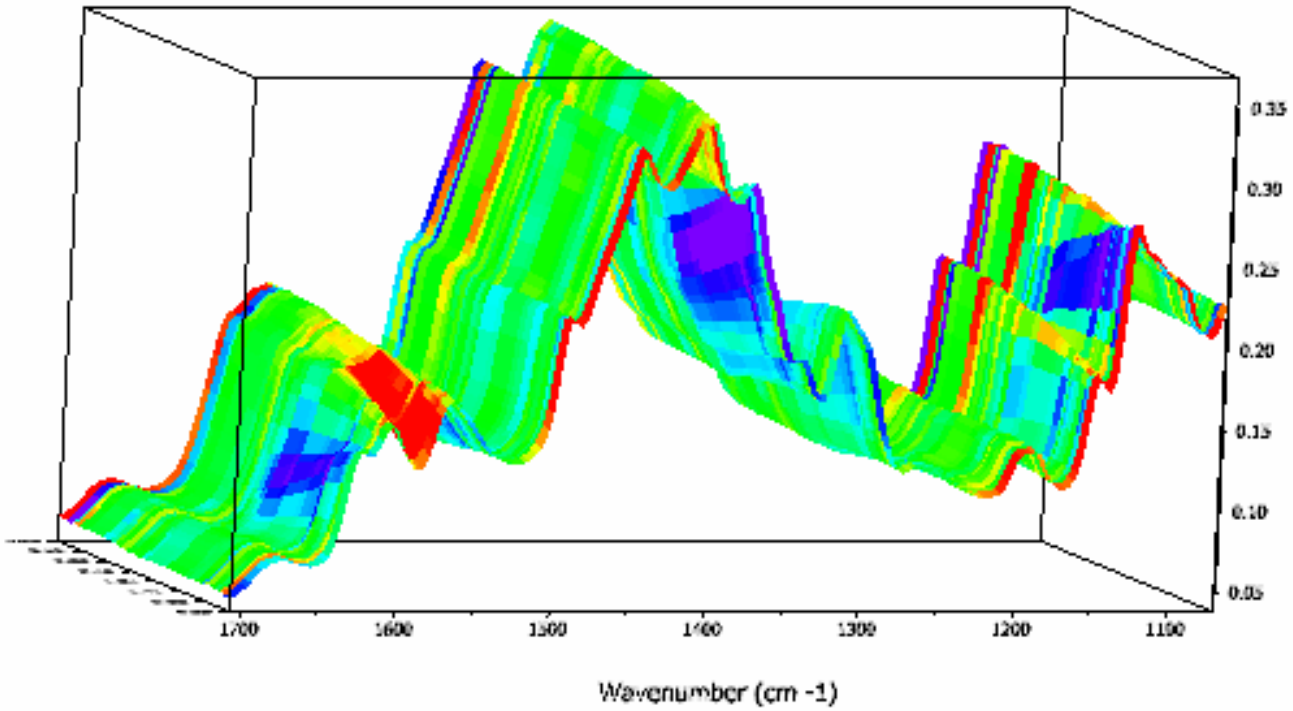
" . . . inverse dependence of the optical yield on the H_2 partial pressure is shown to be due to trapping of the [rhodium diastereomeric] adducts by reaction with H_2 and, thus, inhibiting their diastereomeric interconversion."

Landis and Halpern, *J. Am. Chem. Soc.* 1987, *109*, 1746-1754

- One published work on pressure dependent ene acid hydrogenation
- Sparse examples of mechanistic studies on pharmaceutically relevant intermediates

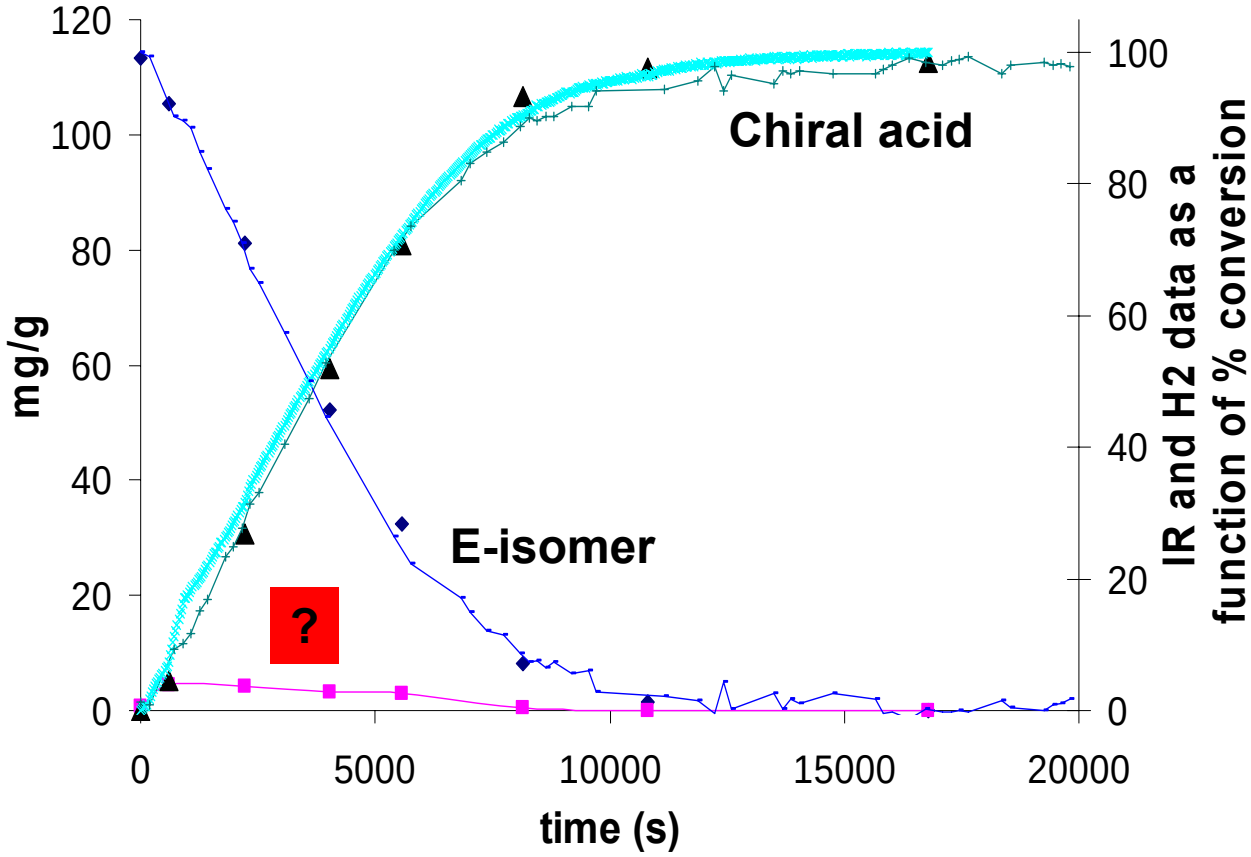
A Closer Look with ReactIR In-situ Analysis





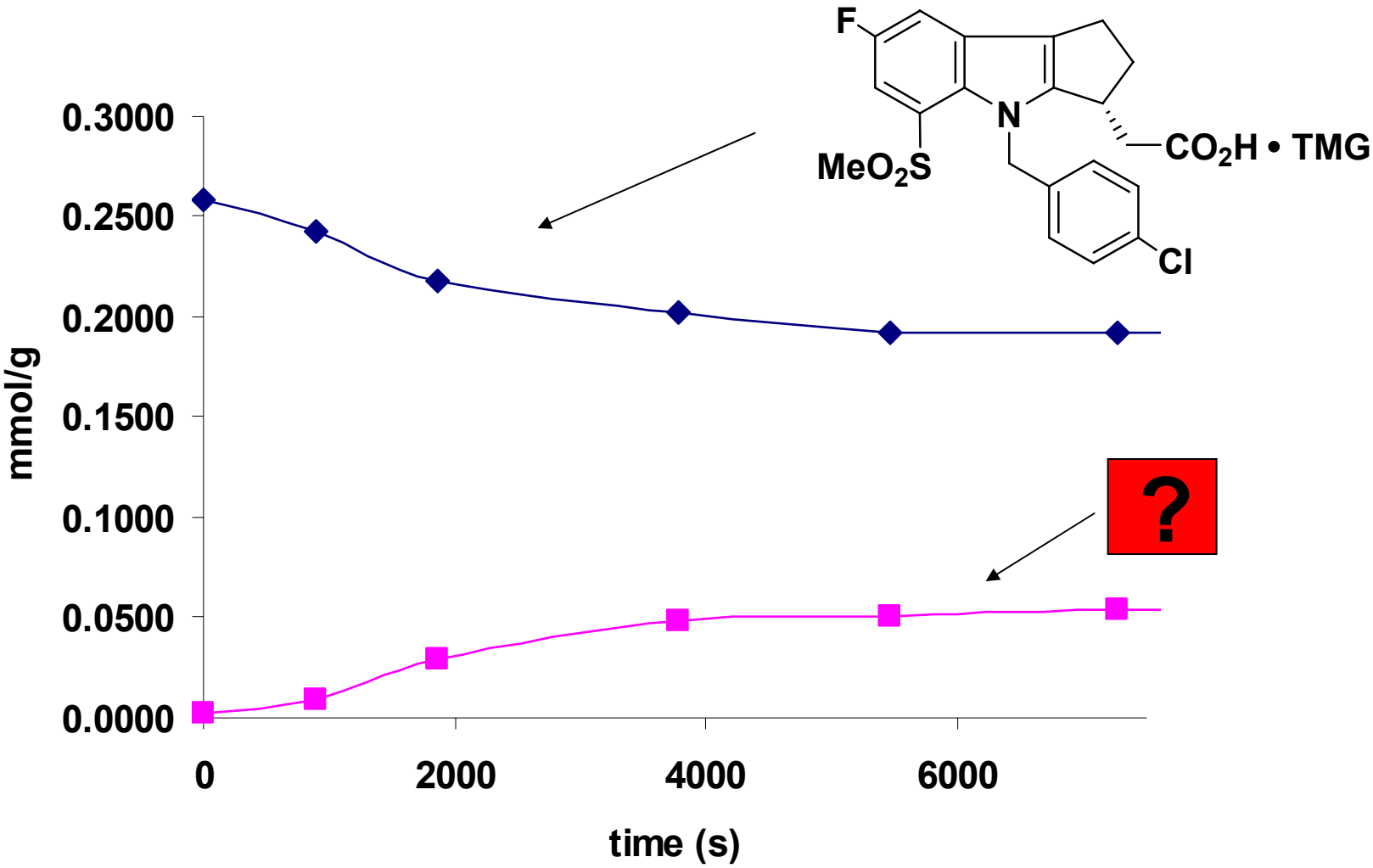
- Derivative plot of reaction profile
- Blue: decreasing intensity
- Red: increasing intensity

In-Situ Reaction Profiling

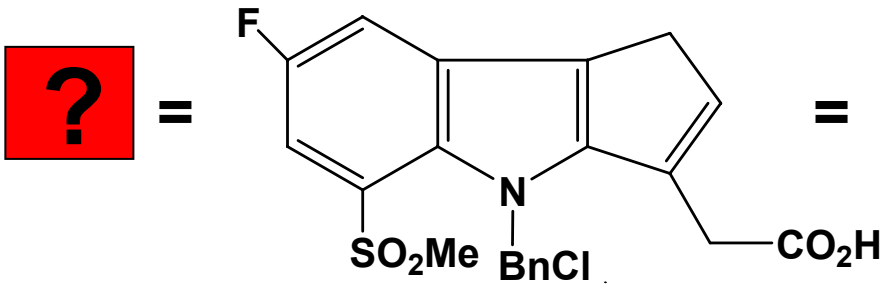


- Product enantioselectivity does not change during reaction
- Small amount of new compound is observed during early stages of reaction

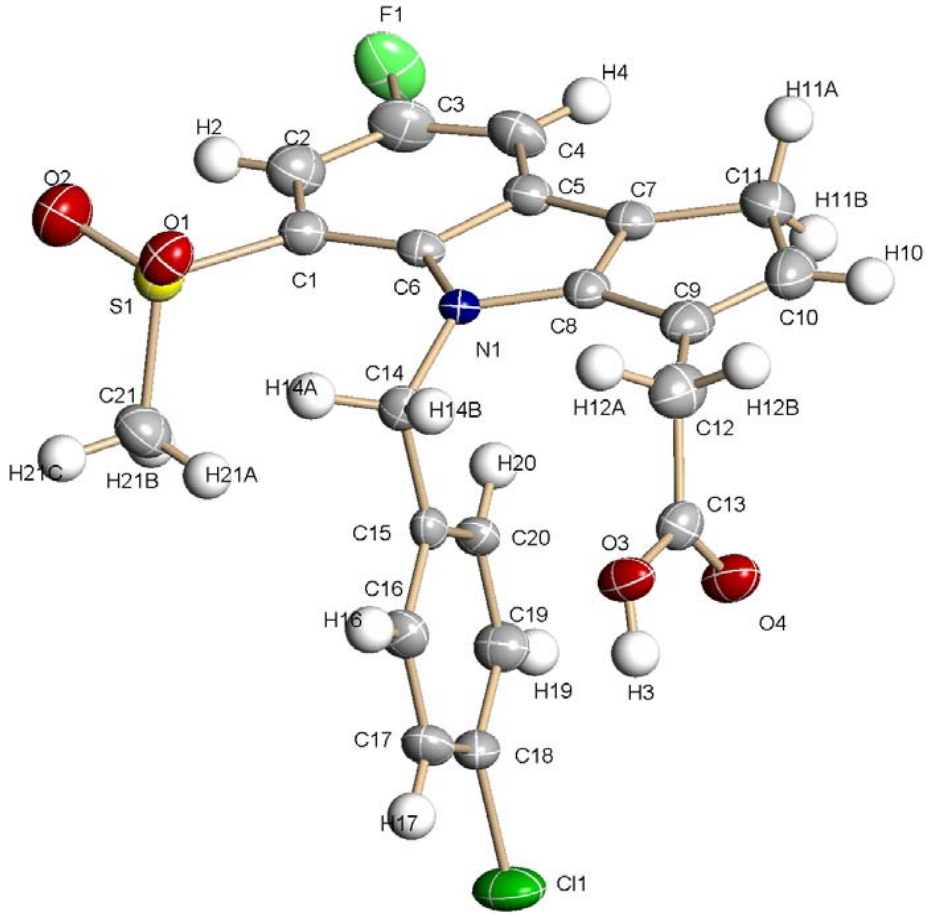
Thermolysis of TMG Ene Acid and Catalyst without Hydrogen



Identification of Intermediate: Endocyclic Isomer



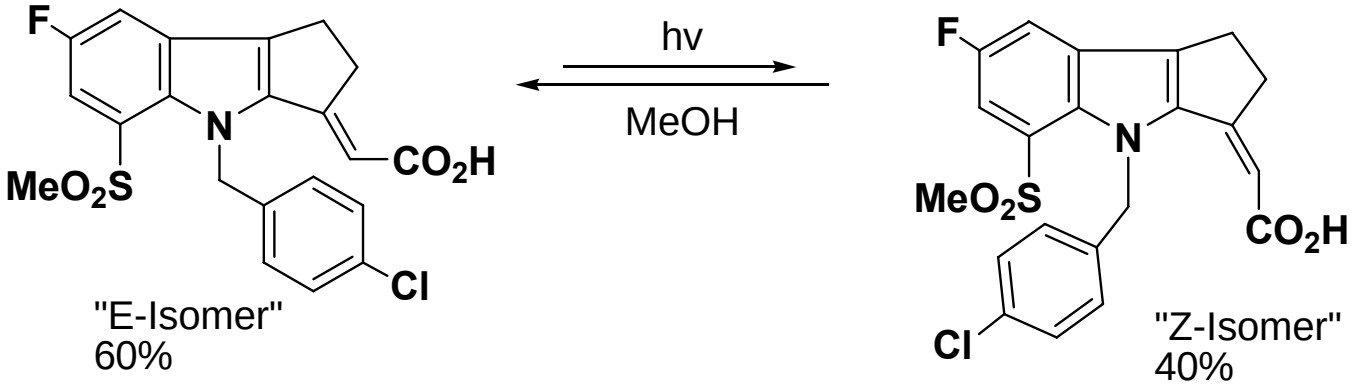
"Endo-Isomer"



ORTEP Diagram of Endo-Isomer

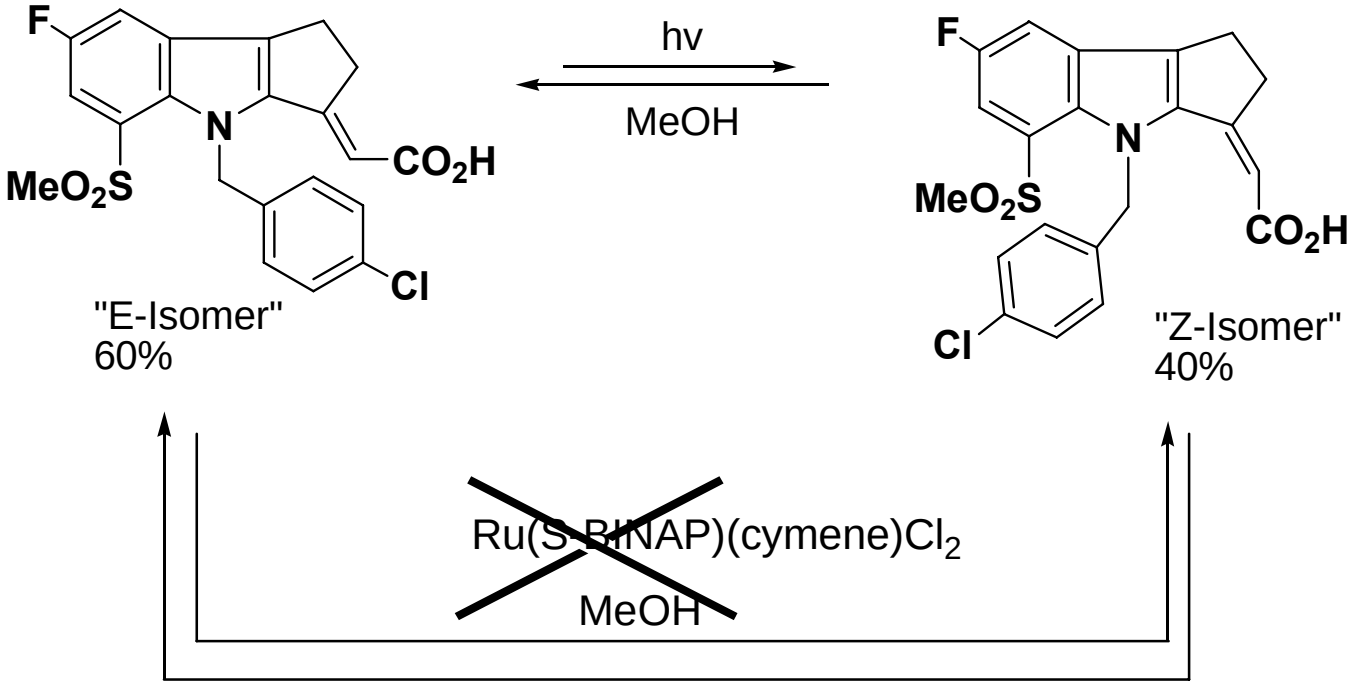
- What about the Z-isomer?

Generation and Reactivity of Z isomer



entry	treatment	A% E	A% Endo	A% Z
1	After 254 nm	60	0	40

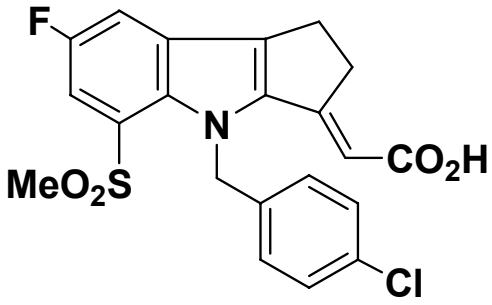
Generation and Reactivity of Z isomer



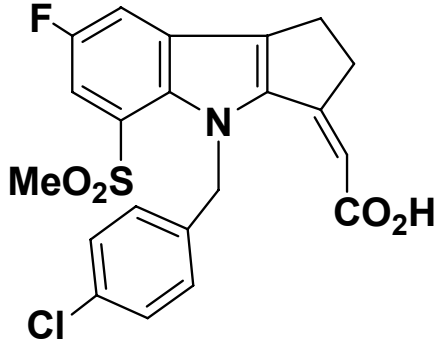
entry	treatment	A% E	A% Endo	A% Z
1	After 254 nm	60	0	40
2	Add Ru catalyst	46	14	40

Theoretical Analysis of Ene Acid Isomers

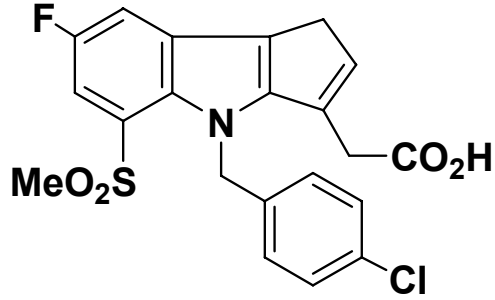
E-Isomer



Z-Isomer



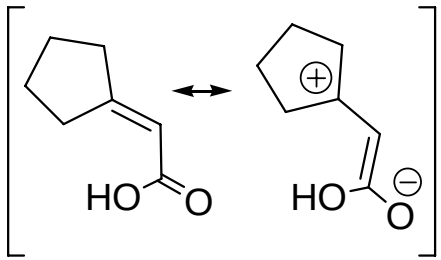
Endo Isomer



HF/3-21G*	0 kcal/mol	+2.8 kcal/mol	+5.5 kcal/mol

Stability: E > Z > Endo

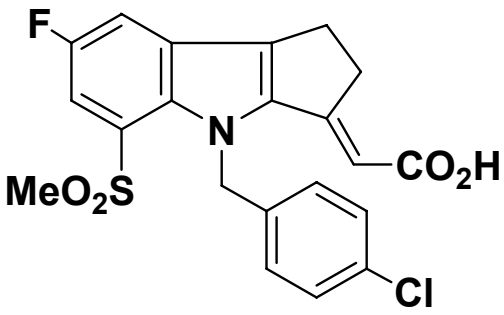
- E-isomer conjugation into carboxylic acid responsible for stabilization



- Large kinetic barrier prevents E/Z interconversion

Hydrogenation Behavior?

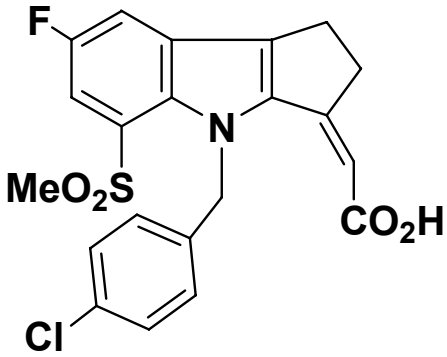
E-Isomer



H_2

ee?

