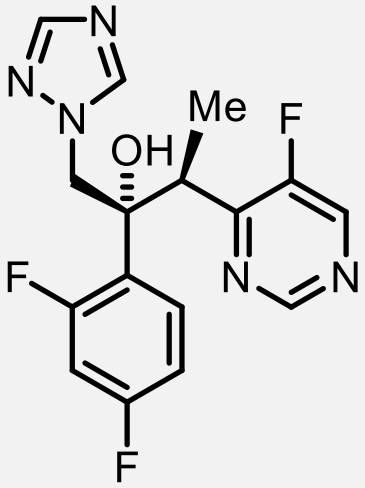
Second Generation Process Development at Pfizer:
Voriconazole: The Reductive Aldol Process



VFEND (voriconazole)

Pat O'Neill

Nordic-Irish Process Chemistry Forum 2023 - Belfast

June 7th 2023

Contents

Our Company: Pfizer Facts & Figures

$81.3B*

REVENUE in 2021*

39**

MANUFACTURING sites worldwide

~79,000

COLLEAGUES around the world

>125

COUNTRIES
in which Pfizer sells products

9

PRODUCTS
with sales greater than **$1B** in 2021

96

PROJECTS
in Clinical Research and Development***

* Pfizer's year in review | Pfizer 2021 Annual Report
** The **Algiers, Algeria** site transfer to Viatris is delayed until the second quarter of 2022. During the interim period, the site will temporarily report into the PGS Local Solids Manufacturing (LSM) network.
*** As of May 3, 2022: Product Pipeline: Pharmaceutical Pipeline for New Drugs | Pfizer

INVESTING IN IRELAND SINCE 1969

Pfizer

Pfizer was one of the first pharmaceutical firms to locate in Ireland and has operated here since

1969

$7bn invested in IRISH OPERATIONS since 1969

The medicines manufactured in Ireland are distributed to approximately 100 countries

4,000 employees

Pfizer employees work in roles across

- Manufacturing
- Research & Development
- Commercial operations
- Global Business Services and Finance

Ireland is a manufacturing base for Pfizer globally. Many of Pfizer's leading medicines are manufactured from Irish sites.

Part of Pfizer's Worldwide Research and Development (WRD) is based in Ireland.

Pfizer Global Supply (PGS)

Our Network

- Aggregation of 25+ companies
- 56 internal manuf. sites
- 130 logistics centers
- 200+ supply partners
- 22,000+ colleagues

Products

- Significant complexity
- 600+ major product groups
- 21,000+ SKUs
- 40+ technologies/ platforms

Key Activities

- Site and Logistics network
- Operational/Supply/ Technical support
- Product co-development, launch, and process optimization
- External partnerships

>175 Markets

>50 Languages

Global Technology & Engineering

Who We Are:

949 Colleagues Globally

25 Pilot Plant & Analytical Labs

~70% of Colleagues Graduate +

Presence in 18 Countries

Why We Exist:

We deliver pioneering manufacturing technology and projects that will define the future of PGS and have a direct impact on patients everywhere.

Where We Are:

GT&E Functions

- Analytical Technology
- External Supply Technology
- Global Engineering
- Large Molecule Technology
- Manufacturing Intelligence
- Medical Device & Combination Products
- **Small Molecule Technology**
- Sterile Injectable Technology
- Technology Excellence

Process Development Centre (PDC) –part of GTE based in Cork

PDC and 2nd Generation Processes

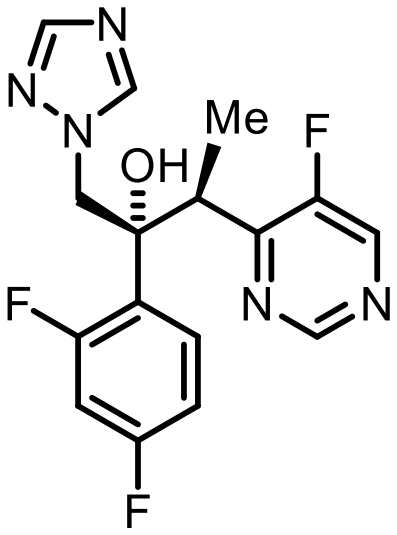
1. PDC– four main focus areas:
   - Develop new routes to existing APIs (2nd generation routes)
   - Site Support/Advanced Process Development/External Supply
   - Support new product development
   - Develop platform technology

2. 2nd generation development constraints:
   - Quality – equivalent, not just meeting specification
   - Existing equipment
   - Compliance – pGTIs, reagents with toxicological concerns, metals
   - Freedom to Operate (FTO)
   - Green(er)
   - Cost

Voriconazole: Background

- Voriconazole (VFEND™) is a treatment for invasive fungal infections, particularly for the immunocompromised
  - **Top anti-fungal agent on the market**

    (2010 revenue ~ $800 MM)



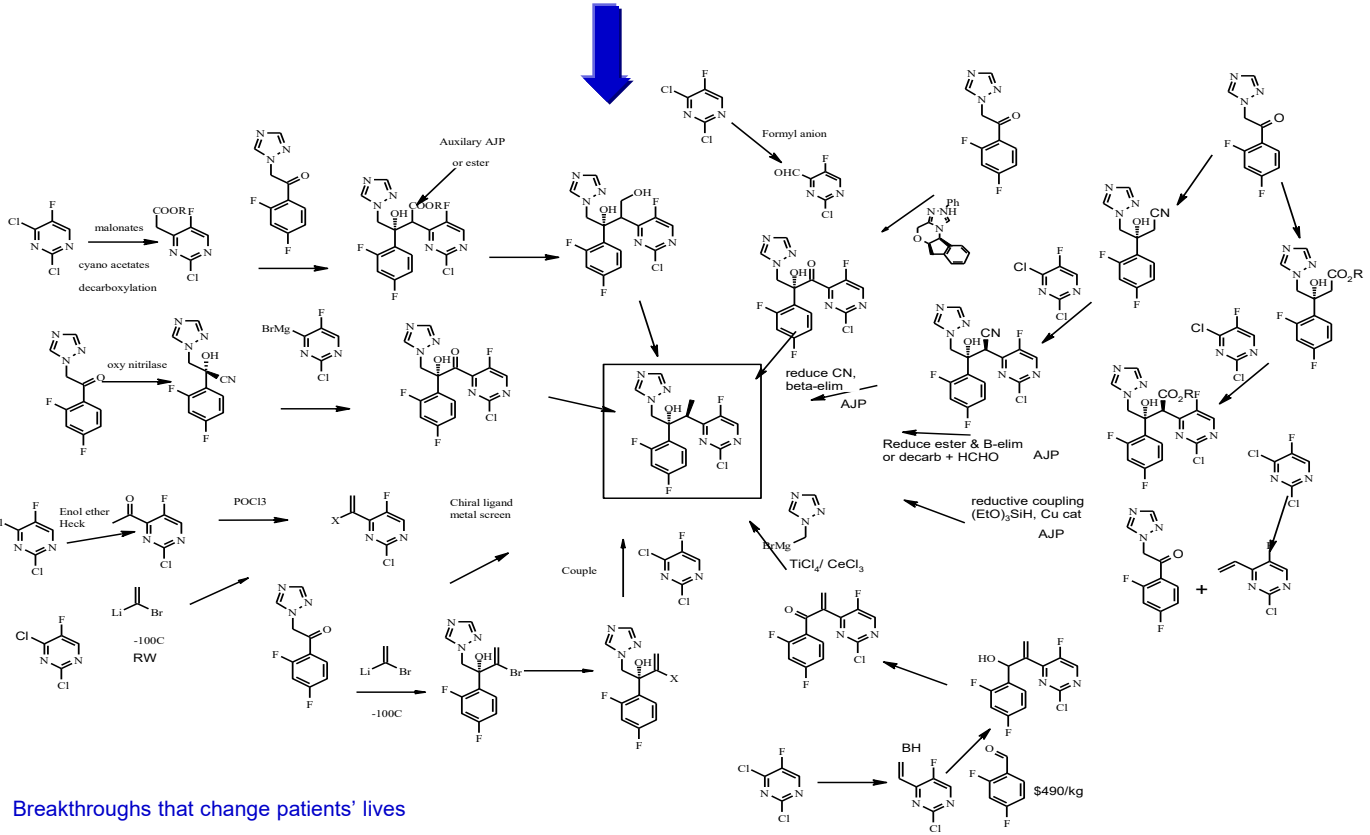
- Loss Of Exclusivity (LOE):
  - Feb 2011 (US tablets)
  - 2016 for other markets (inc. EU)
- Challenge from organisation:
  - Reduce footprint required to manufacture API
  - Reduce total cost of API >50%

VFEND (voriconazole)

Second Generation Workflows 1

IDEA GENERATION

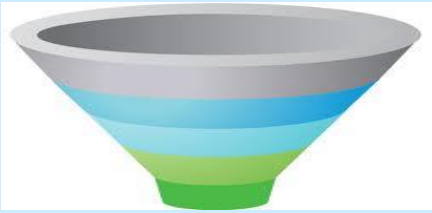
- Global brainstorm initiated to search out best ideas
- Ideas from PDC, API-TG, PGS, CRD
- “Open Innovation” RFP issued to >50 CROs
- **OUTPUT >40 new routes to API**