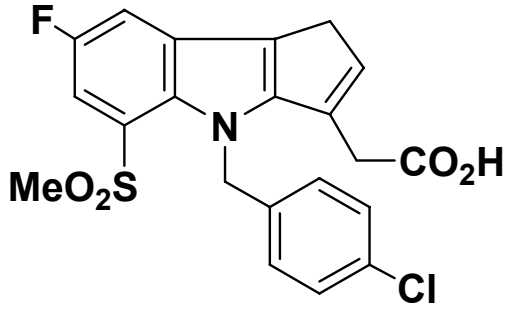
Z-Isomer



H_2

ee?

Endo Isomer

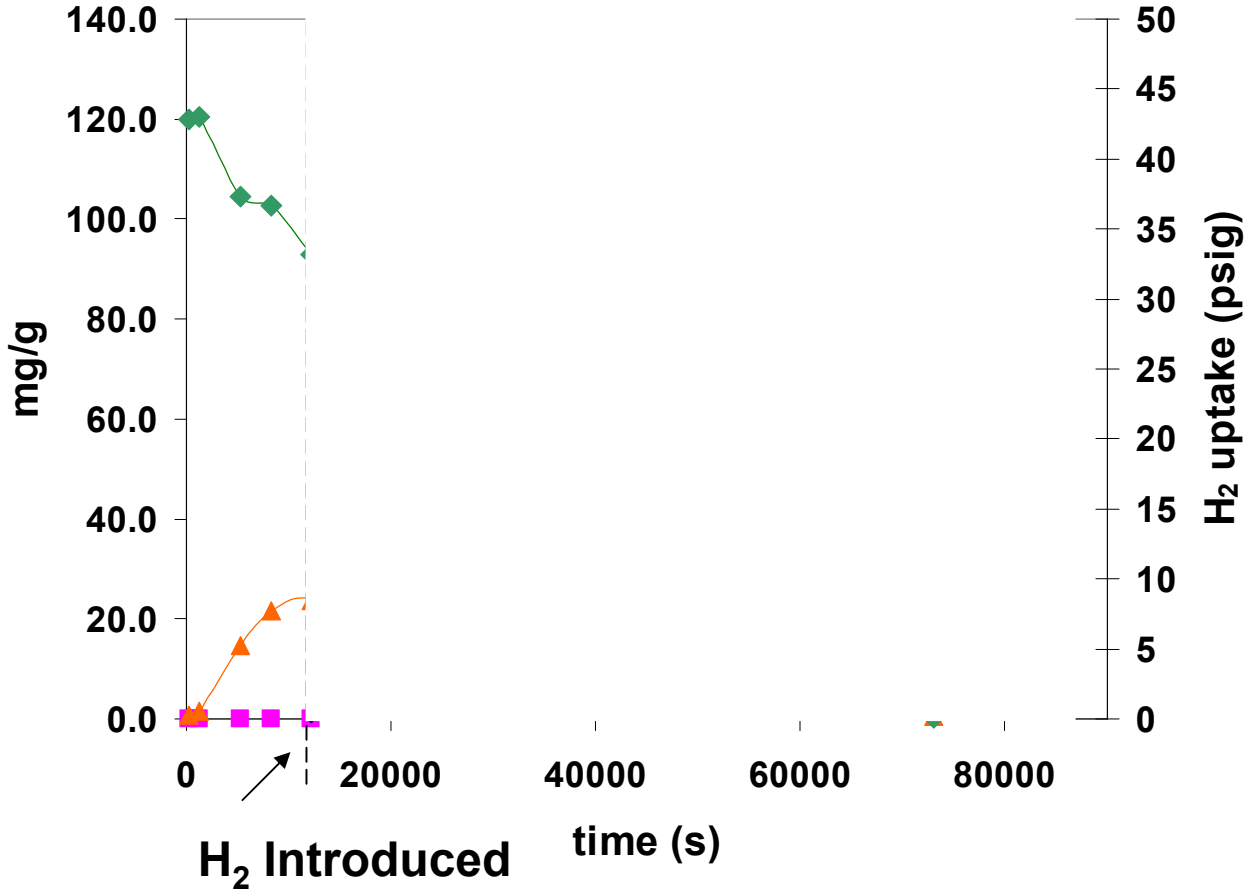


H_2

ee?

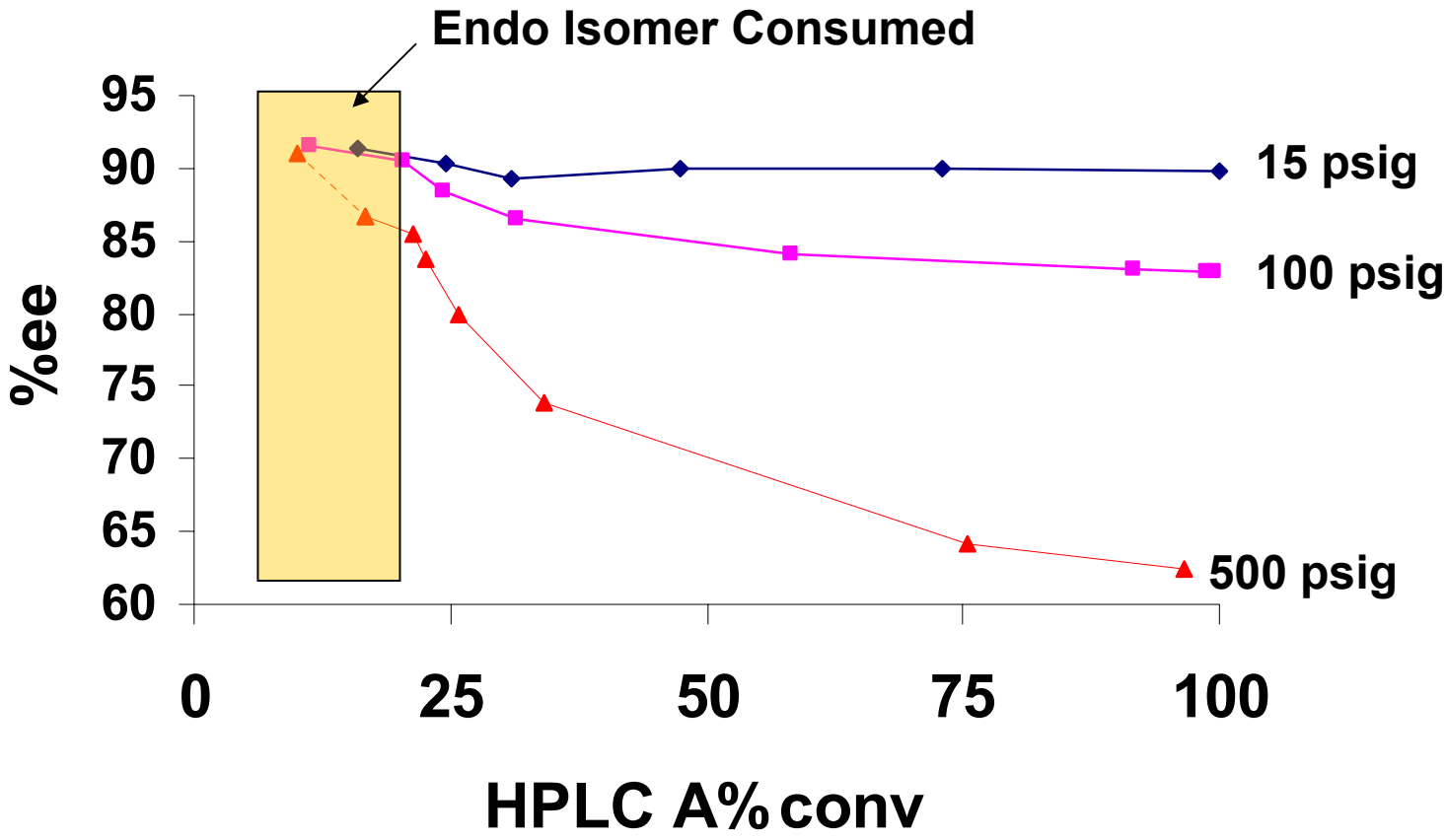
- Understanding individual behavior under hydrogen should facilitate mechanistic understanding of pressure dependence

Hydrogenation of E/Endo-Isomer Mixture



- Endo isomer more reactive
- Little change in ee over reaction
- ν_{max}(isomerization) ≈ ν_{max}(hydrogenation)

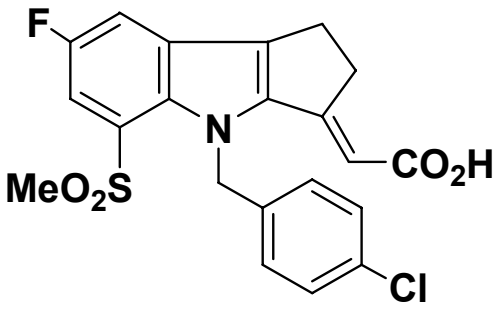
Hydrogenation of E/Endo Mixture



- ~90% ee obtained at early conversions for all pressure examined
- Rules out pressure dependent enantioselectivity for endo-isomer

Hydrogenation Behavior?

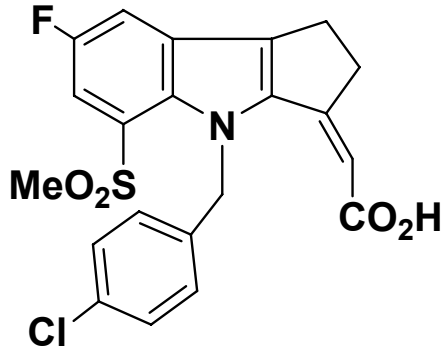
E-Isomer



H_2

ee?

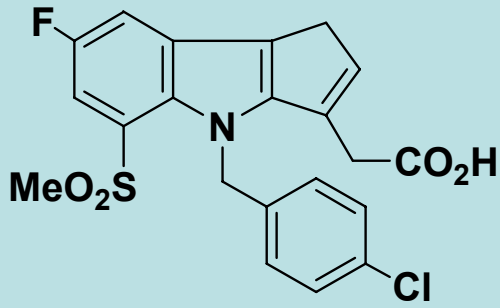
Z-Isomer



H_2

ee?

Endo Isomer

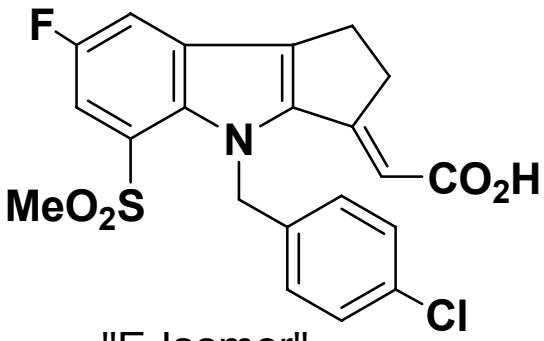


H_2

ee pressure independent

- **Endo isomer hydrogenation enantioselectivity independent of pressure**

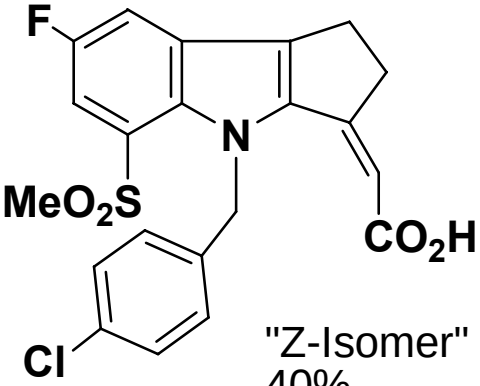
Calculation of Z-Isomer Ee Pressure Dependence



"E-Isomer"
60%

hv

MeOH



"Z-Isomer"
40%

[Ru], H_2

91% ee @ 25 psi

82% ee @ 105 psi

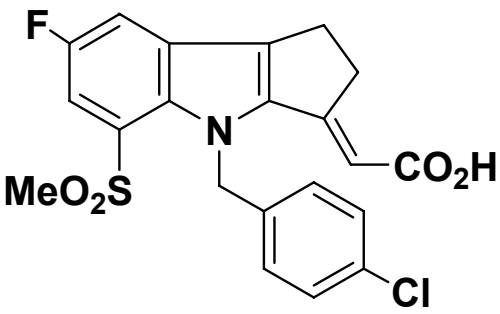
[Ru], H_2

H_2 (psi)	%ee	%ee (calc)
25	59	5
105	46	-13

$$\%ee_{Z\text{-isomer}} = \frac{\%ee_{total} - (\%1\text{-}E \times \%ee_{1\text{-}E})}{\%1\text{-}Z}$$

Hydrogenation Behavior?

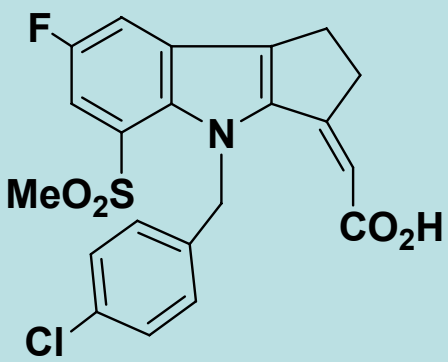
E-Isomer



H_2

ee?

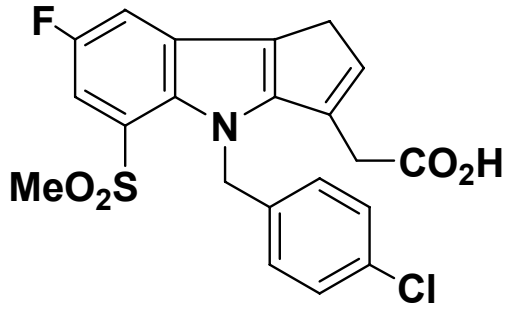
Z-Isomer



H_2

ee pressure dependent

Endo Isomer

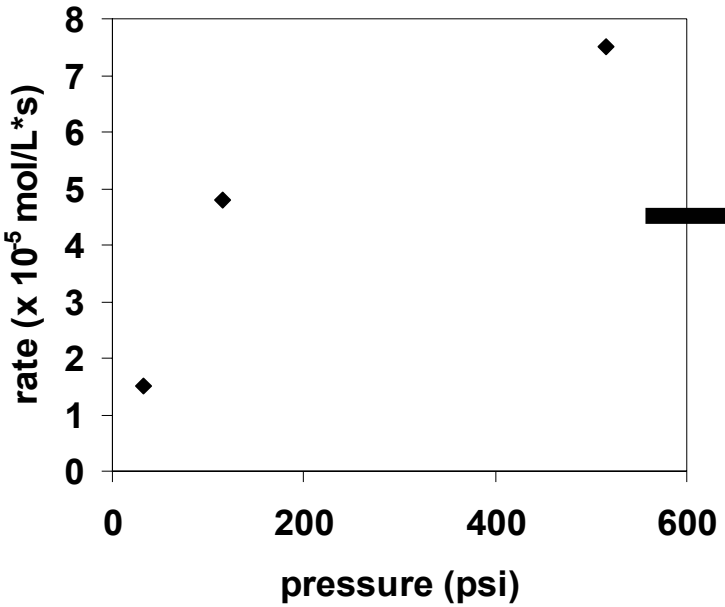


H_2

ee pressure independent

- Z-isomer is pressure dependent
- Direct measurement of E-isomer difficult due to competing isomerization
- Circumvent via manipulation of rate data?

Calculation of E-Isomer Hydrogen Dependence



Assumptions: Rate of 1-Endo Hydrogenation is Instantaneous *and* Rate of Isomerization is independent of Hydrogen Pressure

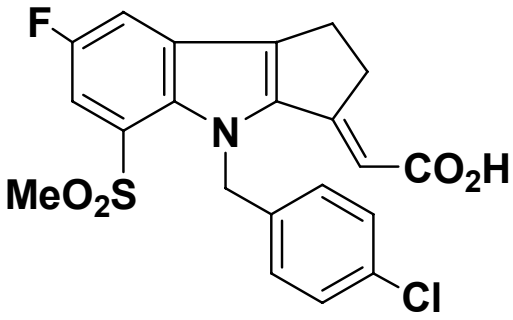
Hydrogen Pressure (psi)	Rate (mol/L*s)	$\%ee_{1\text{-}E}$ (calculated)
0	1.4×10^{-5} *	NA
33	1.5×10^{-5}	63
115	4.8×10^{-5}	74
515	7.5×10^{-5}	36

$$\%ee_{E\text{-isomer}} = \frac{\%ee_{total} - \left(\frac{r_{isom}}{r_{1\text{-}E} + r_{isom}}\right) \times \%ee_{1\text{-}Endo}}{\left(\frac{r_{1\text{-}E}}{r_{1\text{-}E} + r_{1\text{-}Endo}}\right)}$$

* = Isomerization rate

Hydrogenation Behavior Summary

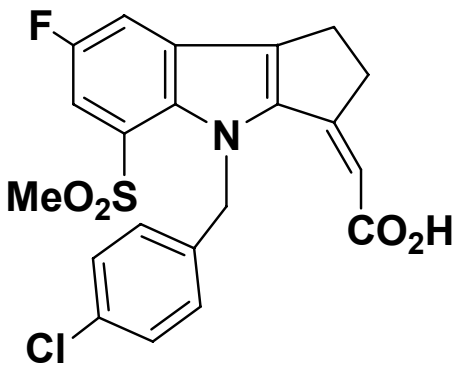
E-Isomer



H_2

ee pressure dependent

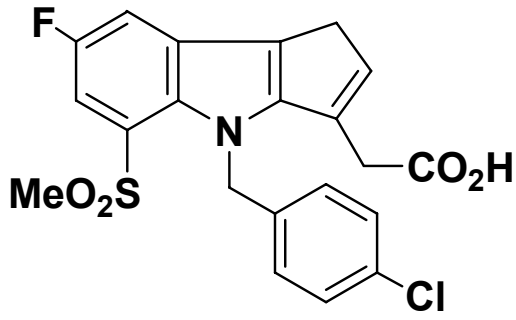
Z-Isomer



H_2

ee pressure dependent

Endo Isomer

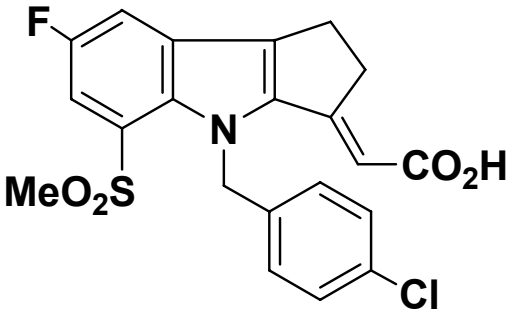


H_2

ee pressure independent

Understanding Difference between E and Endo Isomers

E-Isomer



H_2

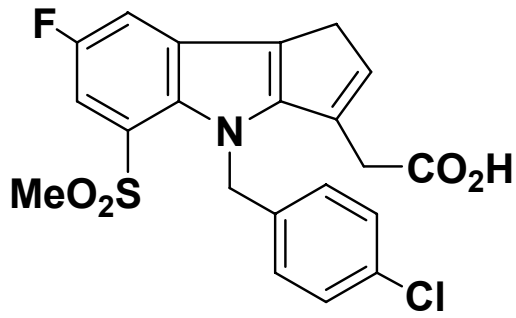
ee pressure dependent

Explain

Rate Difference

Ee Difference

Endo Isomer

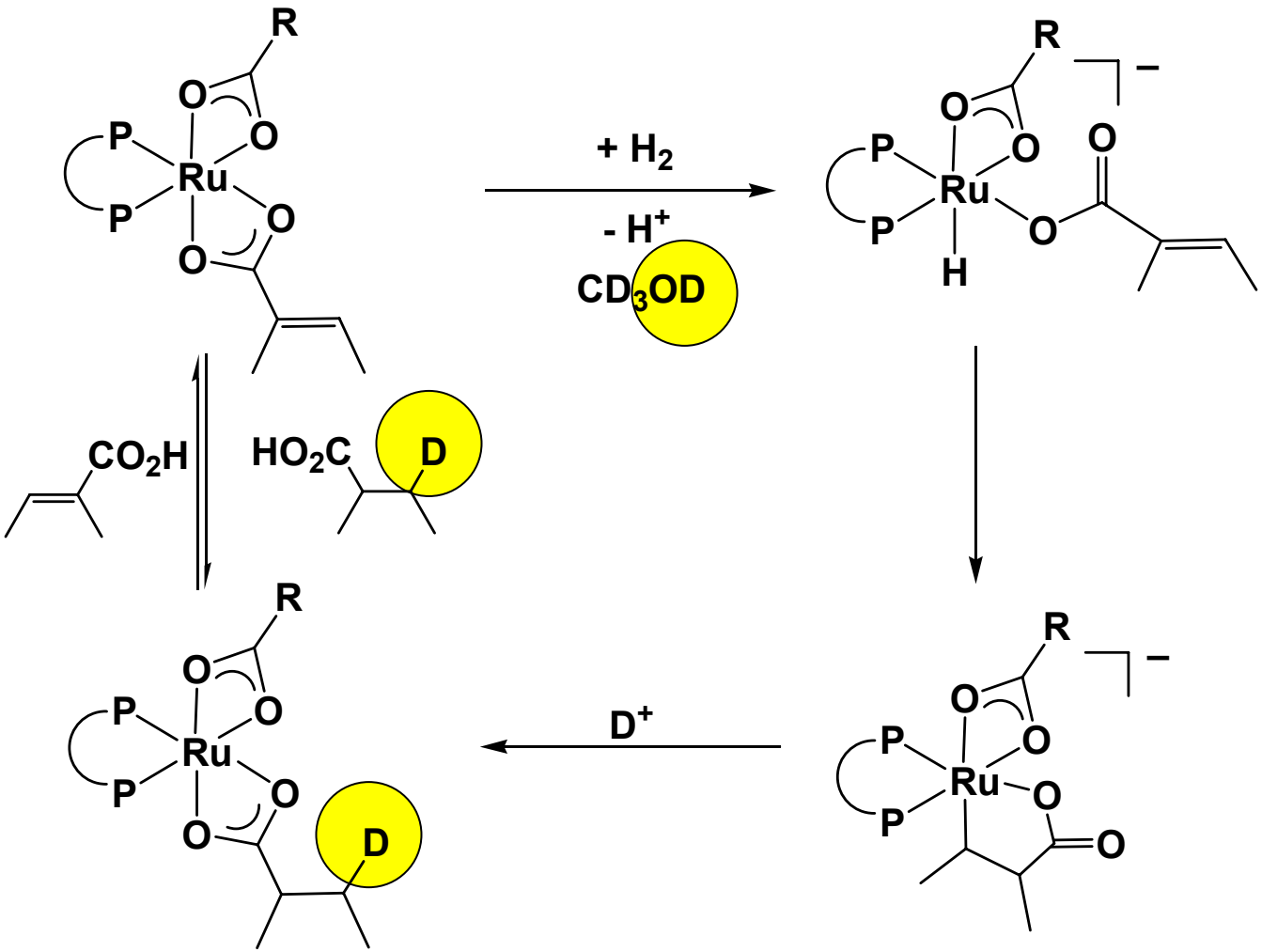


H_2

ee pressure independent

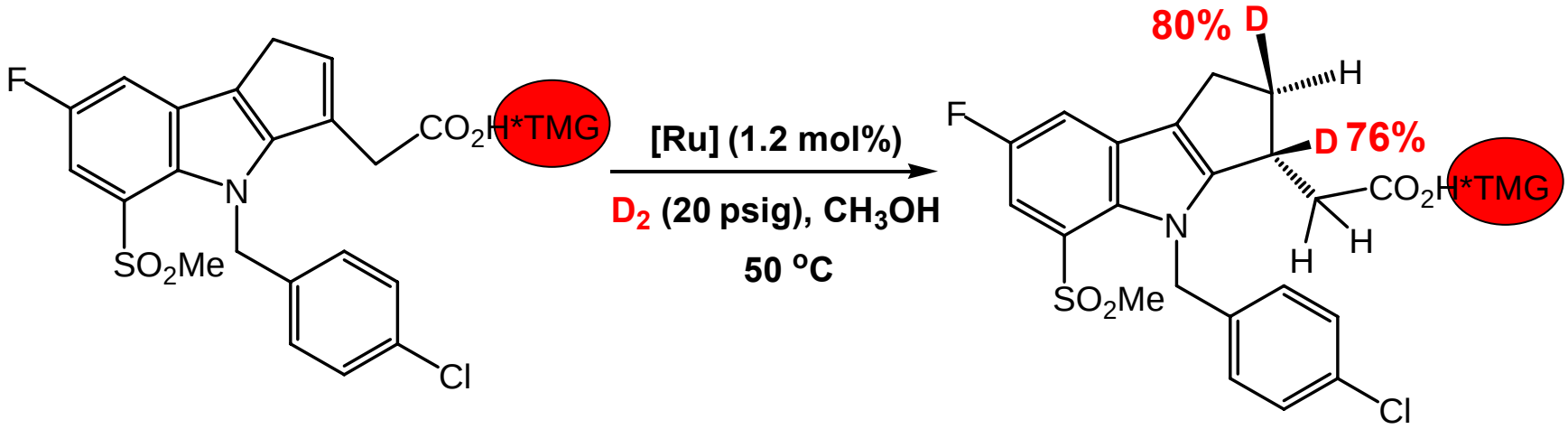
Deuterium Labeling Studies

Ene Acid Hydrogenations: Mechanism



Ashby, M. T.; Halpern, J. J. Am. Chem. Soc. 1991, 113, 589

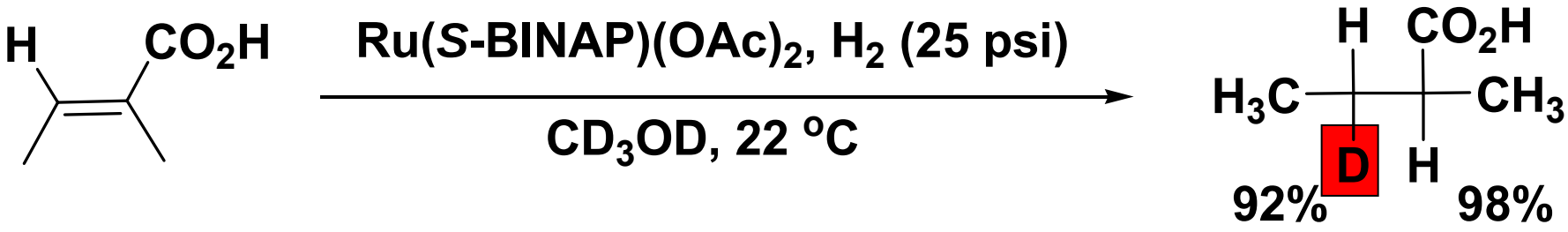
Deuterium Labeling Experiment: Evidence for Hydrogenolysis



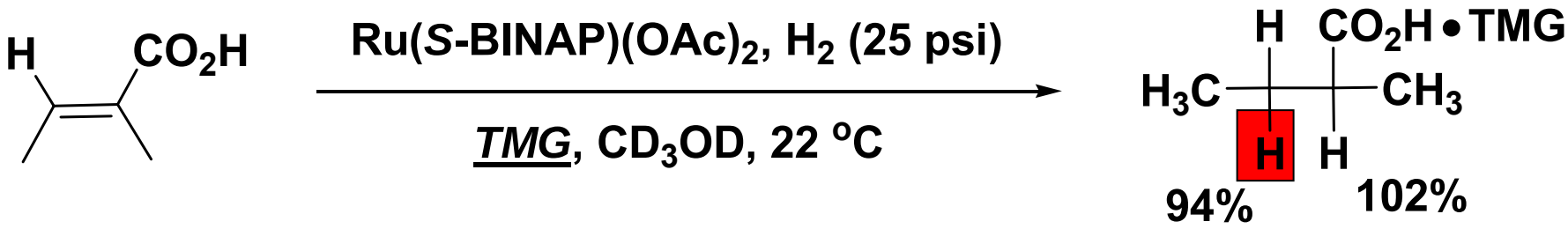
- Deuterium observed in both positions
- Different from classic ruthenium mechanism
- Evidence for Hydrogenolysis *not* Protonolysis
- Difference due to presence of base?

Re-evaluation of Halpern Mechanism Under Basic Conditions

- Without base- Solvent incorporation observed

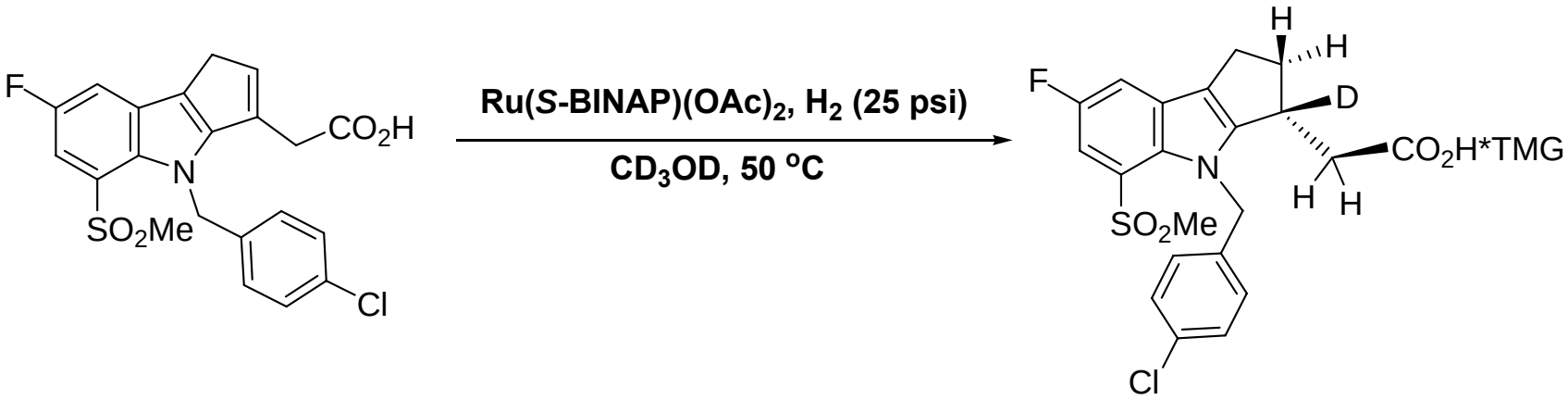


- With base- Solvent incorporation not observed



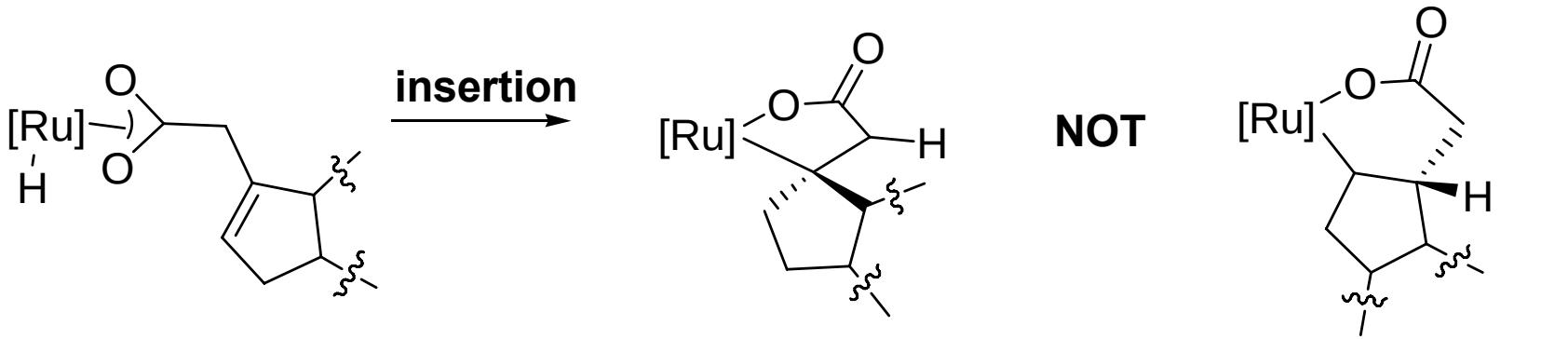
Conclusion: Mechanism of product removal from metal determined by solution pH

Hydrogenation of Endo Isomer without Base?



- **Solvent incorporation is now observed under "neutral" conditions**

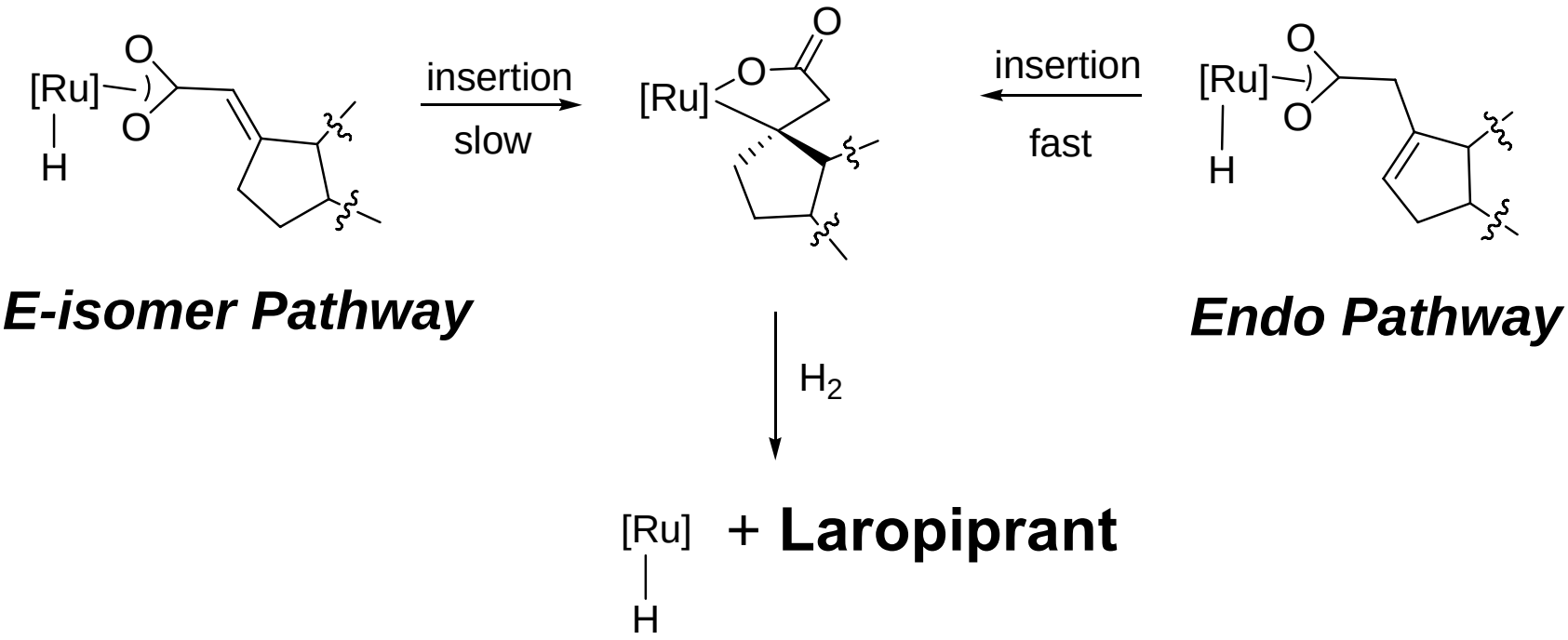
- **Evidence for protonolysis AND for 5-membered insertion intermediate:**



5-membered ring **6-membered ring**

Insertion Mechanism Explains Rate and EE Difference

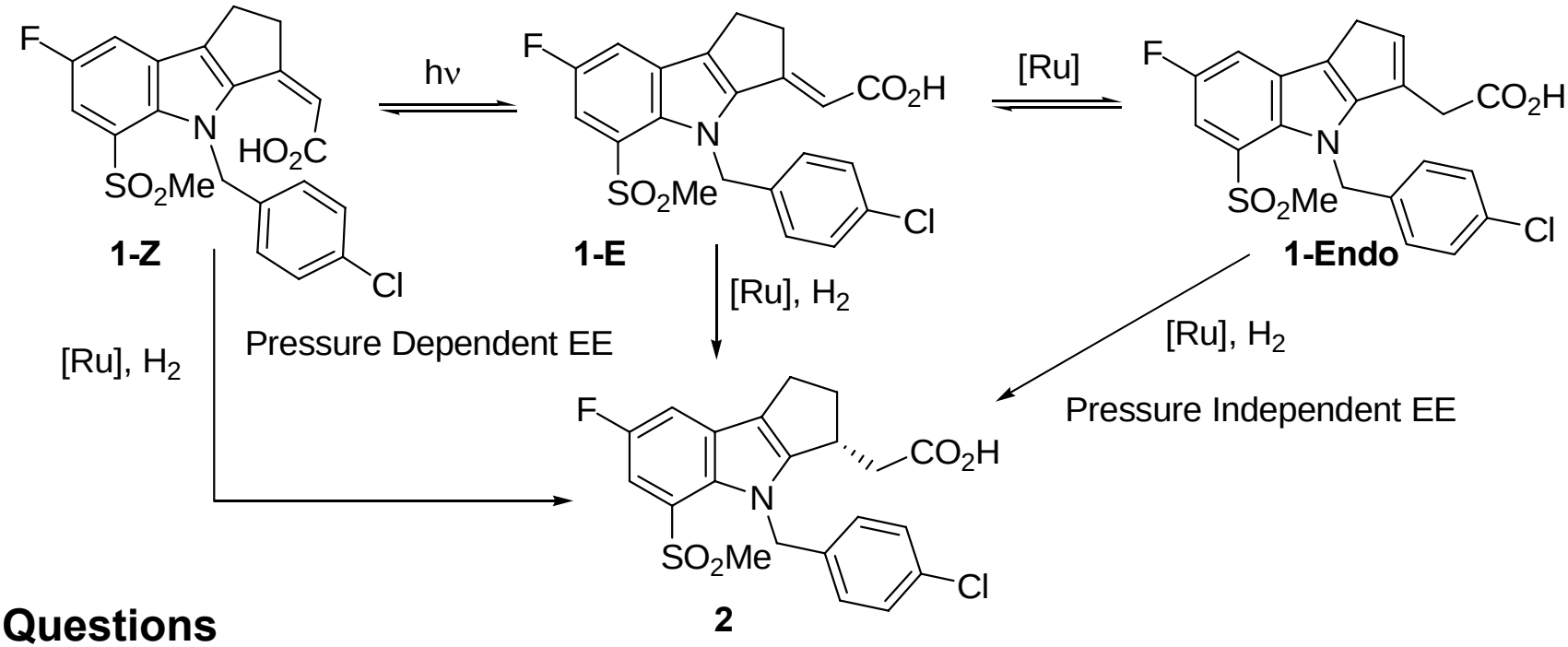
Same intermediate!



- **Rate difference attributed to difference in energy between two insertion steps**
- **Attainment of TS insertion geometry easier for β,γ-olefin (more flexibility)**
- **Endo isomer gives higher ee because both carboxylate and olefin can pre-coordinate– analogous to dehydroamino acid reductions**

Current Mechanistic Picture/Summary

Answers

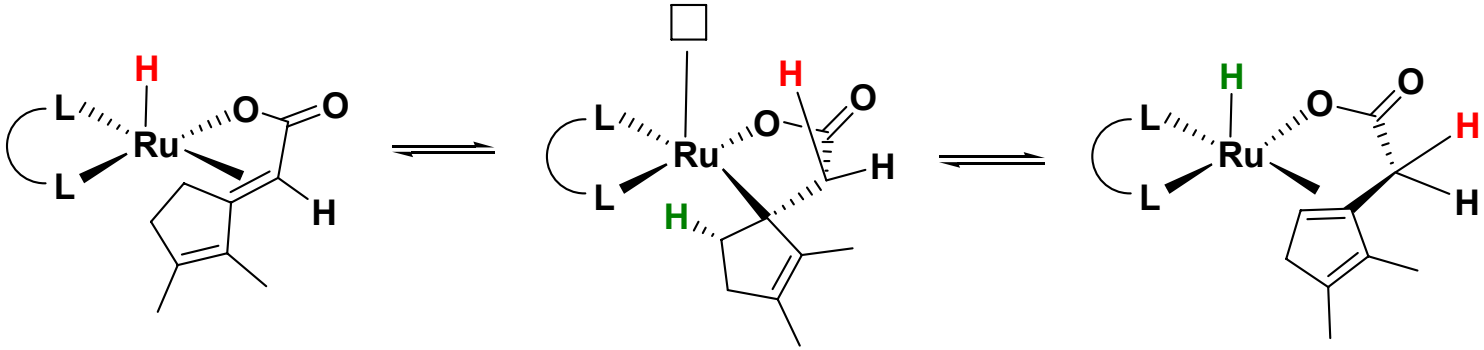


Questions

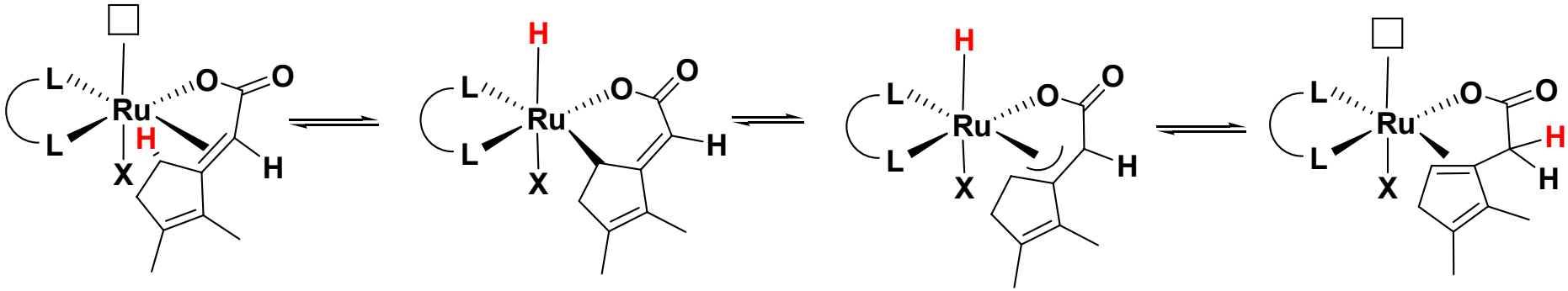
- **On molecular level, what is basis for pressure dependence?**
- **Is isomerization rate truly pressure independent?**