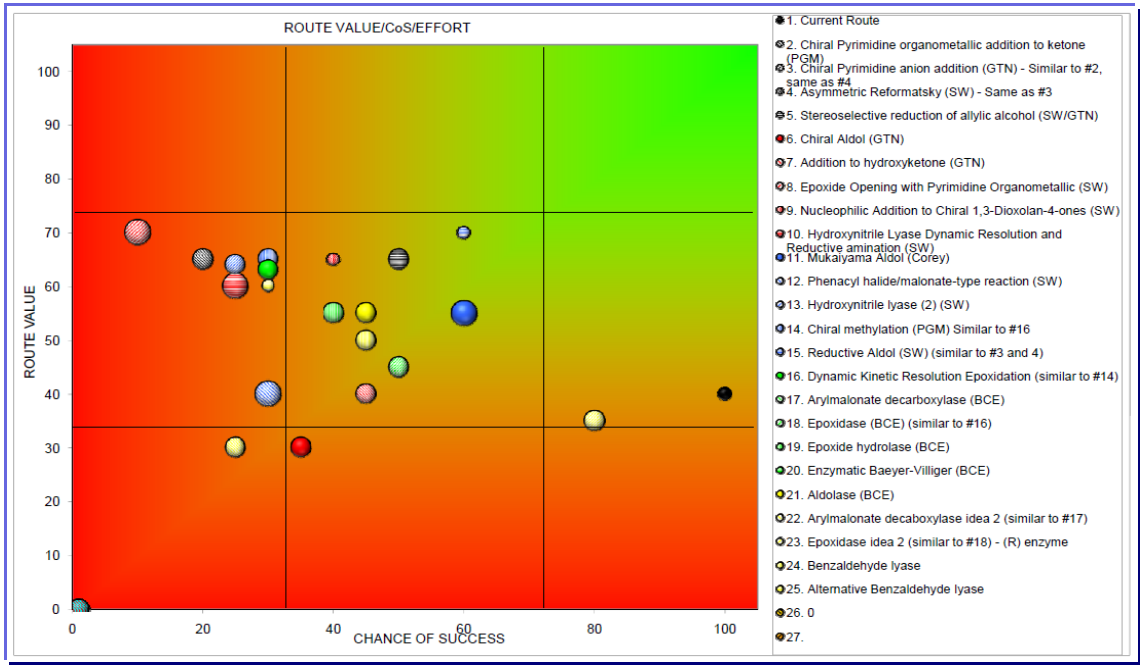
Second Generation Workflows 2

IDEA GENERATION

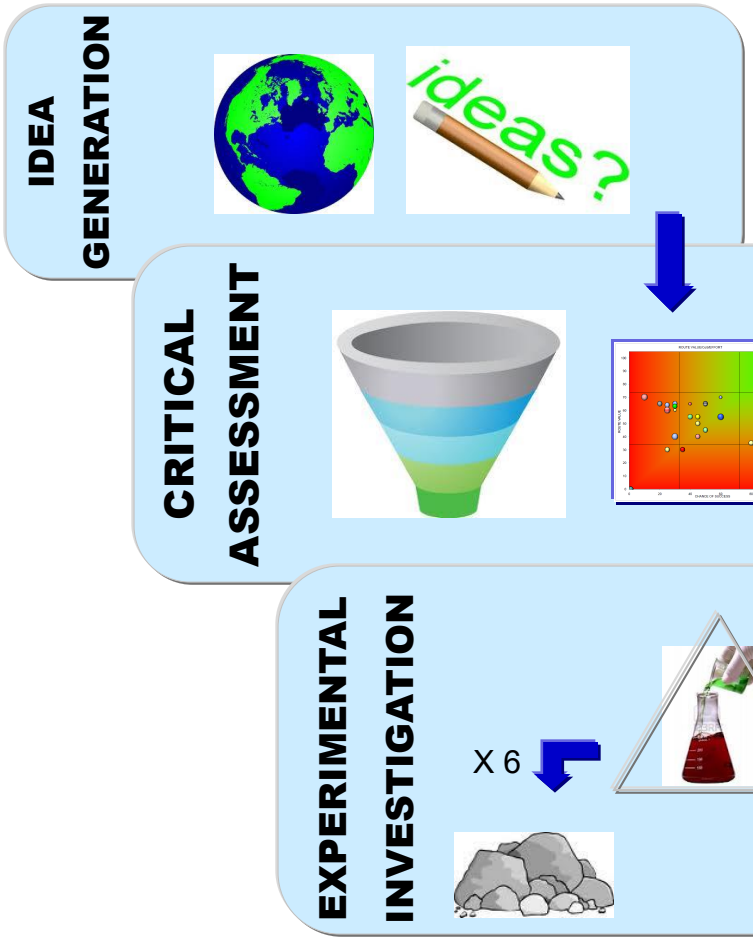
CRITICAL ASSESSMENT

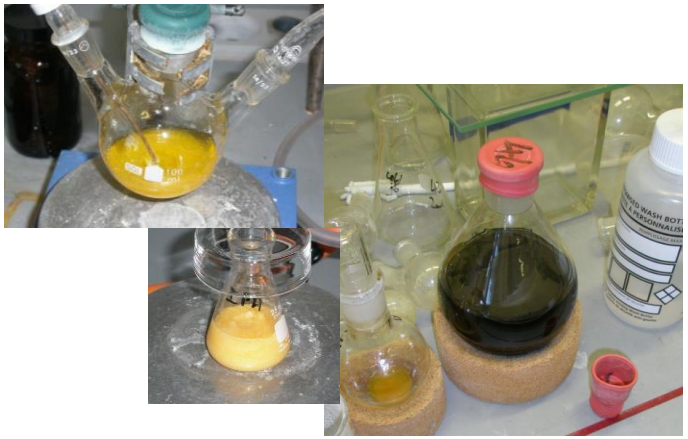


- Multi-faceted critiquing tool used to prioritise ideas
- Wide range of Criteria – Economics, Probability of Success, Precedence, Legal FTO, Safety, Throughput
- **OUTPUT = 7 high priority routes to API**



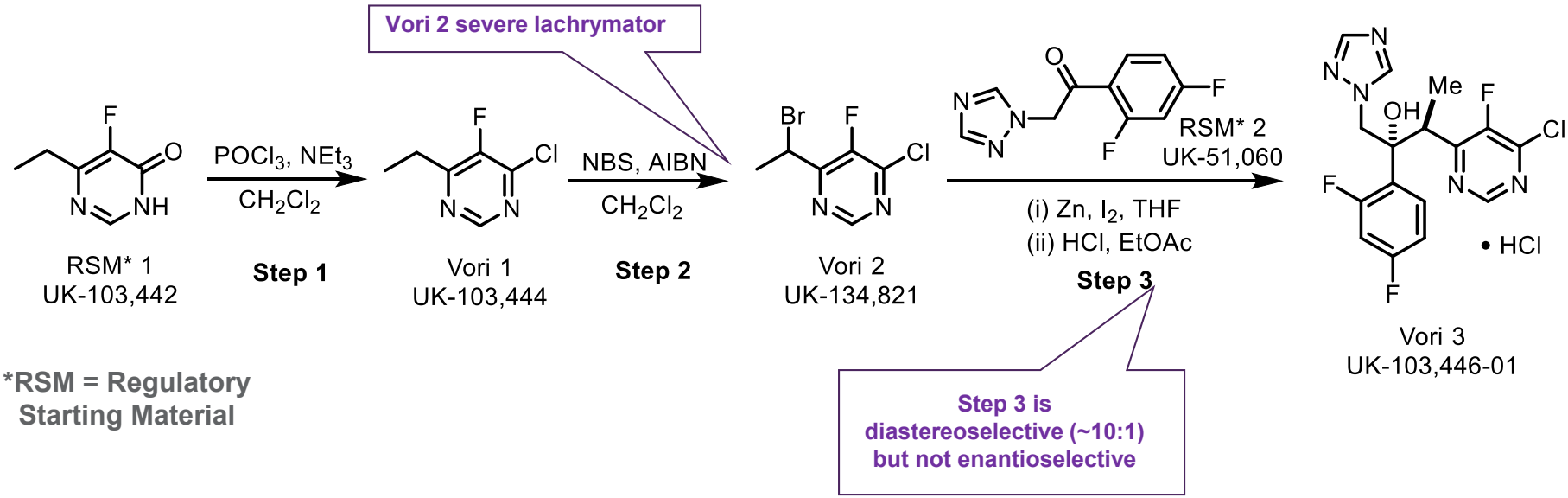
Second Generation Workflows 3

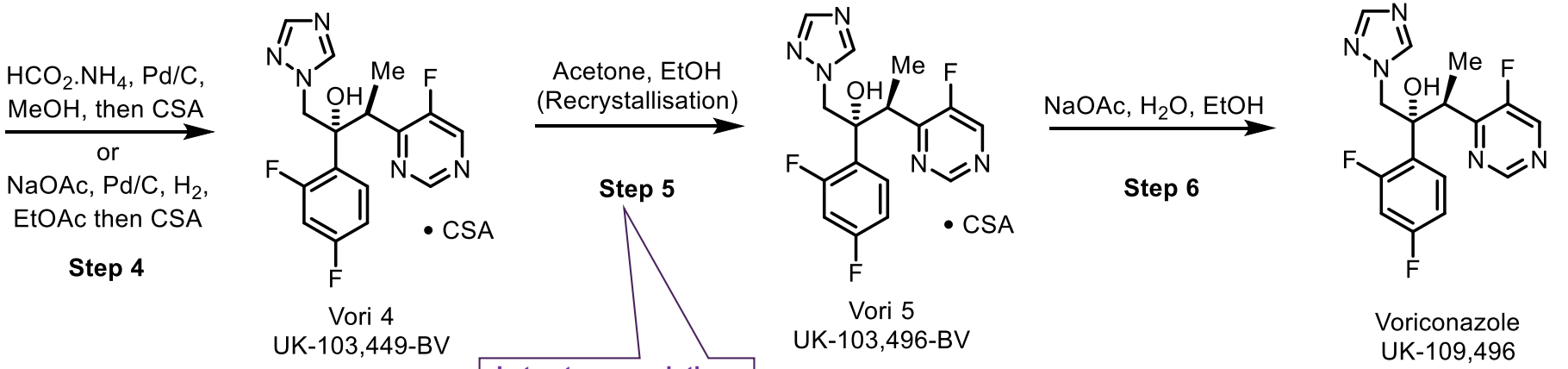




- Experimental design for all 7 routes
- Kill experiments identified for each route
- Synthesis of key starting materials and reagents