E to Endo Isomerization Mechanisms

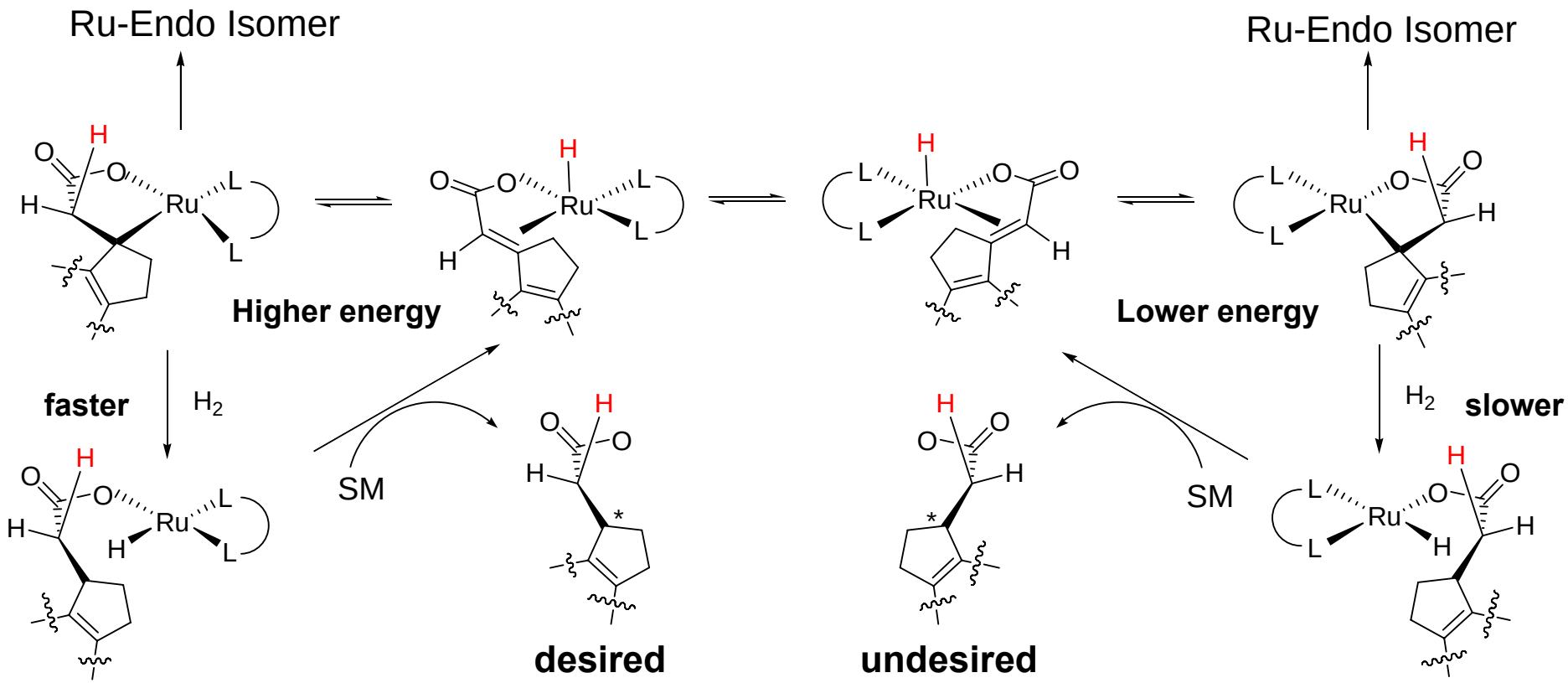
- **Hydride Insertion Mechanism**



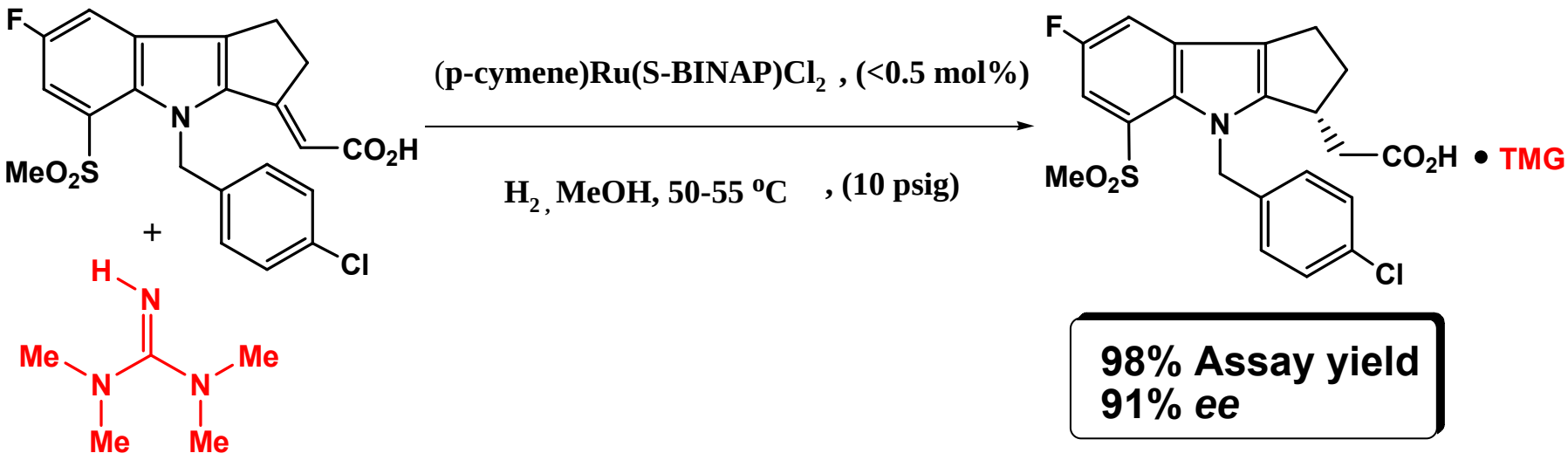
- **Allylic C-H Activation Mechanism**



Proposed Hydrogenation Mechanism



Optimized Asymmetric Hydrogenation

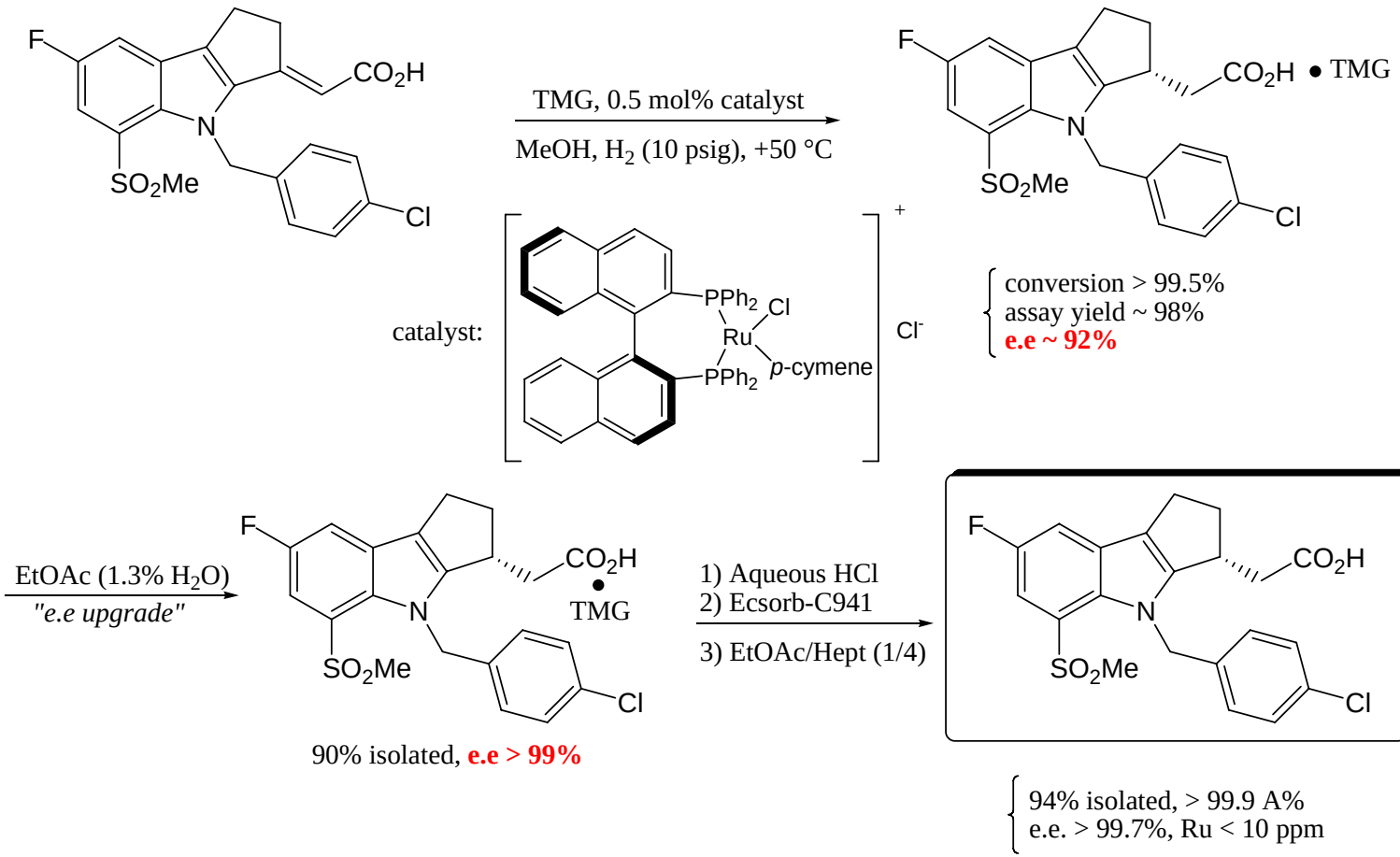


- **Tetramethylguanidine (TMG) used as base to solubilize "*Ene-Acid*", and *ee* upgrade.**

- **Catalyst prepared *in-situ*. Low hydrogen pressure crucial for good enantioselectivity.**

- **Catalyst loading : <0.5 mol% (<0.5% CH_3CN, *ene-acid* washed w/ MeOH ("wet cake")**

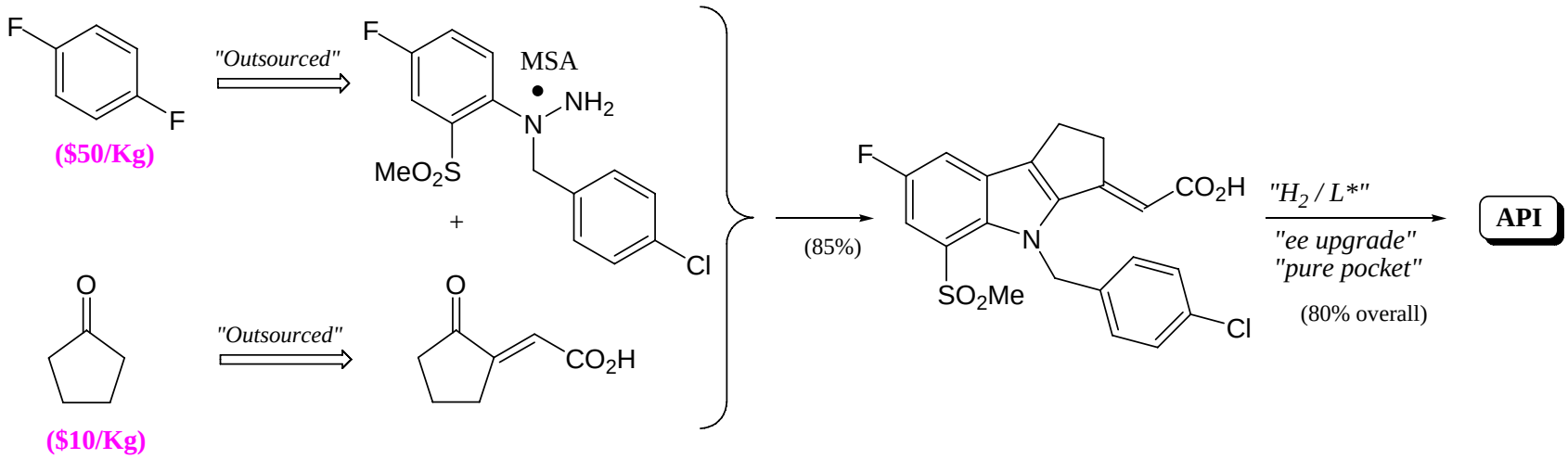
Asymmetric Hydrogenation and Final Processing



- Crystallization of the TMG salt from "wet AcOEt" : *ee* upgraded to 99% (90% isolated yield).

- Salt break. Ecosorb treatment (Ru removal). Crystallization of API from AcOEt/Hept (96% isolated yield).

Summary



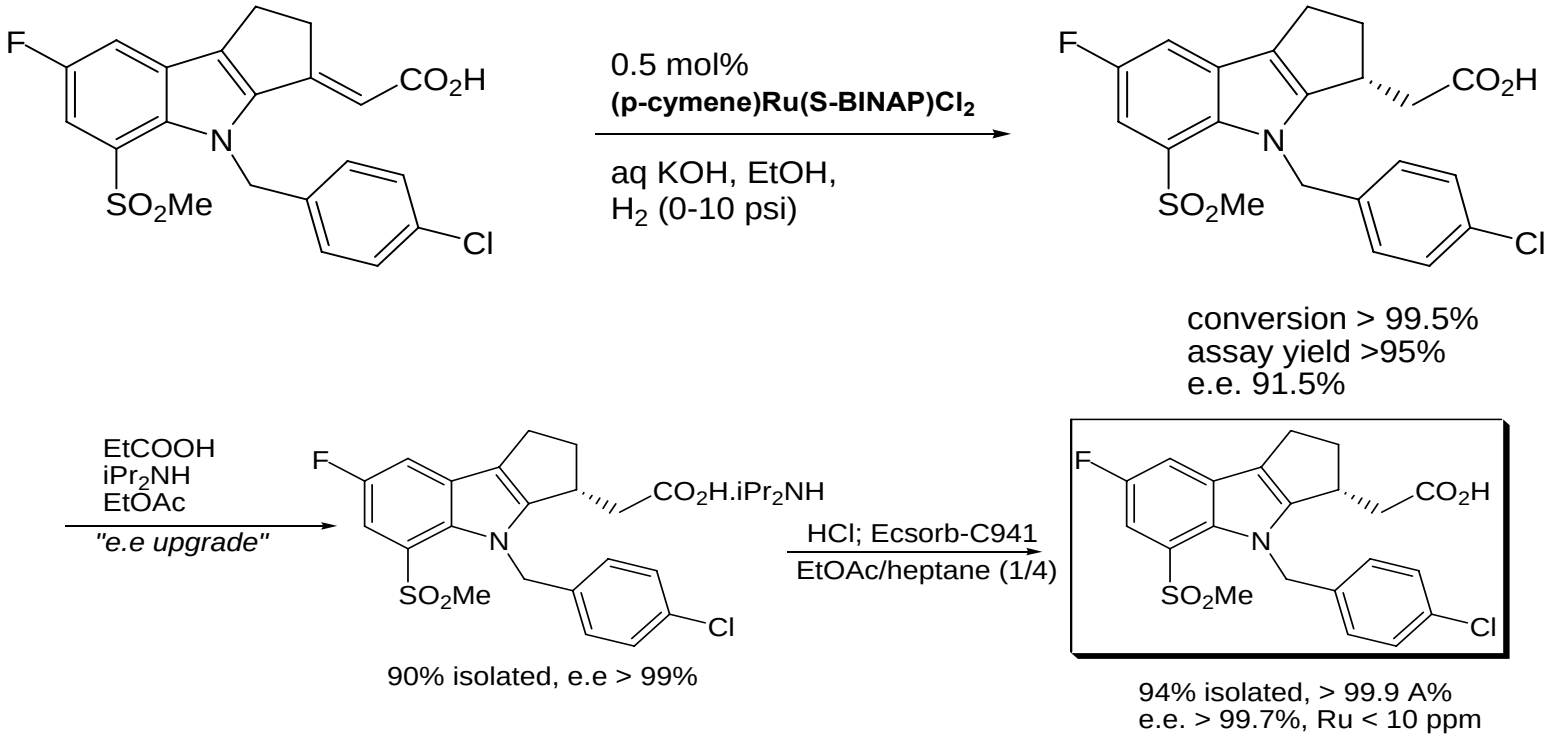
- **Convergent synthesis, high-yielding (2 chemical steps, 68% overall yield).**

- **Asymmetric synthesis: chiral center set in the last step.**

- **Cheap starting materials. Outsourced crystalline Intermediates.**

- **Manufacturing route identified.**

UPDATE: Optimized Asymmetric Hydrogenation and Isolation



- **The use of KOH eliminates the need for TMG, TMG somewhat unstable to reaction conditions poisoning catalyst.**
- **DIPA salt crystallization affords more robust ee upgrade and rejection of catalyst.**

Acknowledgments

Process Research

Kevin R. Campos
Karen M. Conrad
Edward G. Corley
Michael C. Hillier
David L. Hughes
Guy Humphrey
Elliot Hunstman
Michel Journet
Jason J. Kowal
Jeffrey T. Kuethe
Peter E. Maligres
Jean-Francois Marcoux
Christopher J. McWilliams
Jeffrey C. Moore
Zhihui Peng
Stella Sarraf
Ali Shafiee
Yongkui Sun
David M. Tellers
Richard D. Tillyer
Mathew D. Truppo
Veena Upadhyay
Audrey Wong
Dalian Zhao

Medicinal Chemistry

Bruno Roy
John Scheigetz

Chemical Engineering R&D

Firoz Antia
Vincent Capodanno
Courtney Griffin
Paul Fernandez
Joe Hinksmon
Mike Hobbs

Analytical Research

Vince Angelico
Lorrie Berwick
Yadan Chen
Charles Moeder
Yan Wu

Pharm R&D

Elizabeth Kwong
Brian Down
Claire Mcneish

… And so many other people!

Thoughts on Outsourcing

- Could a CRO (Contract Research Organization) have made the first 600 g delivery via the modified medicinal chemistry synthesis?
  - Yes – probability of success ~90%
- Could a CRO have developed the existing synthesis such that it could be run in the prep lab and pilot plant to make 10's of kg of drug
  - Yes – probability of success ~60%

Thoughts on Outsourcing

- Could a CRO have developed the final process based on the new indole synthesis coupled with the asymmetric hydrogenation?
  - Unlikely – probability of success ~10%
- Could a CRO run the fully developed final process in its pilot and production facilities?
  - Yes – probability of success ~90%
  - What is being done – outsource hydrazine and ketone and the GMP process is the Fisher Indole reaction, AH coupled with e.e. upgrade and final purification

Thoughts on Outsourcing

- What do CRO's do best?
  - Bull through medicinal routes and prepare early quantities of drug
  - Do modest development on medicinal routes and run them in preparative (lab and pilot plant) facilities
  - Develop new processes for relatively straight-forward small molecules
  - Run developed and demonstrated processes in their prep, pilot plant and manufacturing facilities

Thoughts on Outsourcing

- What do old fashioned process chemists and new process chemists who want to follow in their footsteps do?
  - All of the things a CRO can do, and…
  - Creatively design and develop elegant processes directed to specific complex small molecule drug candidates and drug products
  - Add to overall chemical knowledge through publication in top journals and participation at meetings

Thoughts on Outsourcing

- Will the industry continue to need good process chemists?
  - Most non-chemical executives in big and little pharma believe that process research is an entity that can be bought – like widgets*
  - Too many scientific, including chemical, executives also believe the same thing

*A generic, often theoretical, item, synonymous with product. The term often is used in hypothetical business examples, for example, “Say a company makes widgets.”

Thoughts on Outsourcing

- Will the industry continue to need good process chemists?
  - The facts say, “Yes!”
  - I have yet to see a well-designed chemical process for a complex small molecule come from a CRO
  - The need for creative process chemists in big pharma to do the most important and complex part of the job still remains and is likely to do so for another generation

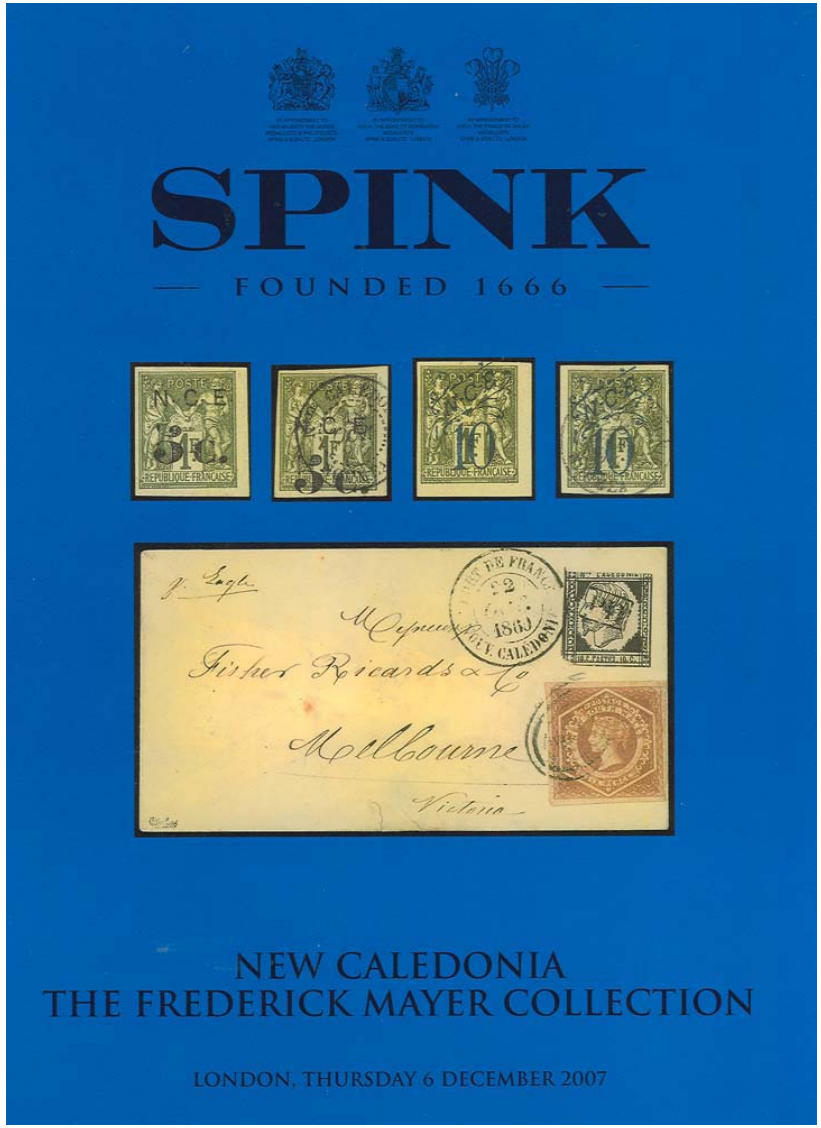
Thoughts on Outsourcing

- The job of process chemists has changed
  - Those aspects of the job which are **most likely** to be successful with a CRO (probability of success >75%) will go to the contract labs
  - Those aspects of the job which are **most unlikely** to be successful with the CRO's will remain with the big pharma companies
- The need for process chemists remains but fewer are/will be working for big pharma companies, and more will be working for CRO's

QUANTUM MECHANICS

All science is either physics or stamp collecting

Ernest Rutherford
1871 - 1937

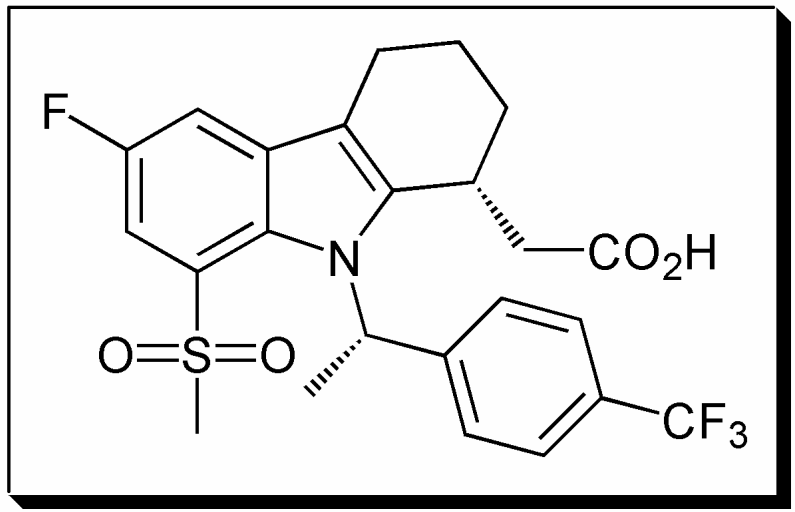


Current SPINK stamp auction in London
I am interested in about 25 lots
The auction starts Dec. 6th at 10:30 a.m.
My SCI lecture is scheduled for Dec 6th 9 – 10 a.m.
Such is life! Can anyone here get me to London in 30 minutes?

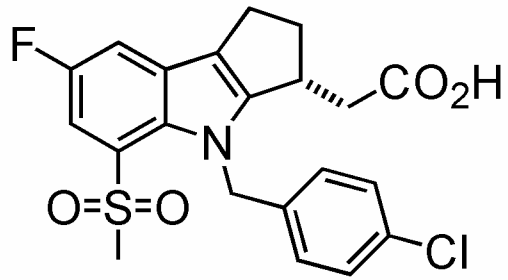
Development of a Novel Stereoselective Fischer Indole Approach to DP Antagonist Back-up L-001174655

Guy Humphrey, Peter Maligres, Chunhua Yang, Jeff Marcoux,
Mike Hillier, Dalian Zhao, Ben Marcune and Ed Grabowski.