1st Gen. Route: Chemistry

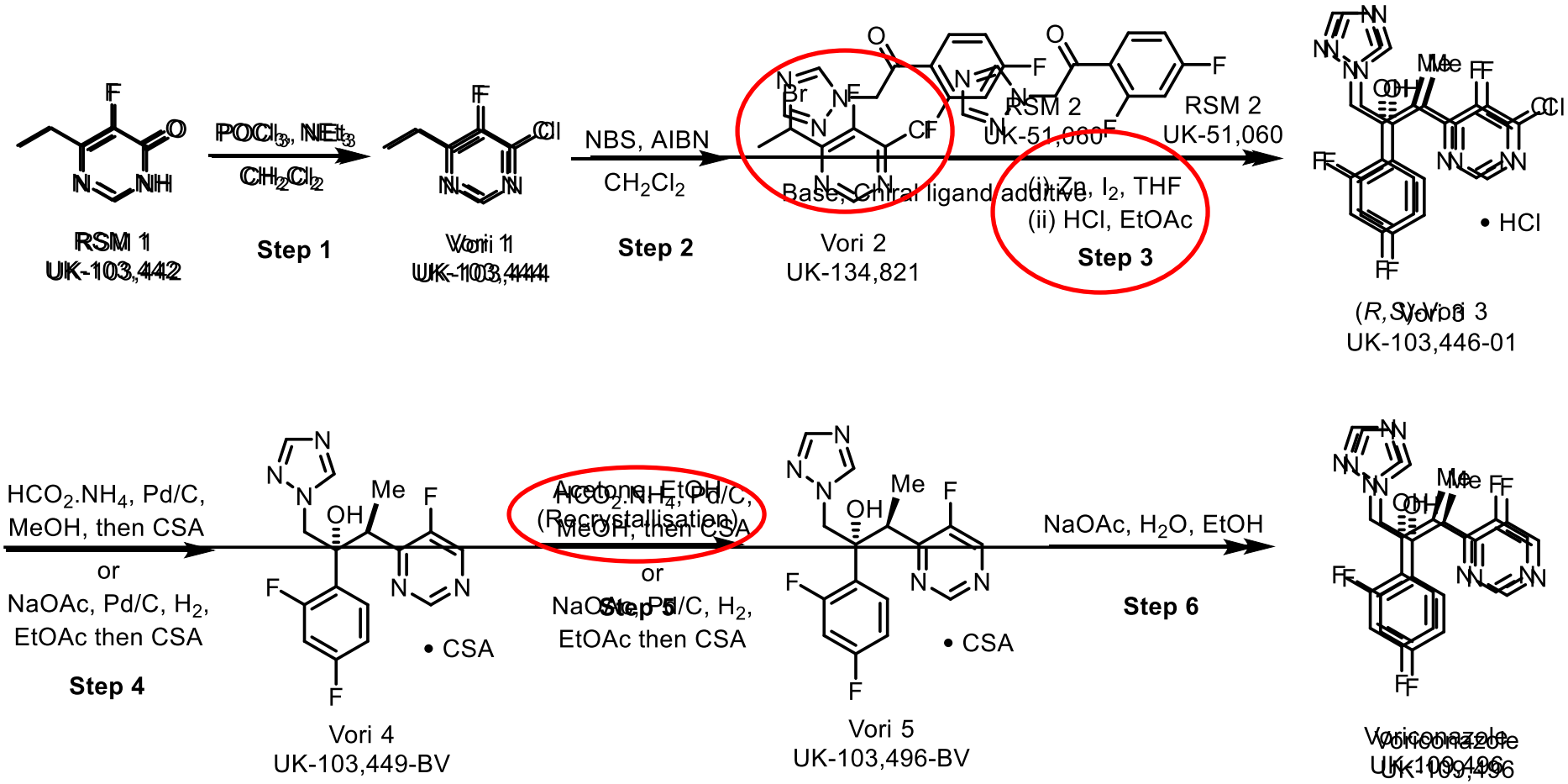




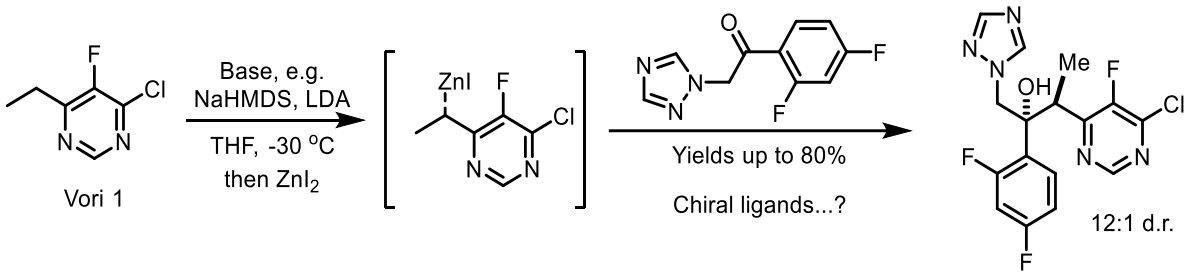
Butters *et. al.*,OPRD, 2001, **5**, 28

Butters *et. al.*, WO1997006160 A1

Modifying the 1st Gen. Route …….

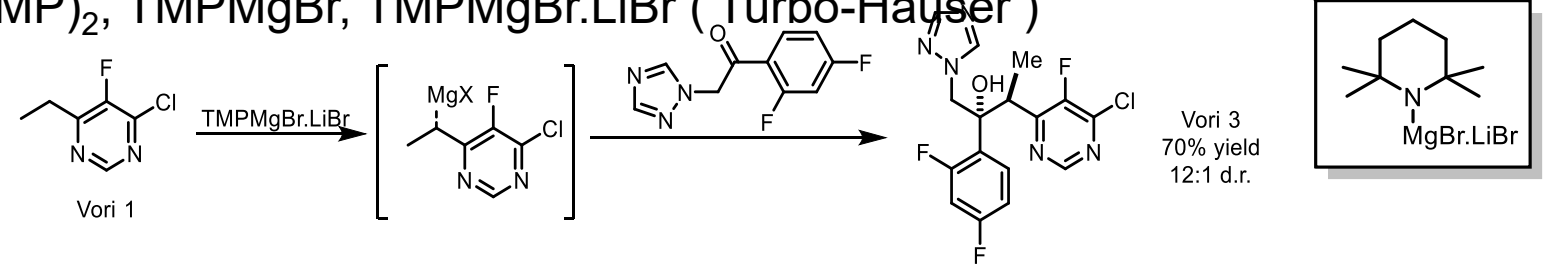


Modifying the 1st Gen……..2



OPRD, 2001, **5**, 28

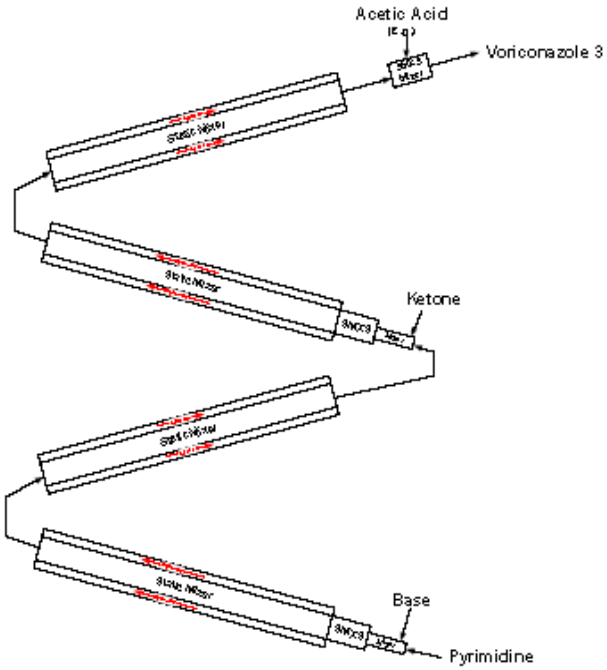
- Some proof of concept studies conducted very early on
  - Transmetallation to Zn (increased stability, 3 eq. required for good d.r.)
  - Chiral alcohols/amines/amino alcohols screened – limited enantioselectivity
- More recently, direct deprotonation using Zn/Mg bases:
  - $Mg(TMP)_2$, TMPMgBr, TMPMgBr.LiBr ('Turbo-Hauser')

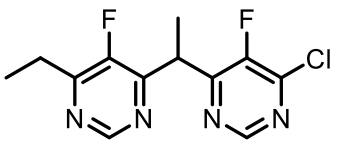


- Direct coupling diastereoselective but not enantioselective
  - d.r. >10:1 but no effect of chiral ligands/chiral bases

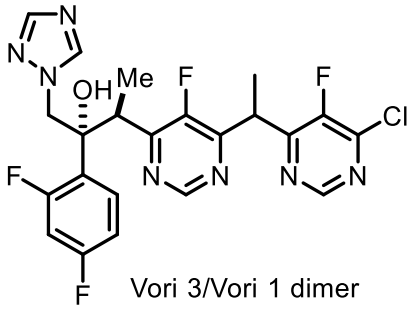
Modifying the 1st Gen……using Flow

- Low temperature required to avoid dimer impurities
  - Less than -40 °C in batch
- Continuous (plug flow) as alternative…
  - Using TMPMgCl.LiCl at -20 °C gave good results…





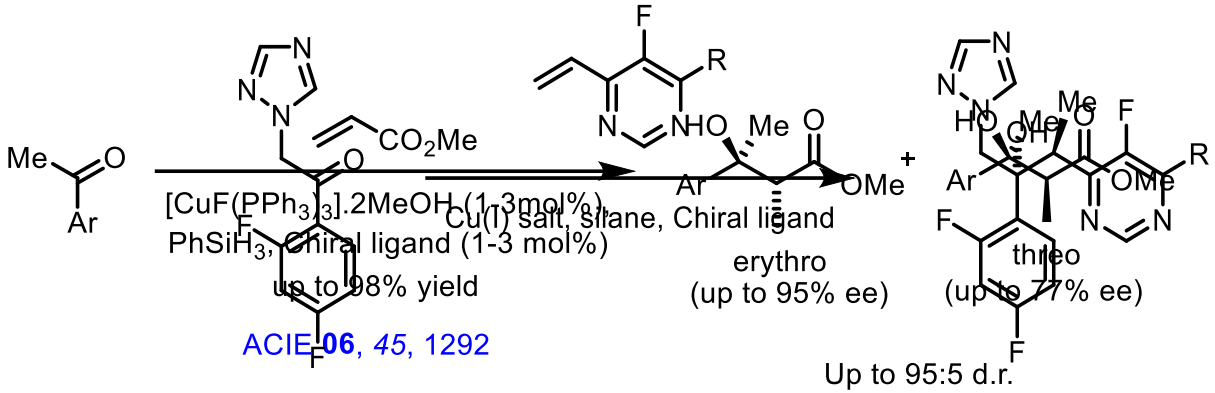
Vori 1 dimer



Vori 3/Vori 1 dimer

TRIAL	Vori 3 area %	Dimer area%
Batch mode at -50 °C	78.5	3.1
Batch mode at -40 °C	45.6	15.1
Continuous mode -20 °C	72.2	3.0