Department of Process Research, Merck & Co., Rahway, NJ.

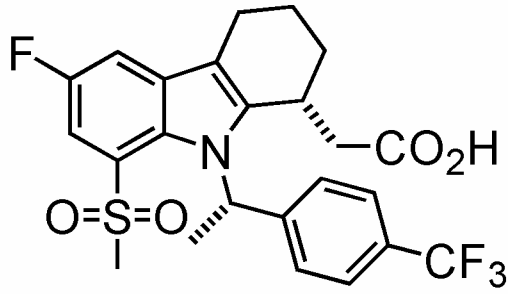


DP Program Compounds

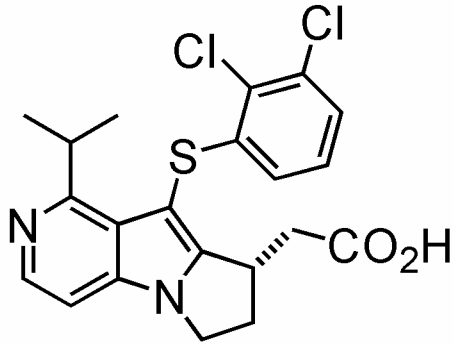


L-000888839
Approved 4Q 2001
Ph IIb Niacin Induced Flushing
Ph IIa Asthma POC

Major Goal: Triple combo
(Niacin, Zocor, 839)
for the treatment of
Atherosclerosis

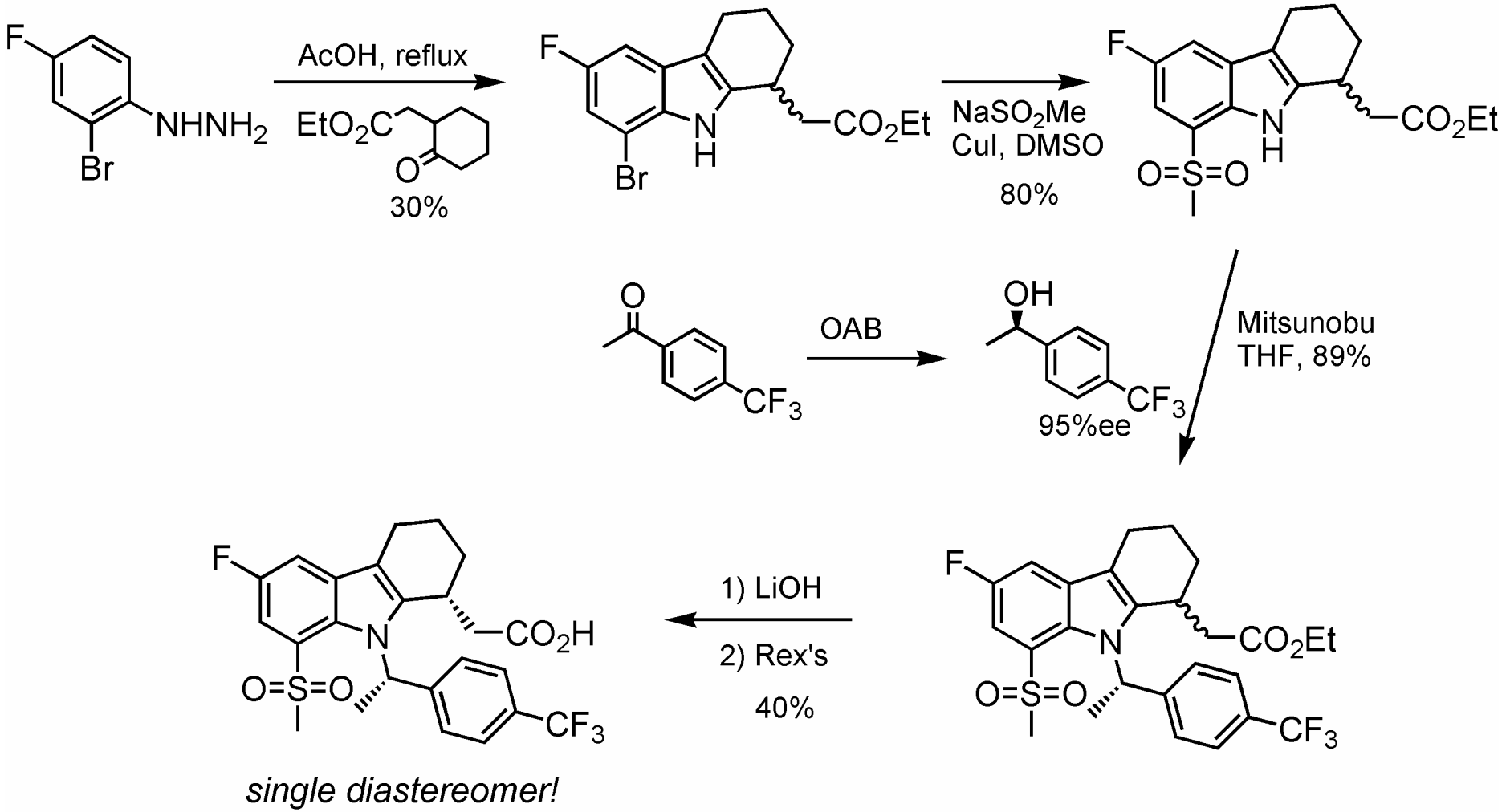


L-001174655
1st Backup (Feb 2004)
14 wk Paradigm
3.5 Kg by June 2004



L-001101351
Alternate Back-up
Approved Feb 2004
On Hold until July

Montreal Med Chem Route



single diastereomer!

6-7 Steps, 8% overall yield, 3 Chromatographies

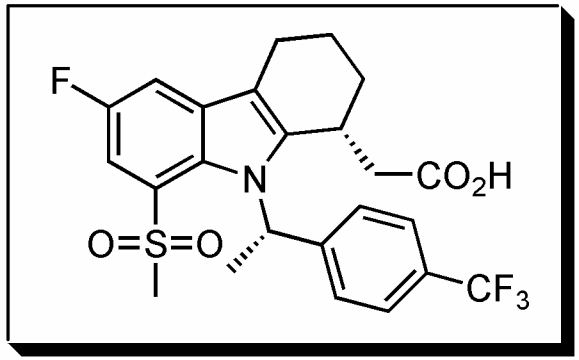
Process Objectives

- Develop Scalable Long-Term (Asymmetric) Route

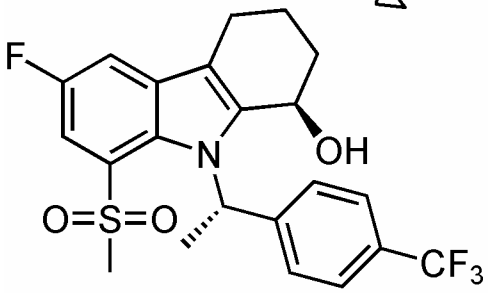
- Define Final Crystalline Form

- Prepare 3.5 Kg to support 3 month SA and Ph I (June 2004)

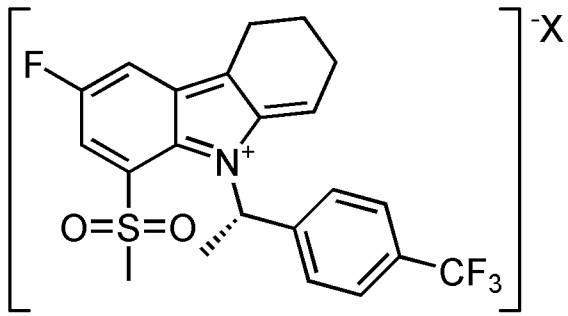
Initial Ideas



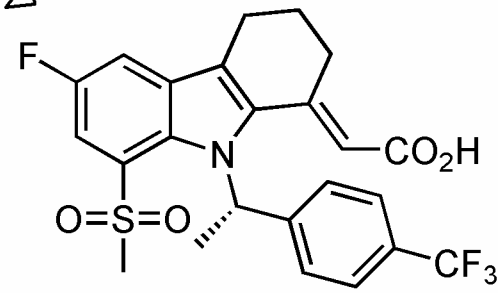
S_N2-Alkylation



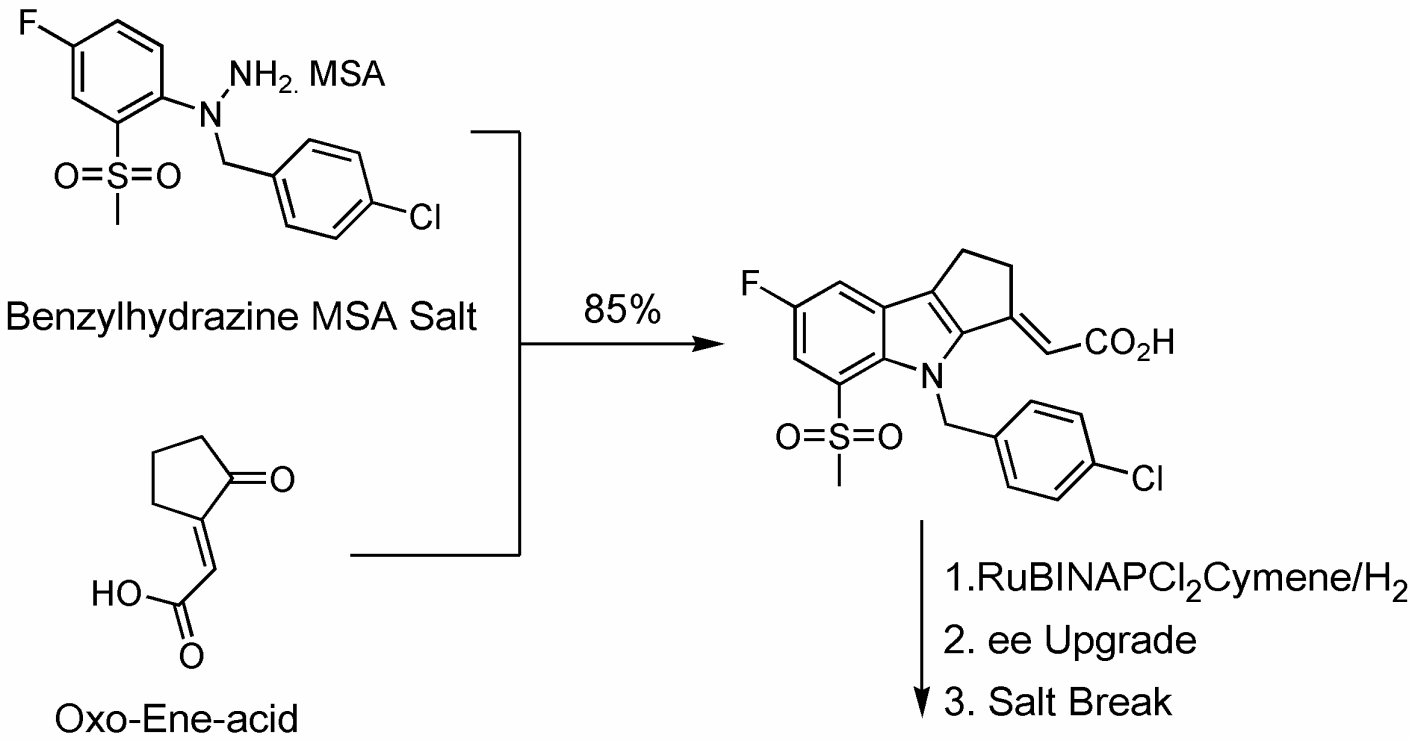
S_N1-Alkylation



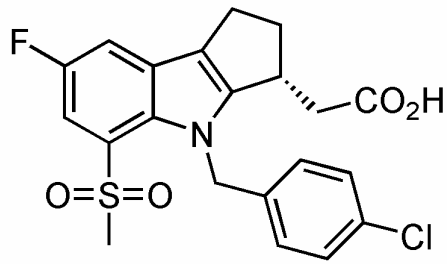
Hydrogenation



Fischer Indole Synthesis of L000888839: Manufacturing Route

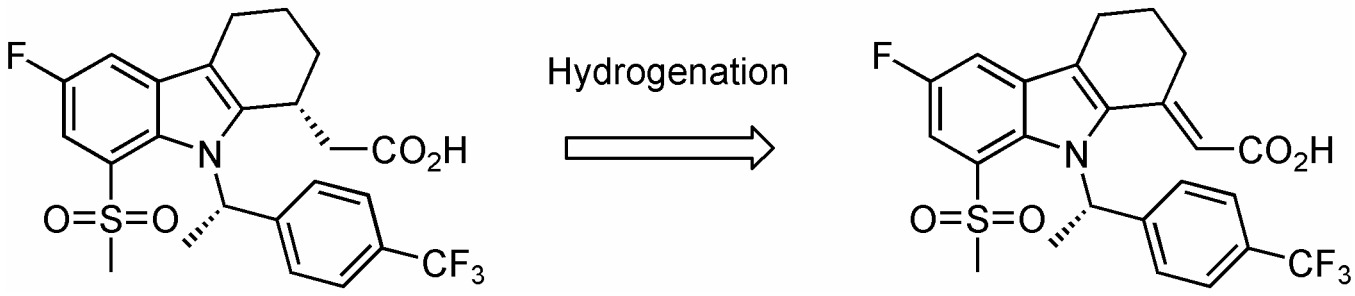


Highly Convergent Asymmetric Synthesis
50% Overall Yield
Cheap Outsourced Intermediates
Pilot Plant 3/4Q 04 for 1MT
3-4 MT in 2005

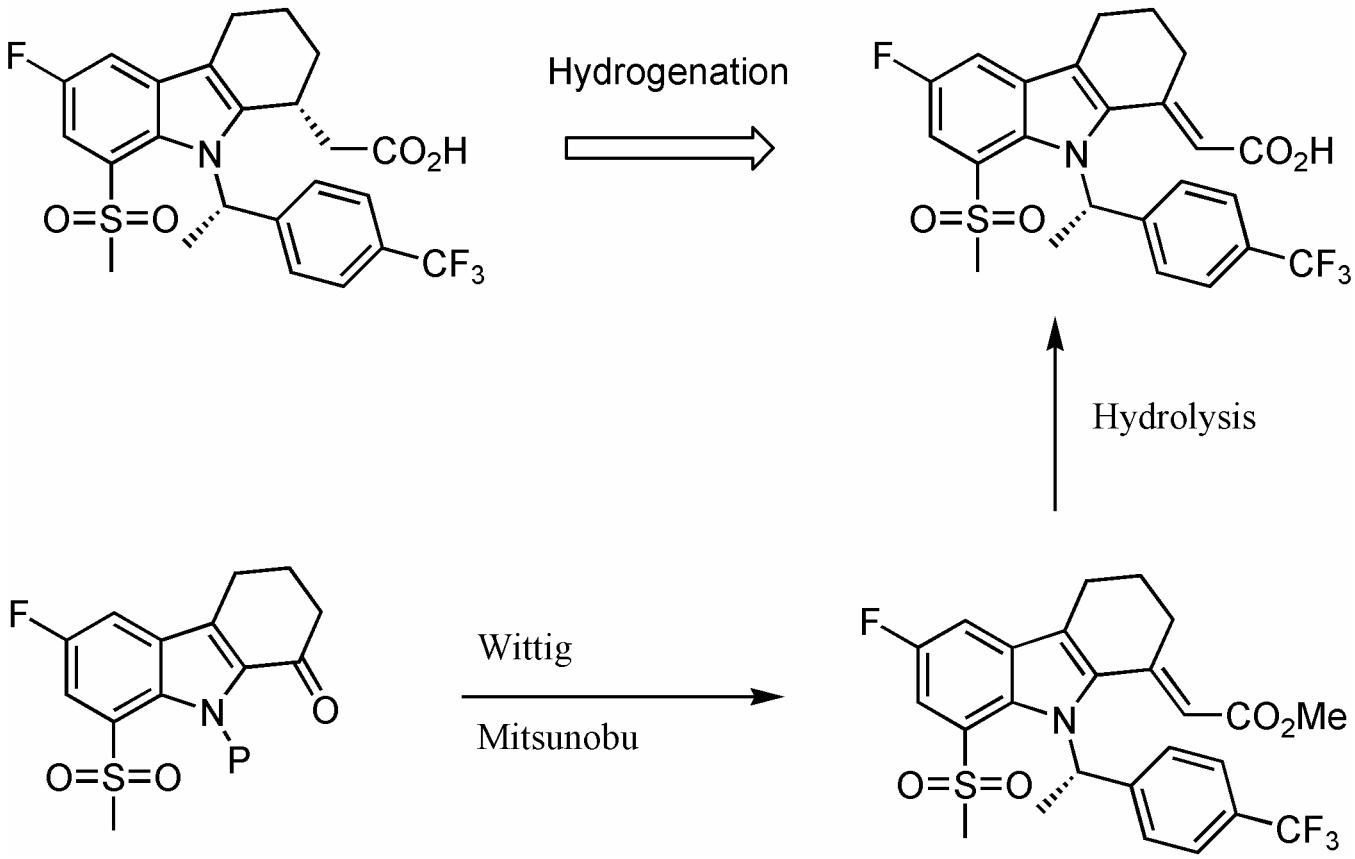


L000888839

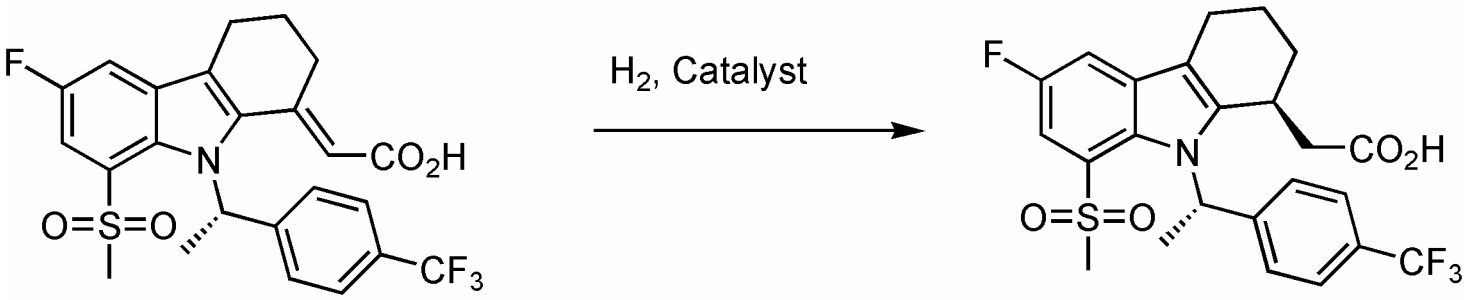
Diastereoselective Hydrogenation?



Diastereoselective Hydrogenation?



Diastereoselective Hydrogenation

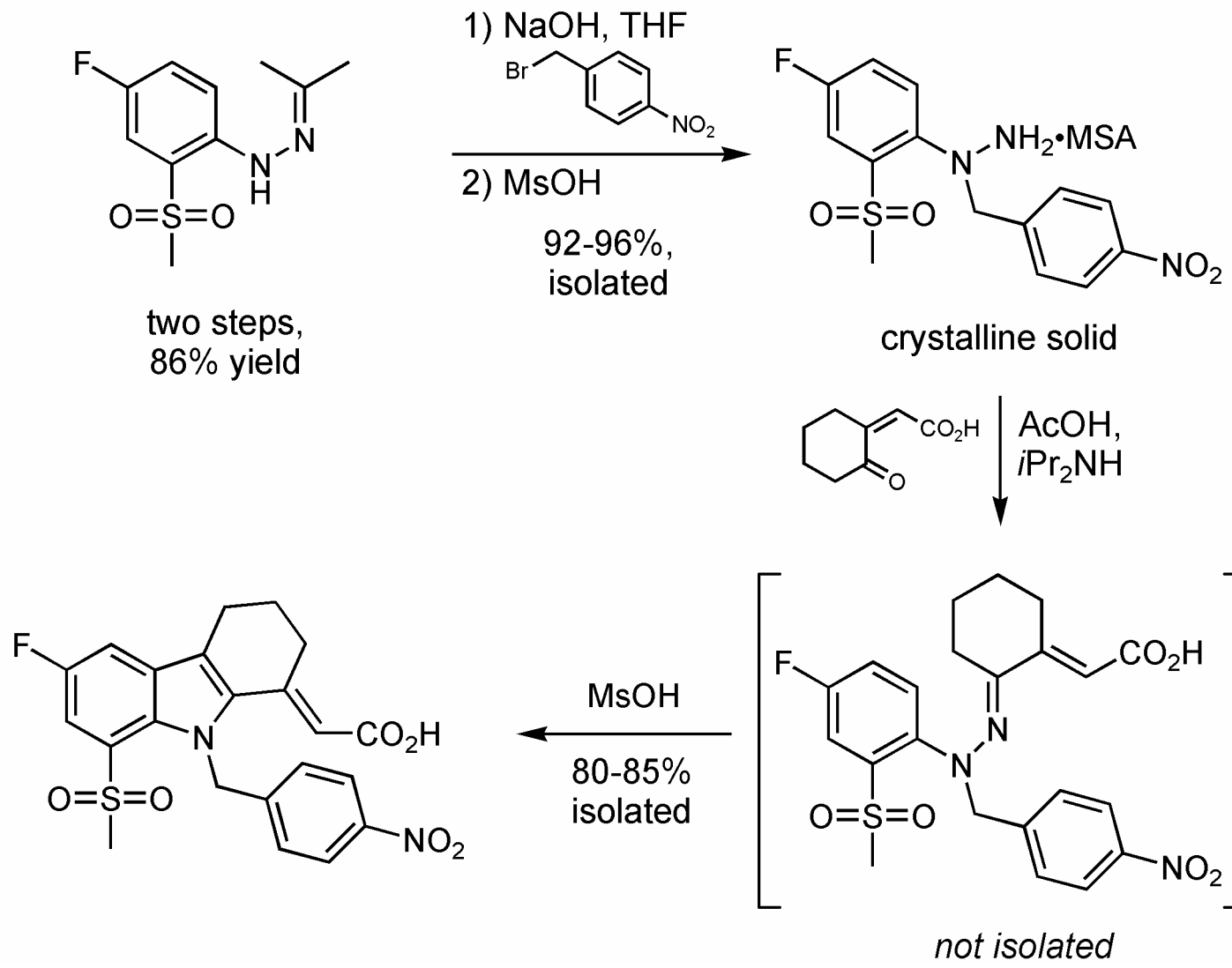


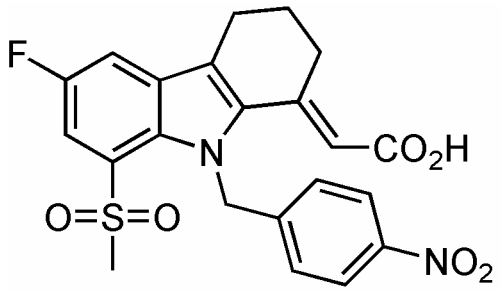
99%ee

Hydrogenation Proceeds the Wrong Way!

Catalyst	Conv., %	dr
Pd/C	99	6:1
(*R*-Binap)$RuCl_2$	99	13:1
(*S*-Binap)$RuCl_2$	80	2:1

Synthesis of Protected Hydrogenation Substrate

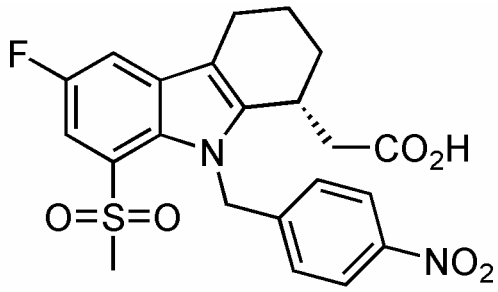




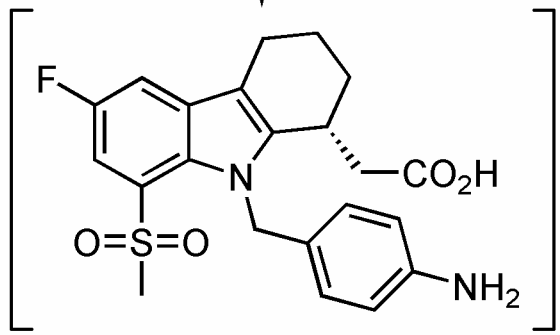
(*S*)-BinapRuCl$_2$•
p-cymene, H$_2$,

MeOH, Et$_3$N

>95%, 84% ee

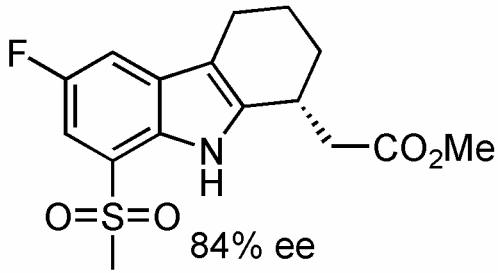


HCO$_2$K, Pd/C,
aq. MeOH



MsOH, MeOH

>95%



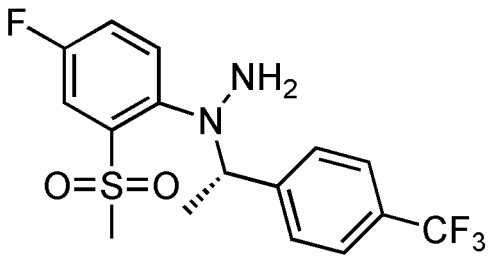
Approx 70%

'655' (25 g)

8 Steps, approx 40% overall yield
Potential Prep Lab Route (as of 03/04)
for 3-4 Kg prep

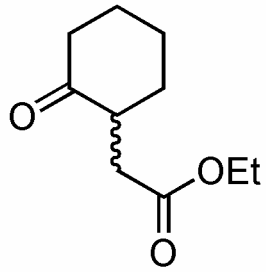
Long-term issues: Mitsunobu!
2 Asymmetric Hydrogenations!

'Home Run' Approach?

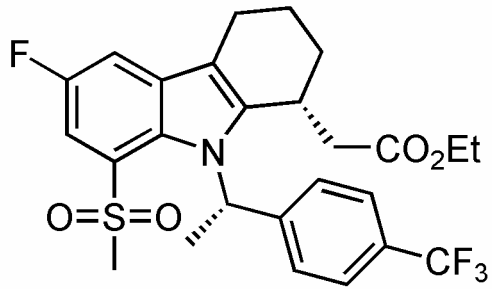


(S)-Benzylhydrazine

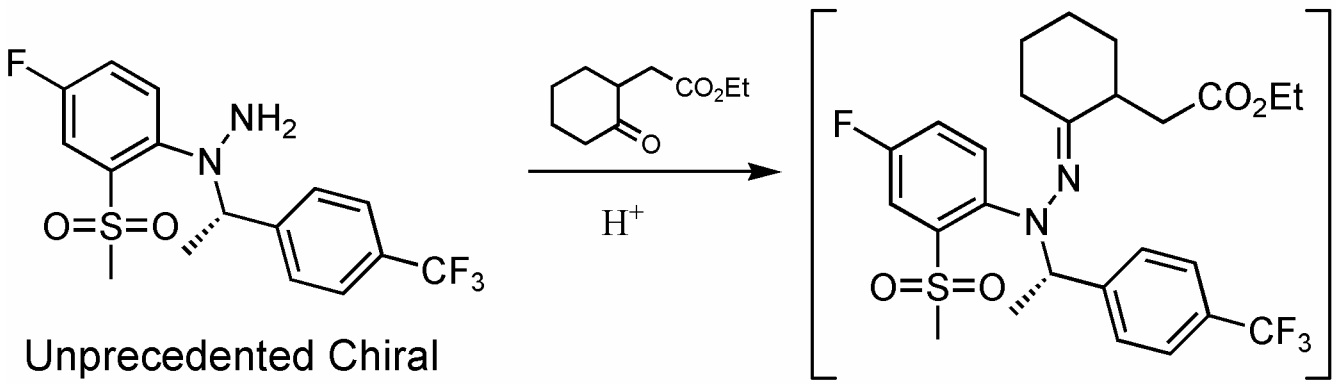
+



Commercially Available
Racemic

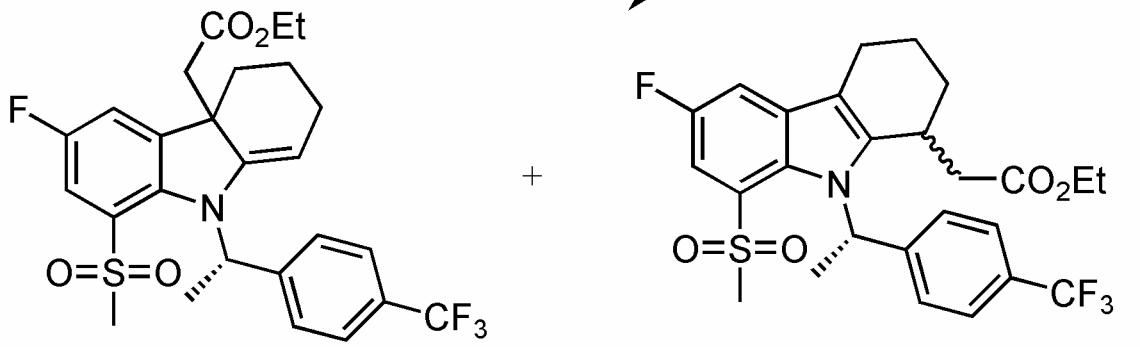


Precedent: Unfavorable at best!



Unprecedented Chiral
Benzyl Hydrazines

Stereoselective Fischer Reaction?

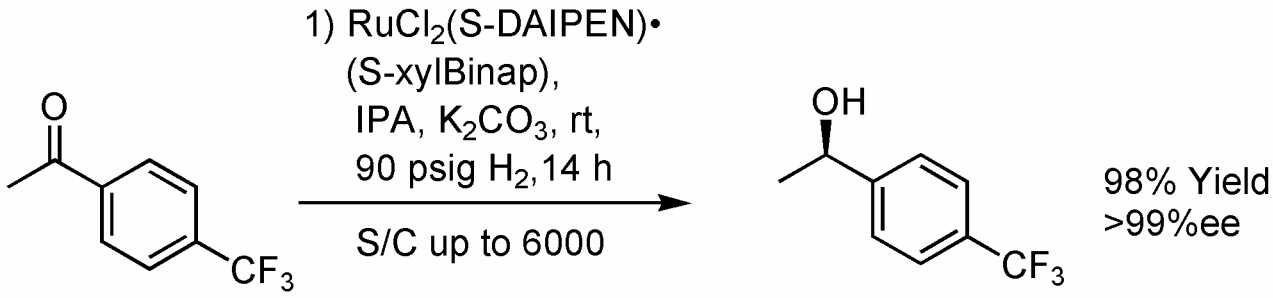


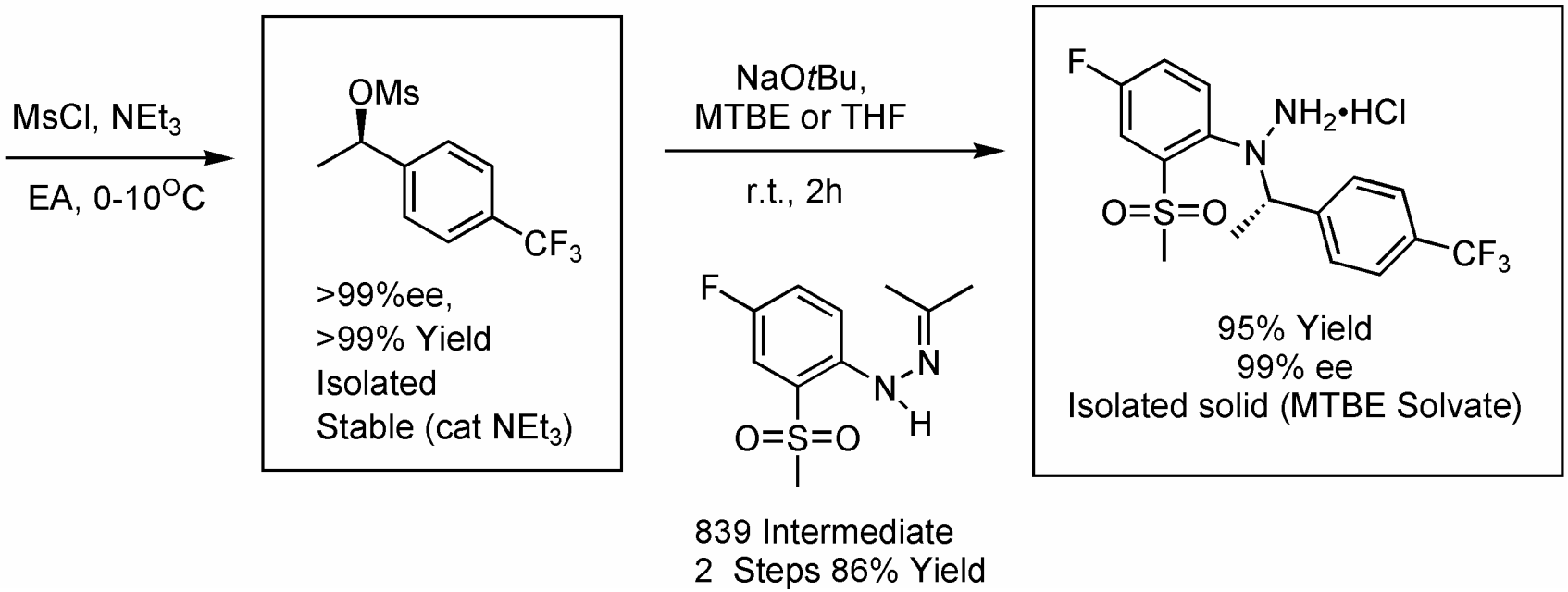
Indolene

Mixture of Indoles

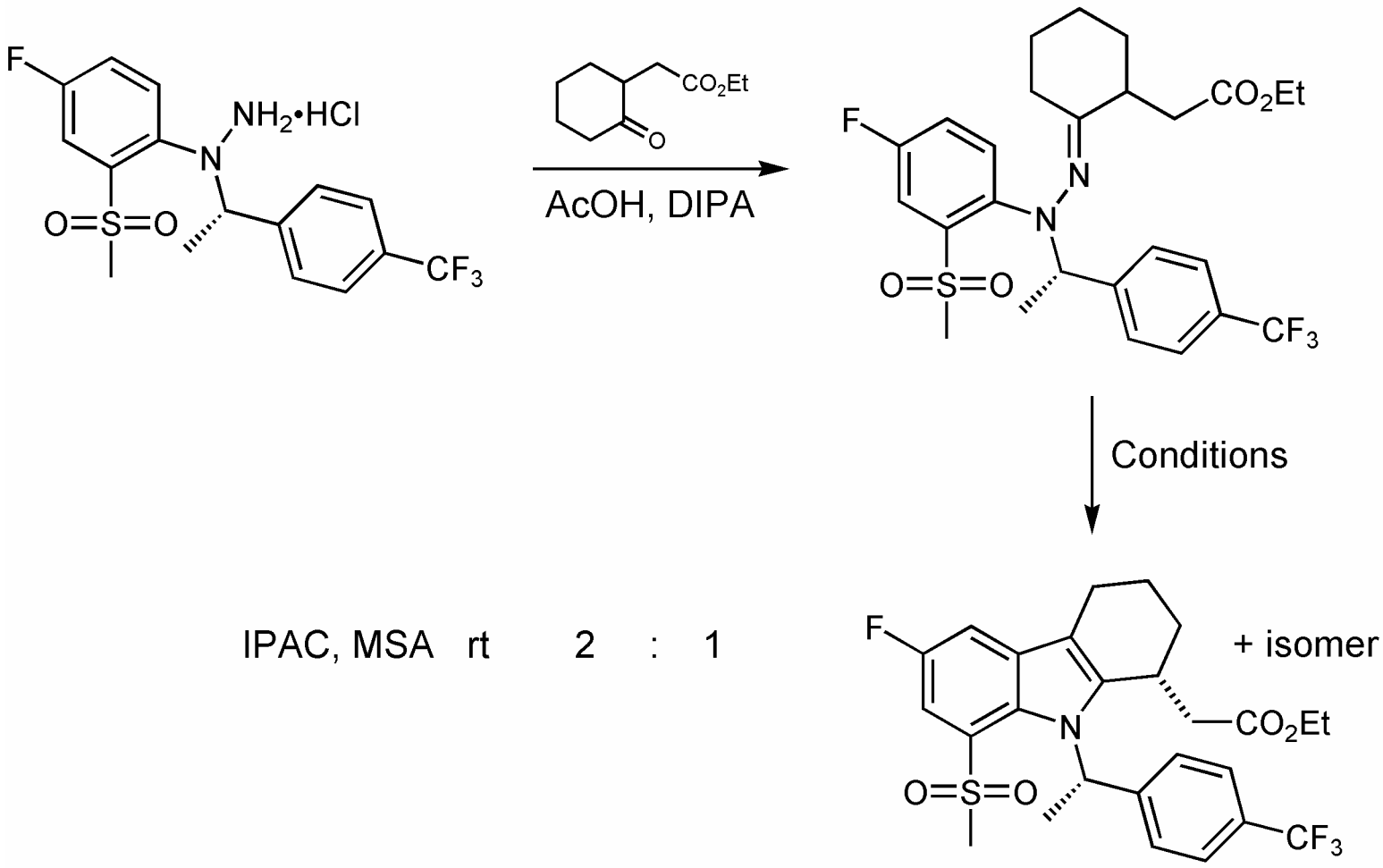
Expected Products

Preparation of Chiral Benzylhydrazine



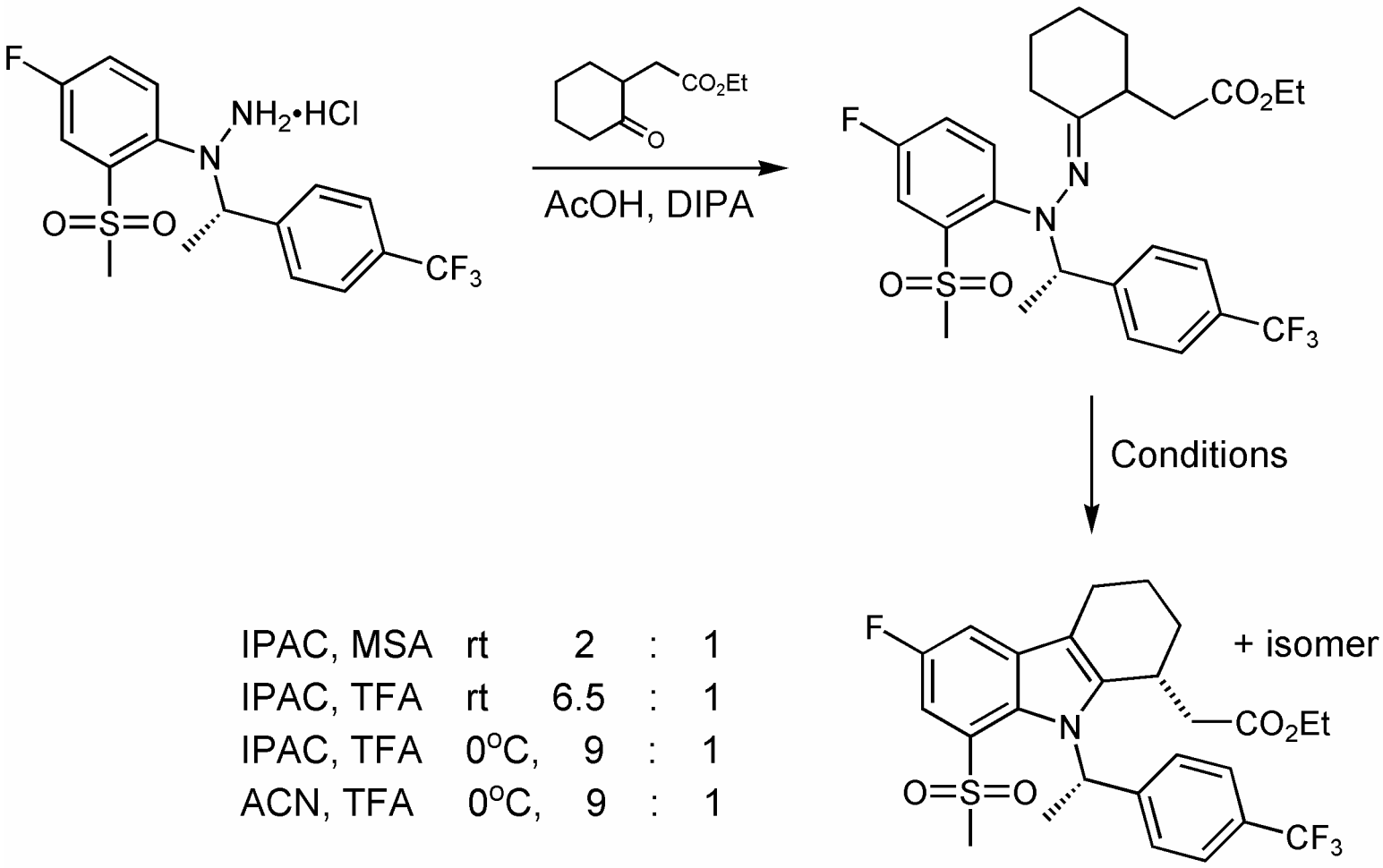


Diastereoselective Fischer-Indole Reaction



Desired Diastereomer is Major Product!

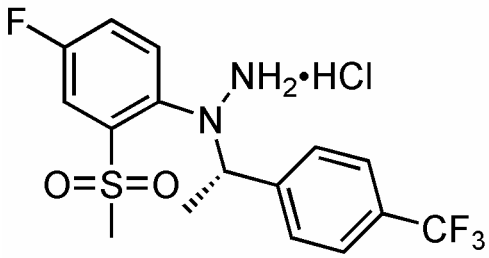
Diastereoselective Fischer-Indole Reaction



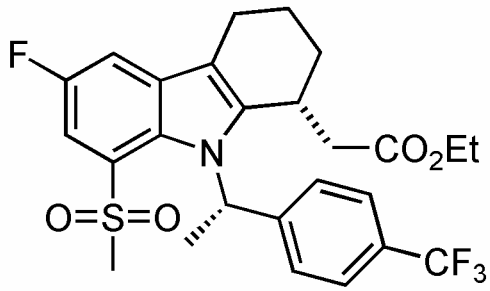
IPAC, MSA	rt	2	:	1
IPAC, TFA	rt	6.5	:	1
IPAC, TFA	0°C,	9	:	1
ACN, TFA	0°C,	9	:	1

Desired Diastereomer is Major Product!

Stereoselective Fischer-Indole: Reaction Profile

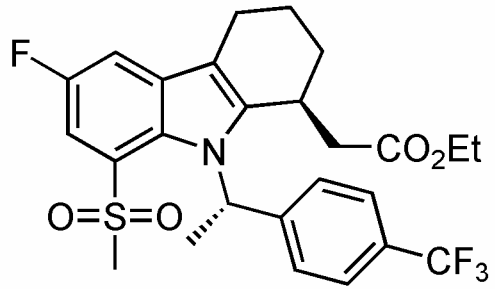


<5 A%

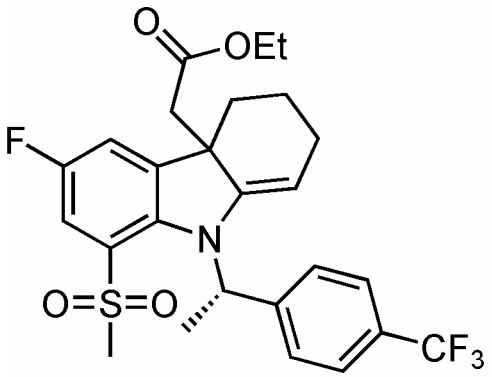


75% AY

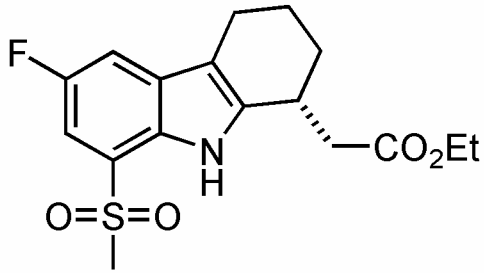
+



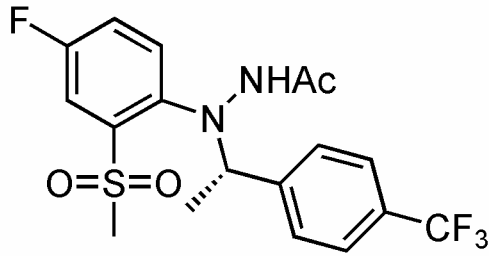
7-8% AY



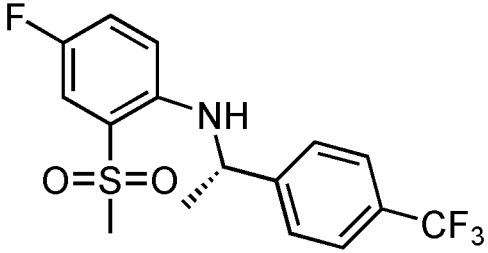
3-5A%



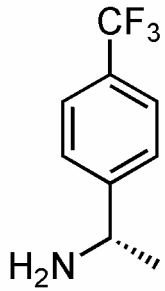
2A%



1-2A%

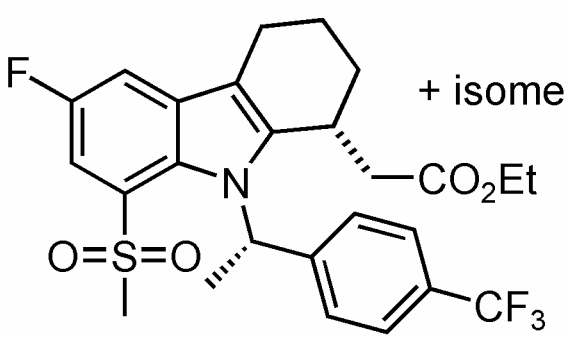


1-2A%



1-2A%

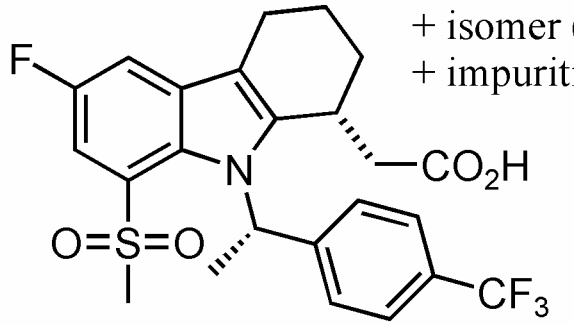
Product Isolation?