Introducing the Reductive Aldol Route



ACIE-**06**, *45*, 1292

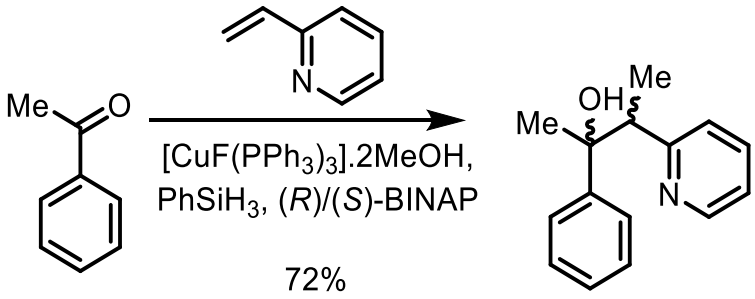
Asymmetric Aldol Reactions

DOI: 10.1002/anie.200503791

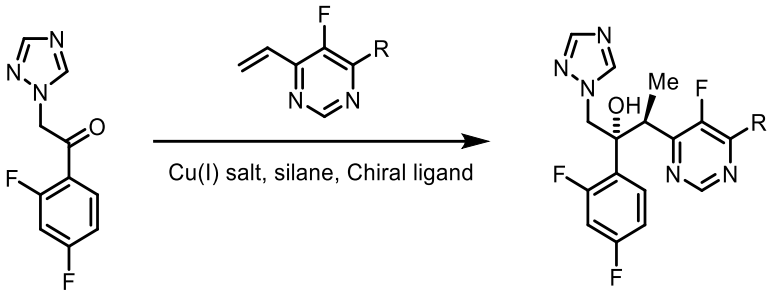
Highly Diastereo- and Enantioselective Copper-Catalyzed Domino Reduction/Aldol Reaction of Ketones with Methyl Acrylate**

*Julia Deschamp, Olivier Chuzel, Jérôme Hannedouche, and Olivier Riant**

- Proof of concept with 2-vinylpyridine:



Reductive Aldol Route –the Vision



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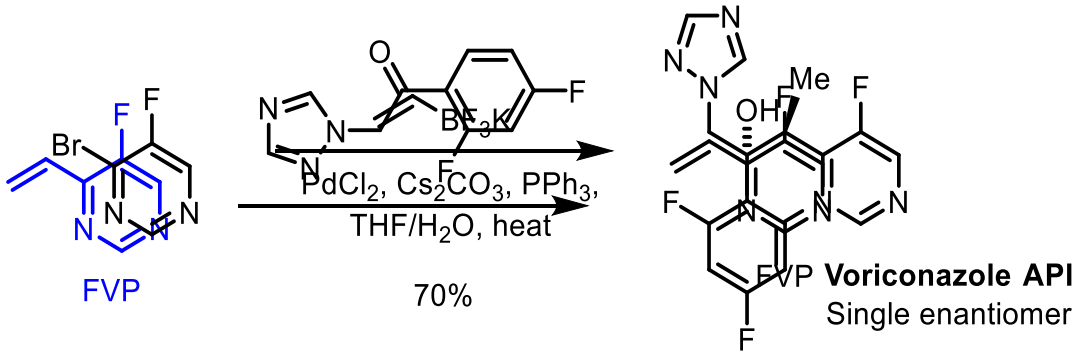
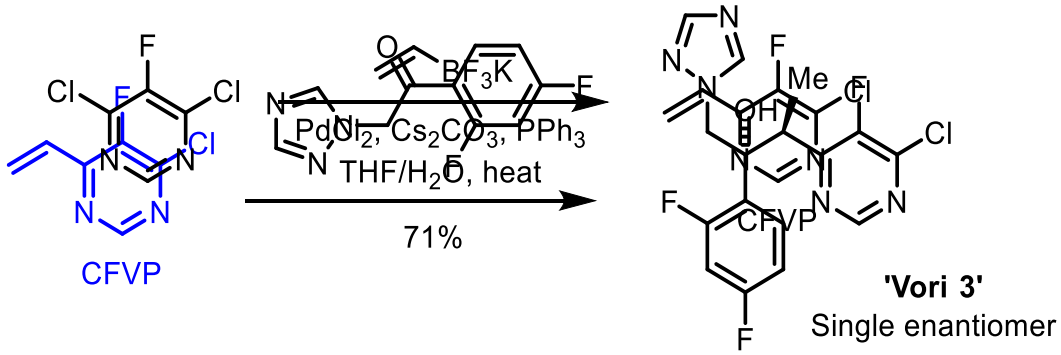
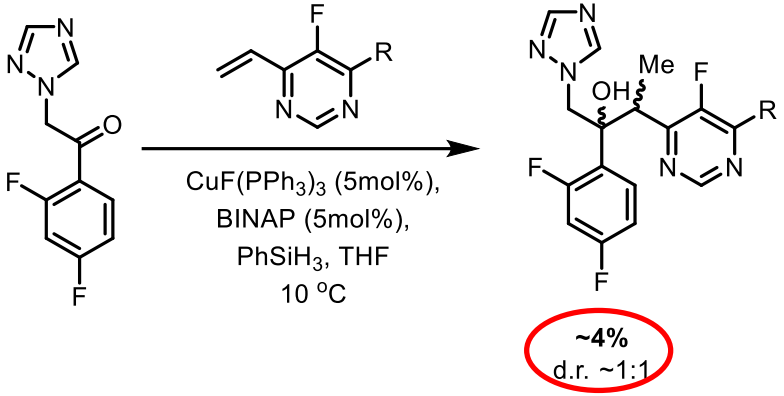


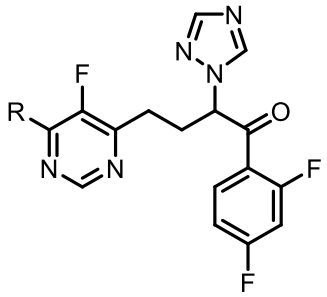


J. Org. Chem., 2006, **71**, 9681

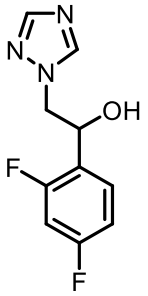
Reductive Aldol Route –initial results

- Initial reactions conducted with $CuF(PPh_3)_3$.MeOH and BINAP

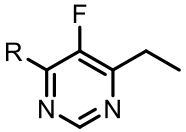




~50%
(based on pyrimidine)