+ isomer + impurities

75% Assay Yield (major diast)

LiOH, MTBE,
MeOH



+ isomer (ester)
+ impurities

>98% Assay yield, 99%ee

??

FINAL PRODUCT

Acid-base extractions not useful

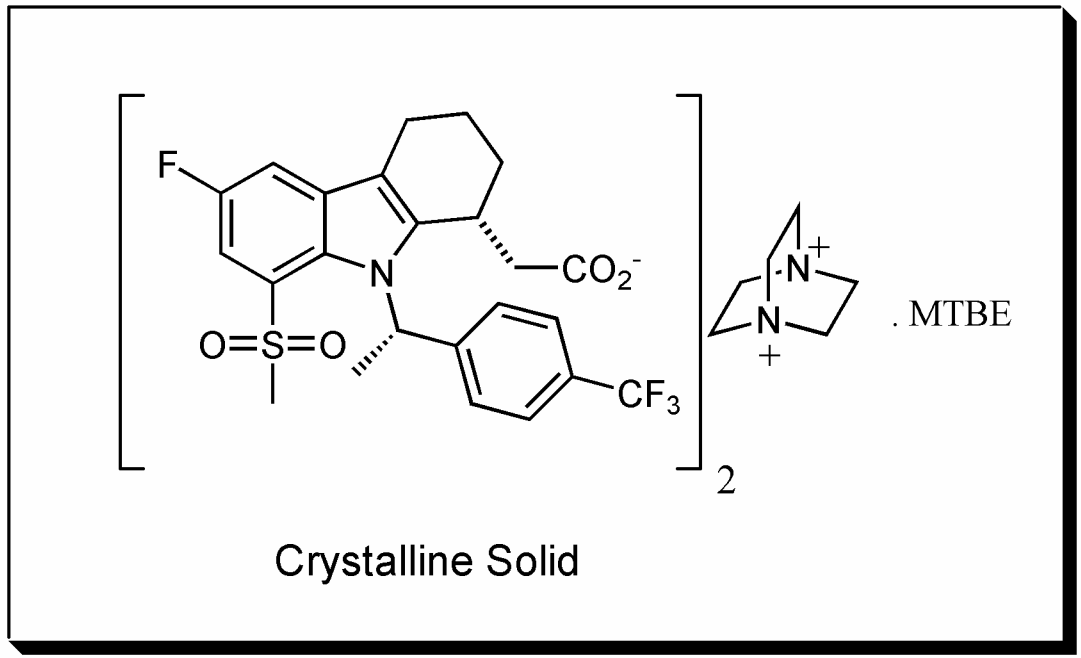
Salt screen. No amine salts

Free-acid. Heavy losses and
poor rejection of impurities

Product Isolation: Breakthrough!

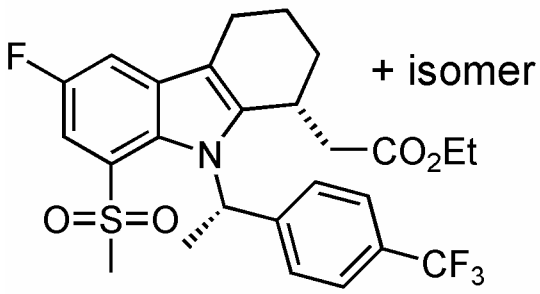
'655

Dabco, MTBE, rt

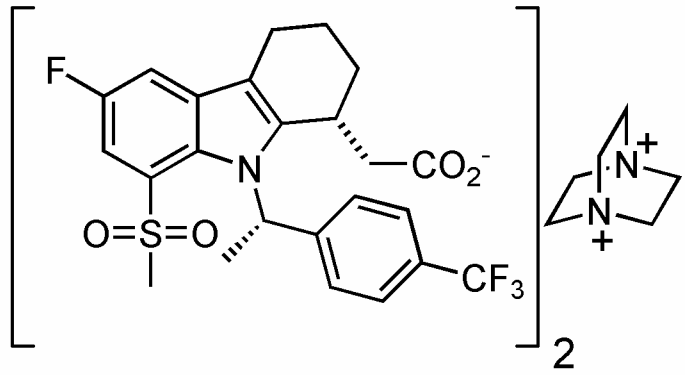


Crystalline Solid

Prep-Lab Campaign: Single Batch



1. LiOH, MTBE, MeOH
2. DABCO, MTBE



75% Assay Yield (major diast)
>99%ee.

67% Isolated Yield from Hydrazine
Crystalline Solid, >99.5A%(210nm)

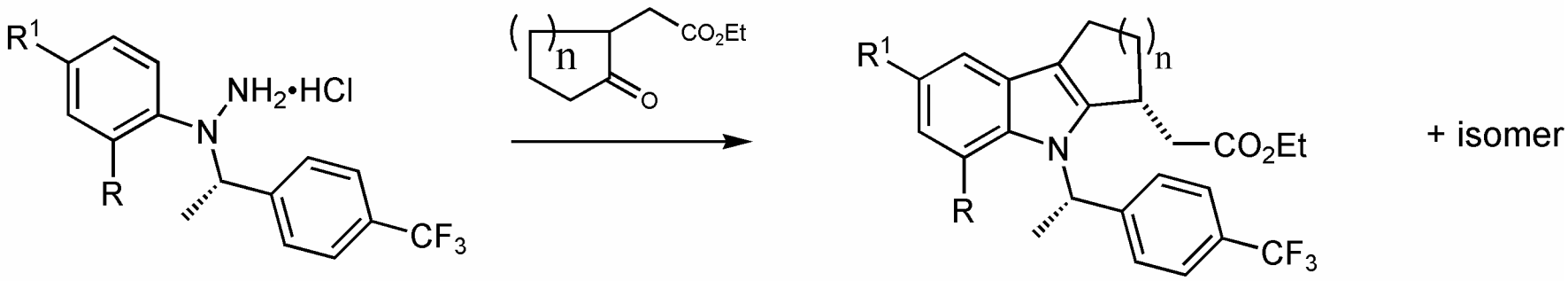
Salt Break
IPA/Heptane
Cryst
92%

655 (Free Acid)

>99.9%ee, >99.5%de
>99.5A% (210nm)

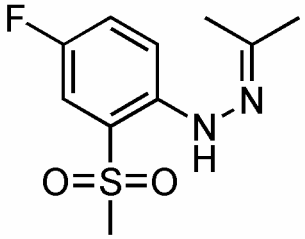
4.24 Kg, Released (Mid June)

Fischer Reaction: Substituent and Ring-Size Effects



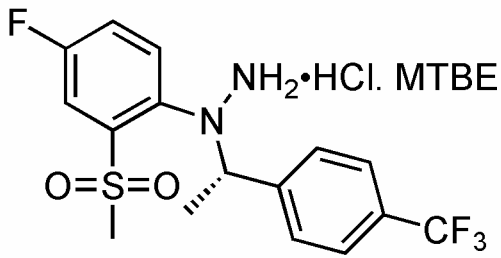
R	R1	n	d.e.	Comments
MeSO2	F	2	9 : 1	75% AY
H	F	2	1 : 1	Clean
Br	F	2	ND	Decomposition
Me	H	2	ND	Decomposition
MeSO2	F	1	ND	Indolene + related
MeSO2	F	3		Unreactive
MeSO2	F	4		Unreactive

Route Summary

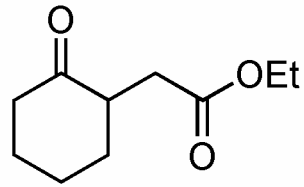


2 Steps 86%
839 Intermediate

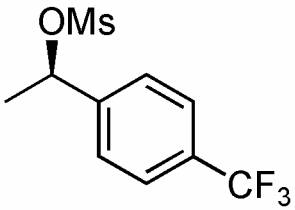
95%



Crystalline, 99%ee, Outsource



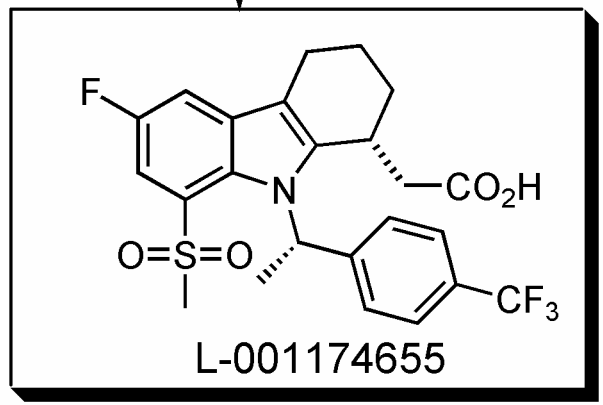
Commercially Available



2 Steps >98%
99%ee

62%

Selective Fischer Cyclization
Hydrolysis
DABCO
Salt break



L-001174655

- 50% overall yield >99%ee, >99.5wt%
- One Asymmetric Hydrogenation Step
- Novel Diastereoselective Fischer Cyclization
- DABCO Salt as Final Purification
- Free Acid Identified as Final Crystalline Form
- First Delivery (4.2 Kg) from long-term route

Acknowledgements

PROCESS RESEARCH

Guy Humphrey
Jeff Marcoux
Peter Maligres
Ben Marcune
Dalian Zhao
Chunhua Yang

CATALYSIS LAB

Chris McWilliams
Dave Tellers
Yongkui Sun

POLYMORPH LAB

Lou Crocker
Jen Chilenski
Arlene McKeown

SEPARATIONS LAB

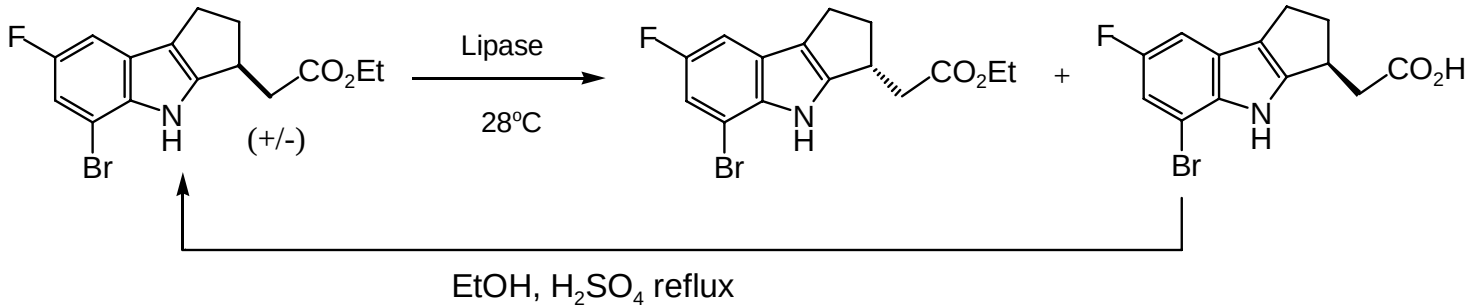
Mirlinda Biba
Chris Welch

MED CHEM

Christian Beaulieu
Daniel Guay
Zhaoyin Wang

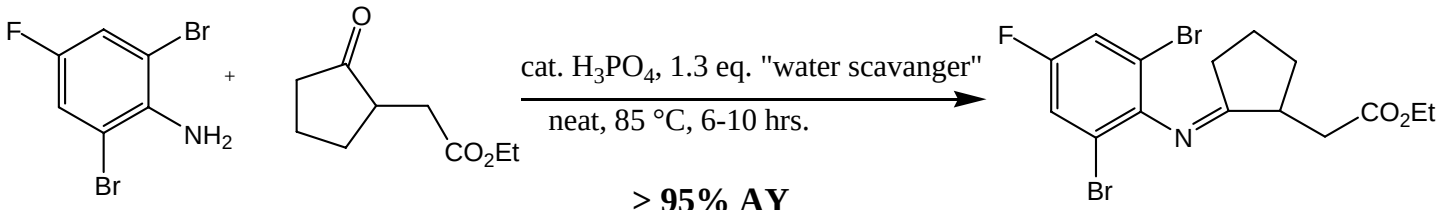
Backup Slides

CAN THE BROMOINDOLE DERIVATIVE BE RESOLVED W/ ENZYME?



- Eliminates Saponification/DCHA salt formation since BromoIndoleEster (BIE) is crystalline.
- Resolution on BIE is actually faster under the same conditions (6 h versus 30 h); potential to reduce enzyme loading.
- Again, the wrong enatiomer racemizes under esterification conditions.

IMINE FORMATION



1.0 eq.

cheap & readily available

1.1 eq.

> 95% AY

crystalline (mp = 35 °C)

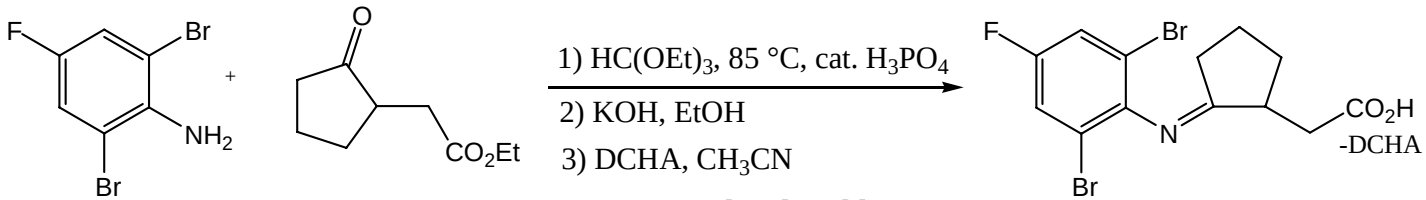
Multiple Sets of Successful Conditions:

WATER SCAVENGER

- Dean Stark: 83% AY (conversion decreases with scale > 50 g)
- Original conditions (neat with triethylphosphite) nearly completely ineffective
- Triphenylphosphite: >95% AY
- Triethylorthoformate (distillation of EtOH): >95% AY

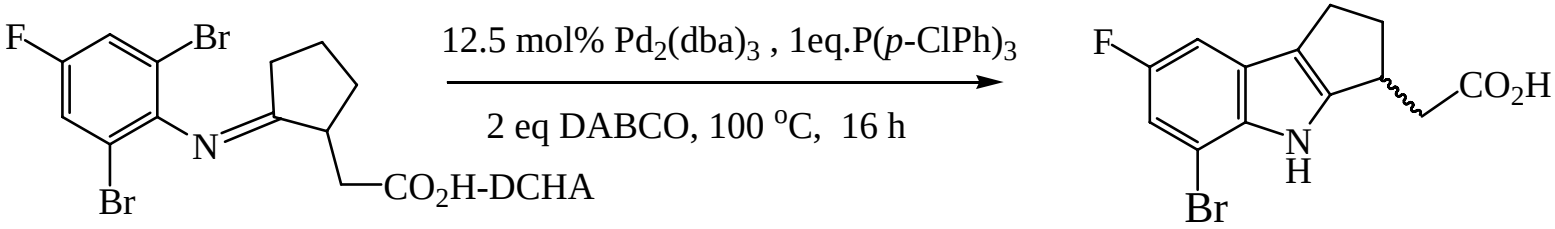
Isolation:

- Direct crystallization of ethyl ester possible but low mp was problematic
- Subsequent saponification/DCHA salt formation gave crystalline material (>95% isolated yield)



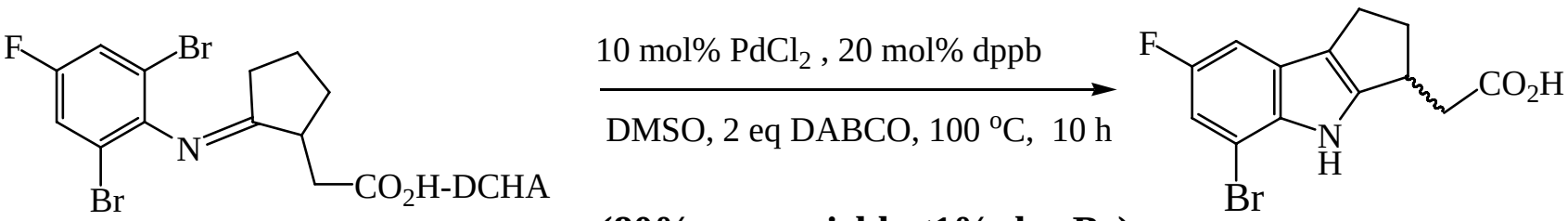
(95% Isolated Yield)

HECK CYCLIZATION



Solvent	% AY	(%conv, % des-BIE)
DMAc	**74**	(86, 2.5)
DMF	**78**	(80, <1)
DMPU	**83**	(88, <1)
HMPA	**92**	(94, 1.1)

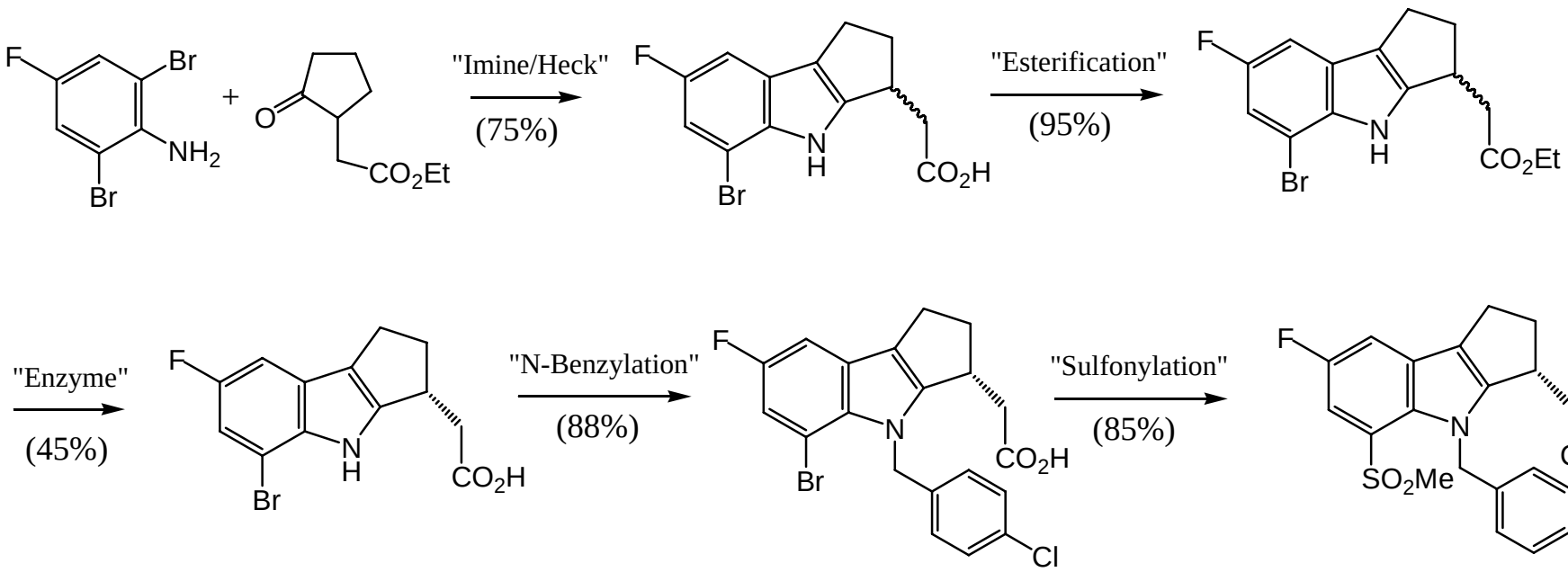
- **Heck reaction has a potential to reach 92% A.Y.**
- Reaction is much faster with DCHA salt versus Imine Ester.
- Reaction requires polar, nonprotic solvent.
- DABCO was superior to all other inorganic and organic bases screened.
- All Pd catalyst screened worked well with P(p-ClPh)3, difference was % des-BIE : Pd2(dba)3 "best However, catalyst loading is high (100 mol% of phosphine).



(80% assay yield, <1% des-Br)

THIRD GENERATION PROCESS "ENZYMATIC RESOLUTION"

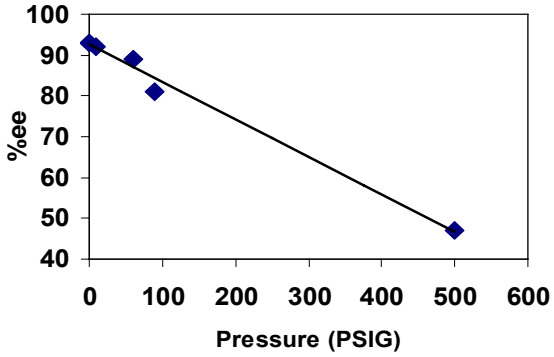
SUMMARY OF THE "PROPOSED" SYNTHESIS (W/O RACEMIZATION)

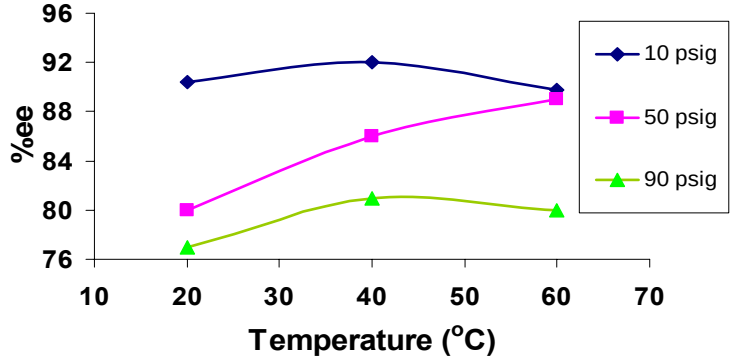


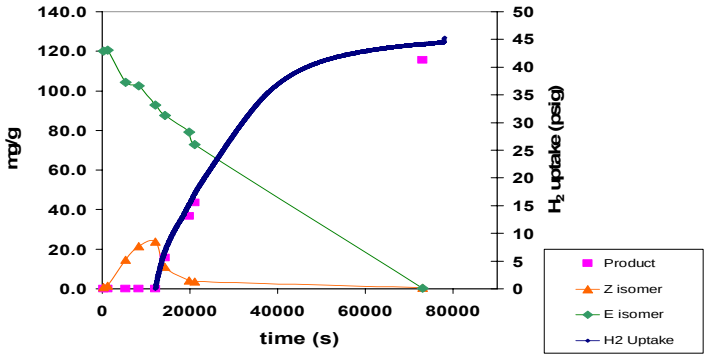
6 STEP PROCESS - 24% OVERALL YIELD (W/O RECYCLE)

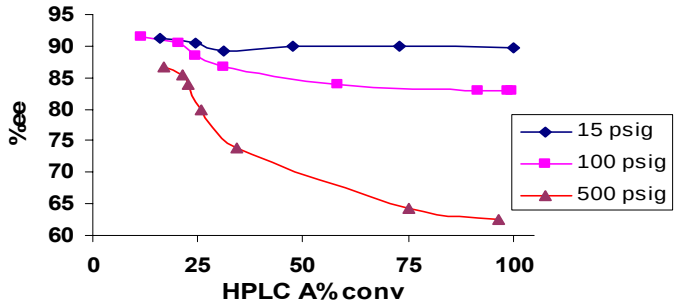
* Bromination has been eliminated but Esterification added to the process (optimization of Heck w/ Indole Ester)
* Process demonstrated on 5 g scale. Still needs some optimization

A Closer Look at Hydrogenation by HPLC & IR, Temperature & Pressure



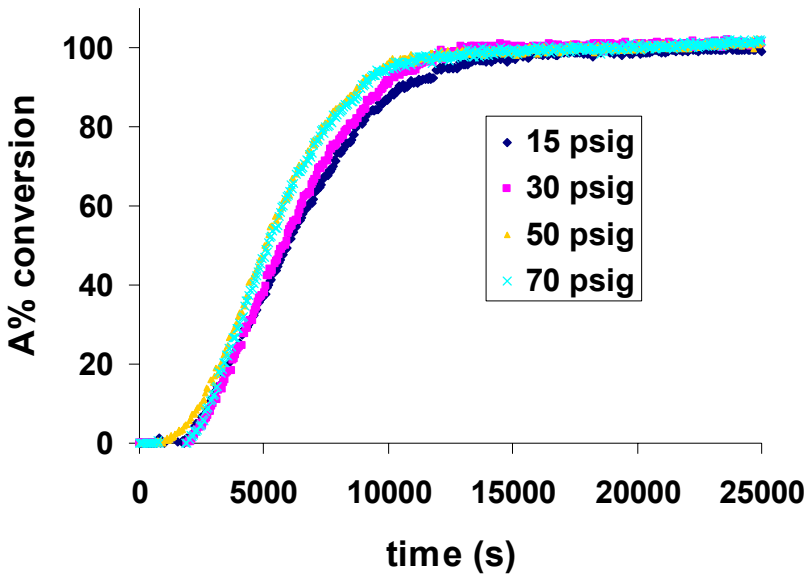


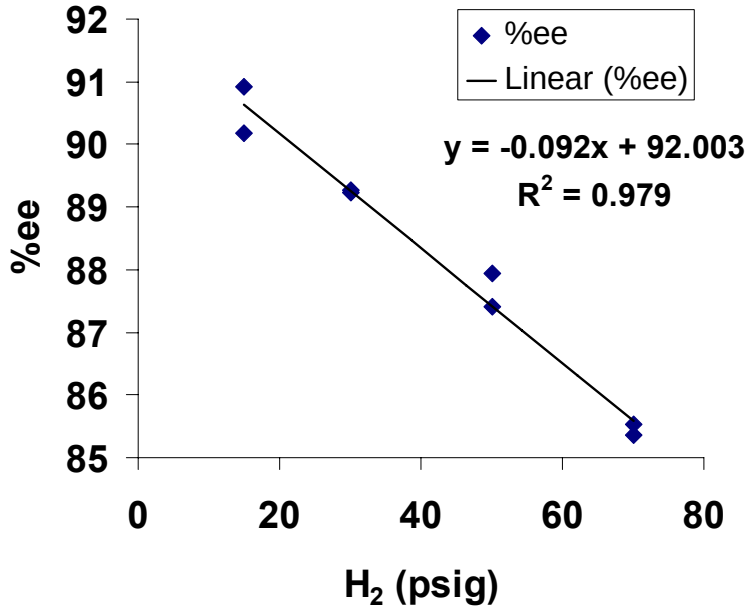




- **Pressure has a drastic effect on the ee, temperature also has an effect.**
- **Small amount of new compound (endo-isomer) is observed during early stages of reaction by HPLC & IR.**
- **~90% ee obtained at early conversions for all pressure examined– rules out pressure dependent enantioselectivity for Endo Isomer, Endo-isomer is more reactive.**

Affect of Pressure on Reaction Rate

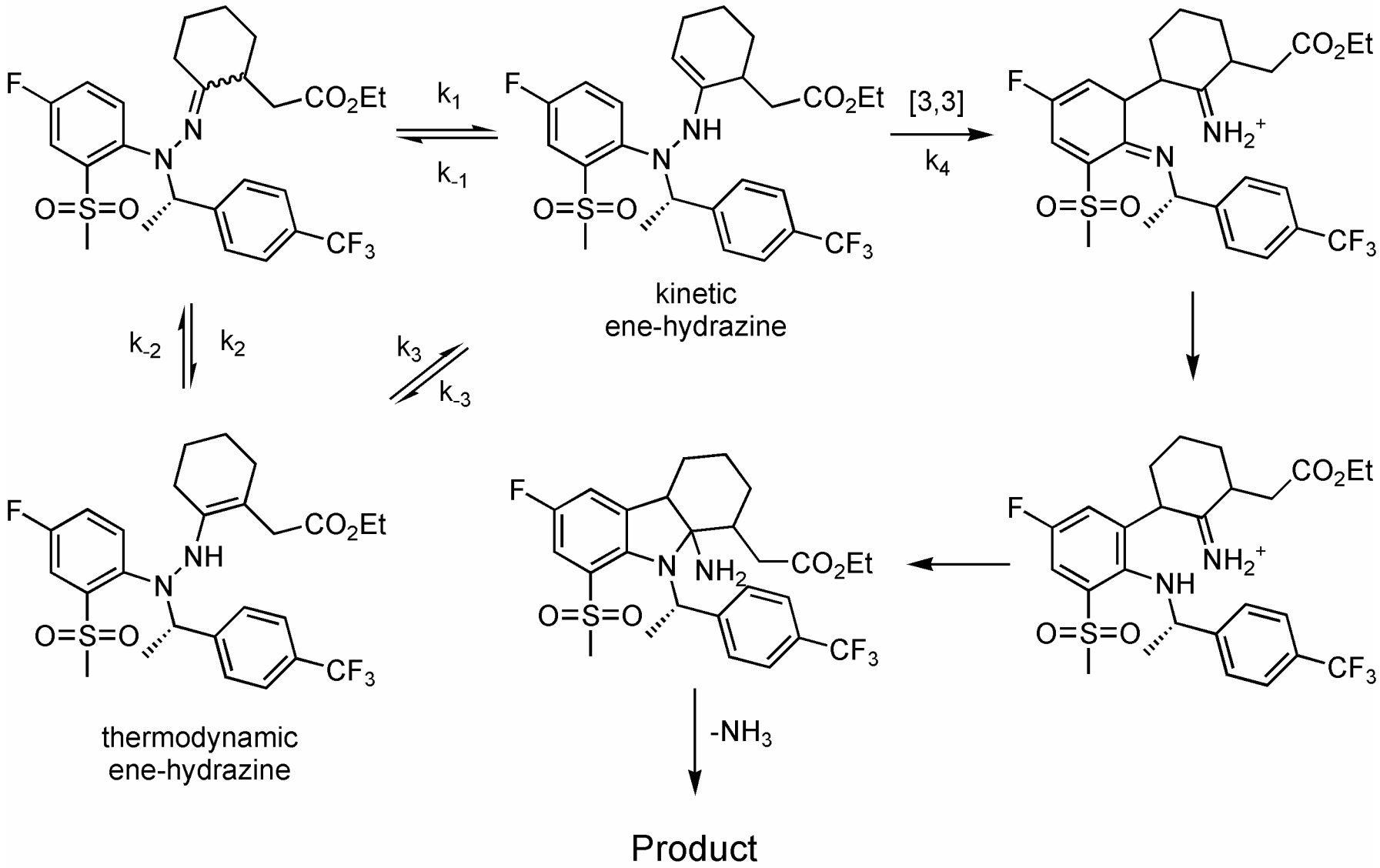




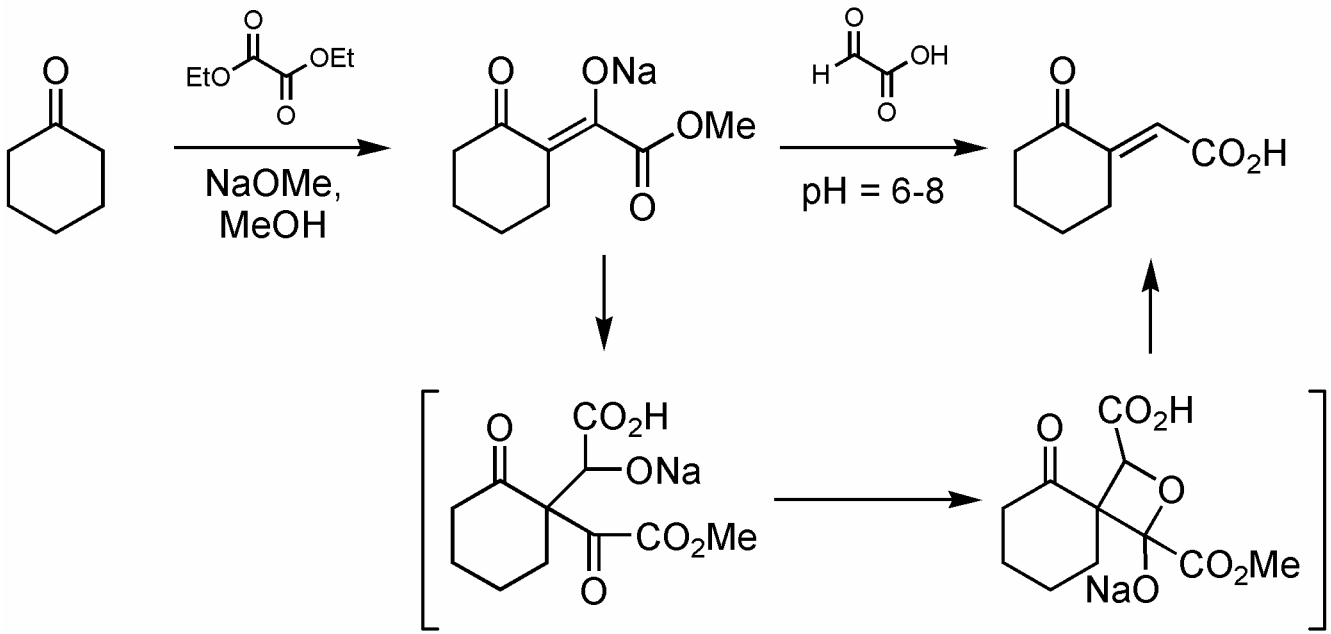
- **Reactions monitored by H_2 uptake with Argonaut Endeavor Instrument**
- **Reactions appears zero-order in hydrogen but there is still a real impact on reaction enantioselectivity!**

Back-Up Slides

Mechanism of the Fischer Indole Reaction

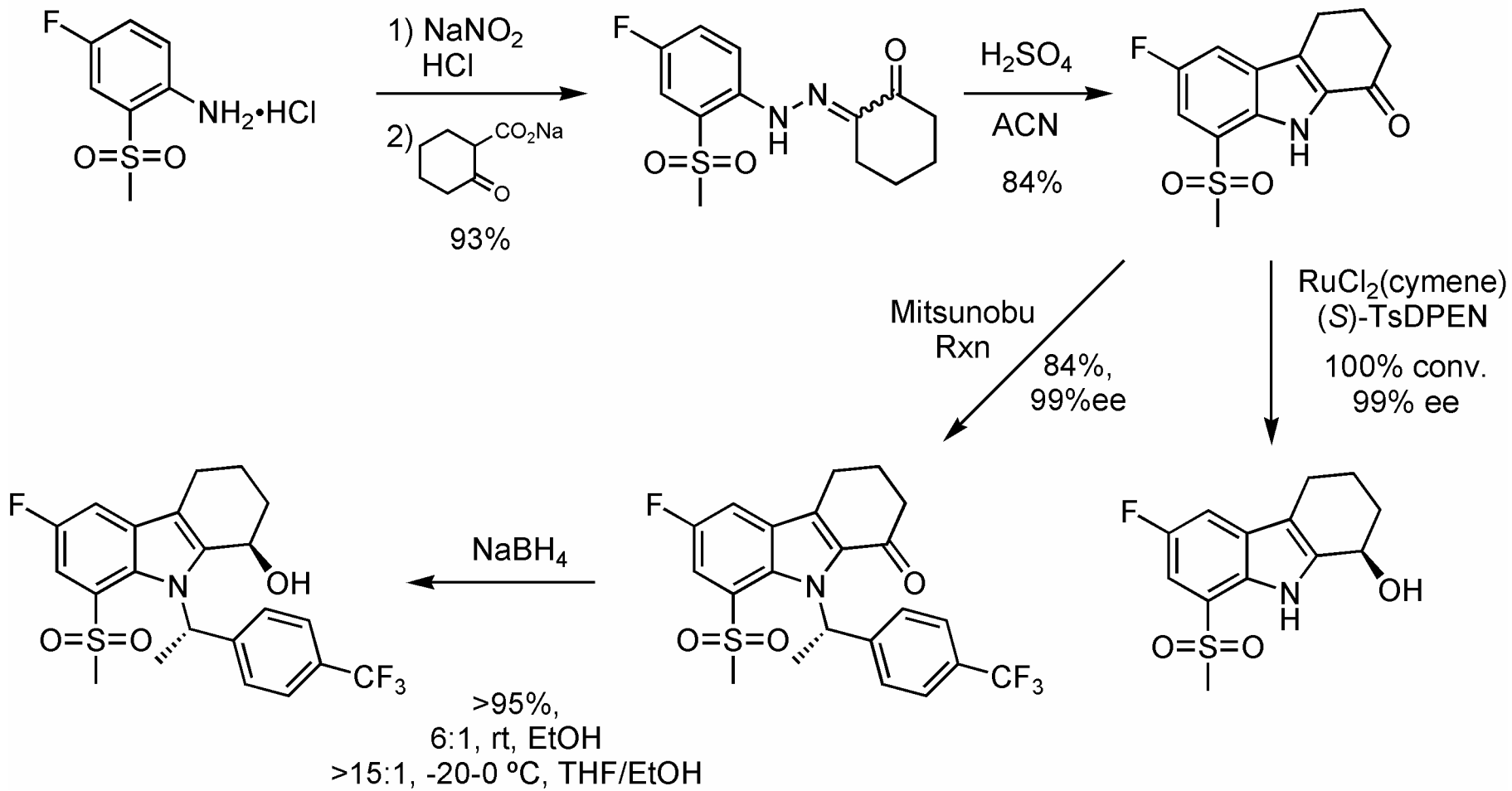


Synthesis of the Oxo-Acid

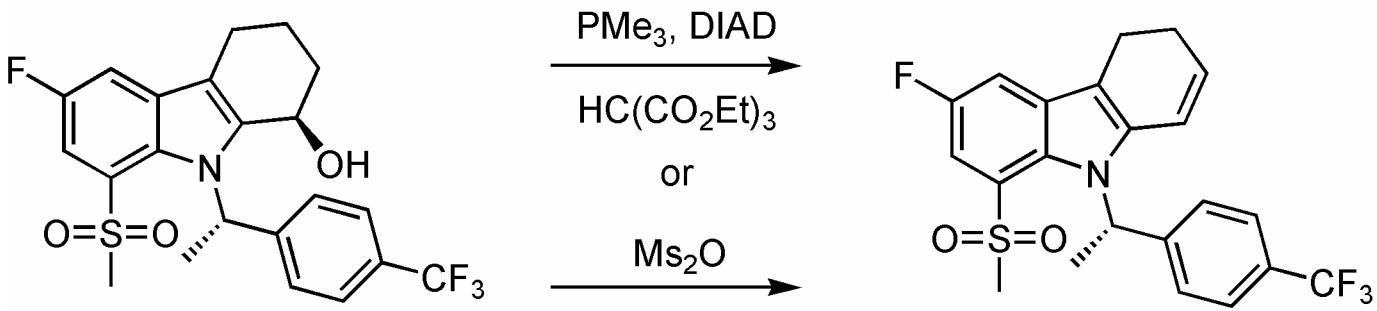


- One Pot Process
- Direct Crystallization or as *i*Pr_2NH salt
- 60% Overall Yield

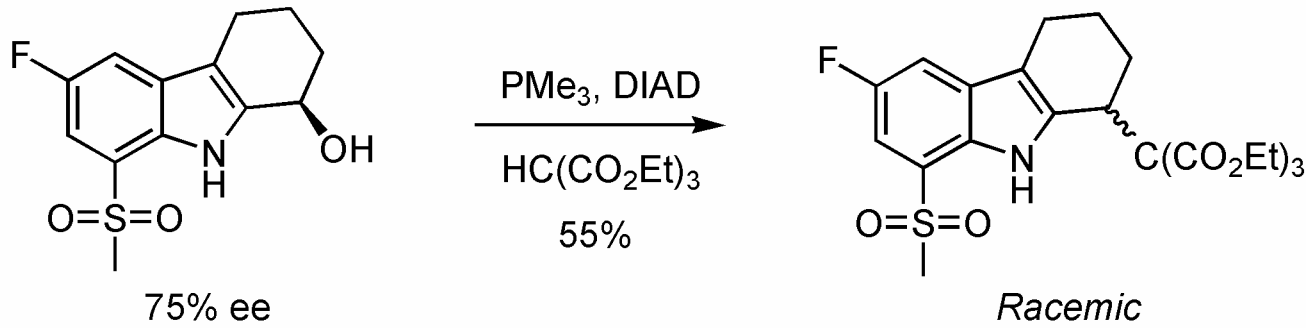
S_N2-Displacement: Starting Materials



S_N2-Displacement: Initial Results



Elimination is Major Product!

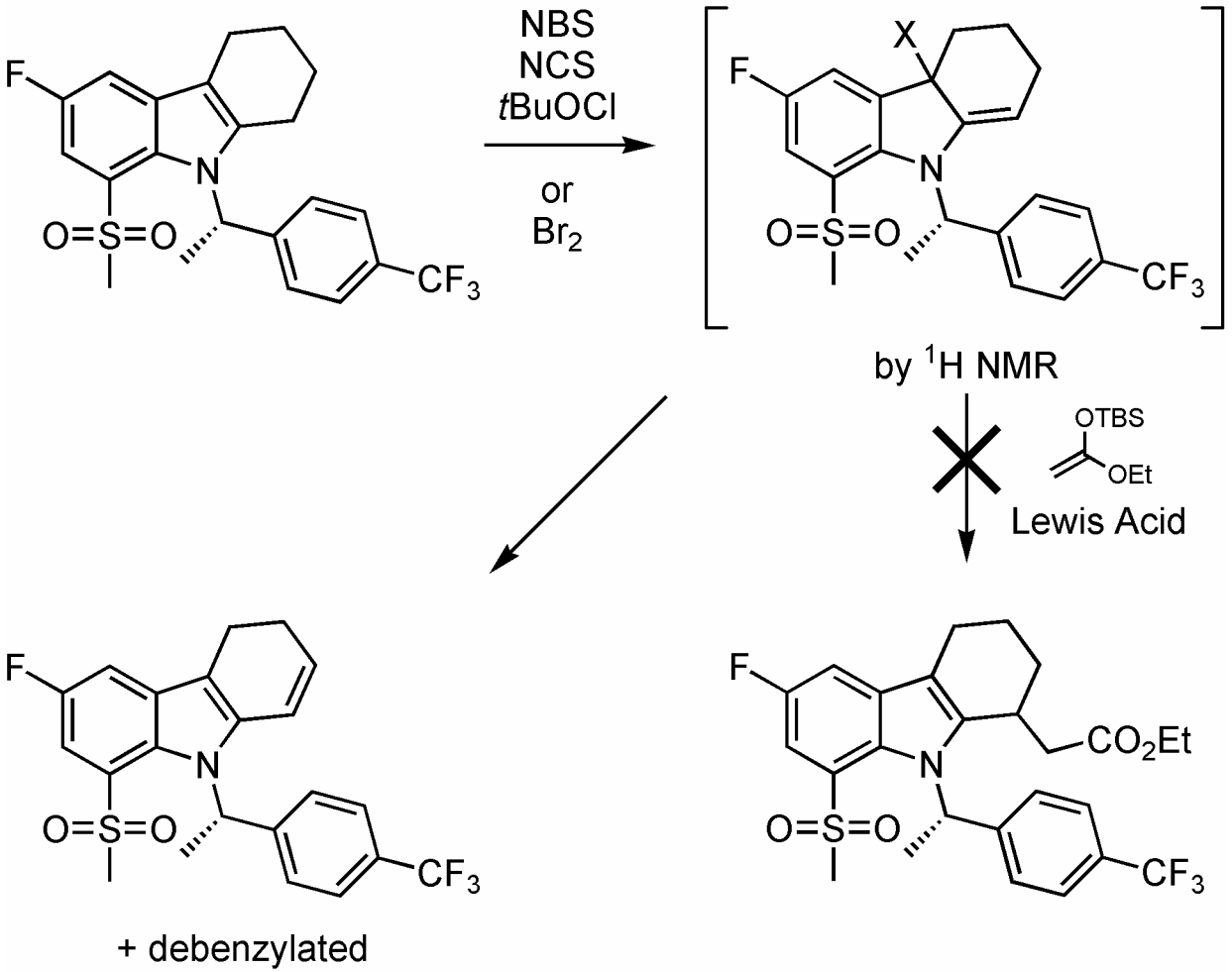


75% ee

Racemic

Unprotected Hydroxyindole Racemizes

S_N1 Alkylation Results



Elimination is major product