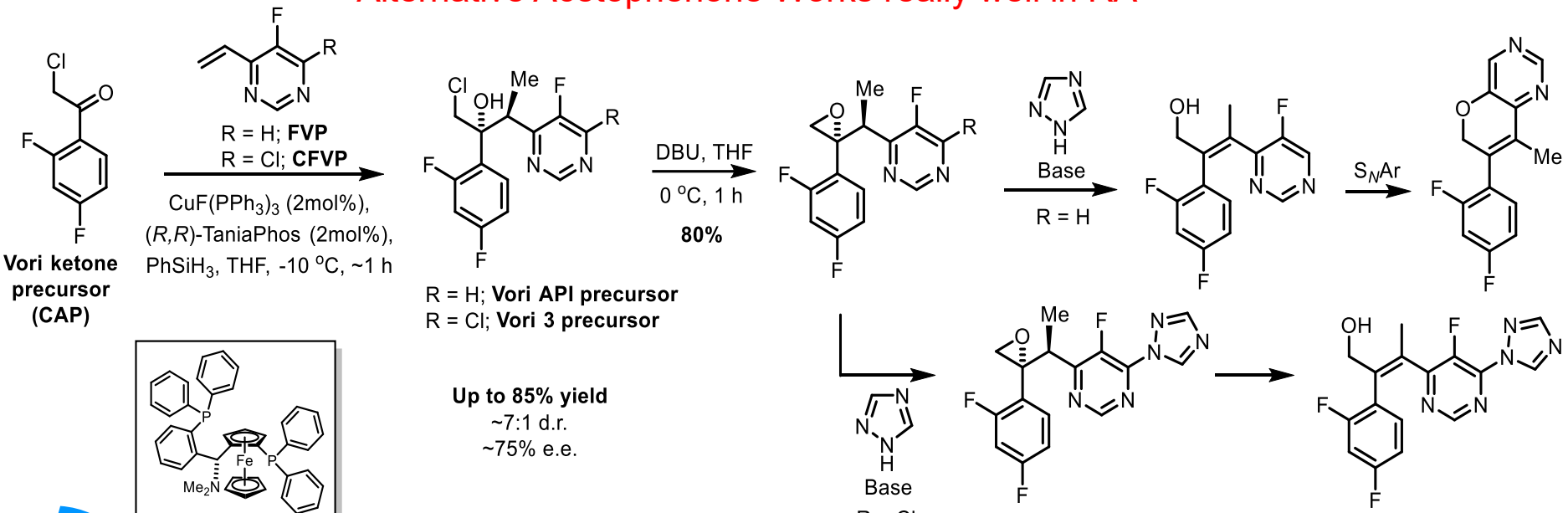


~30%
(based on ketone)



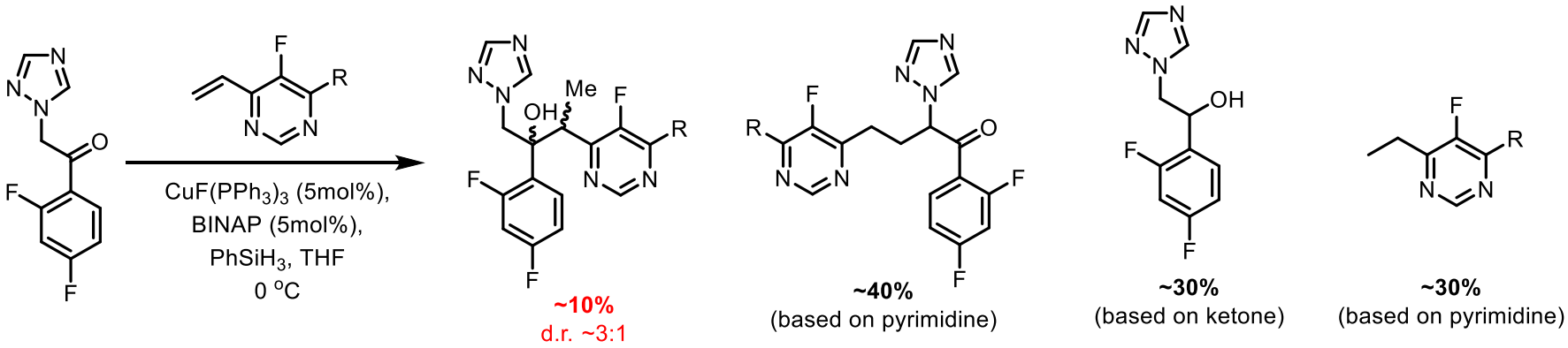
~35%
(based on pyrimidine)

Alternative Acetophenone Works really well in RA

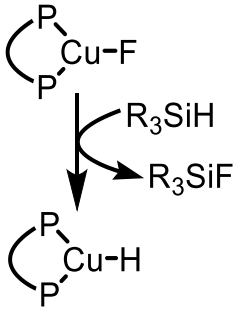


Effect of Temperature

From 4 to 10%!



Reductive Aldol Proposed Mechanism

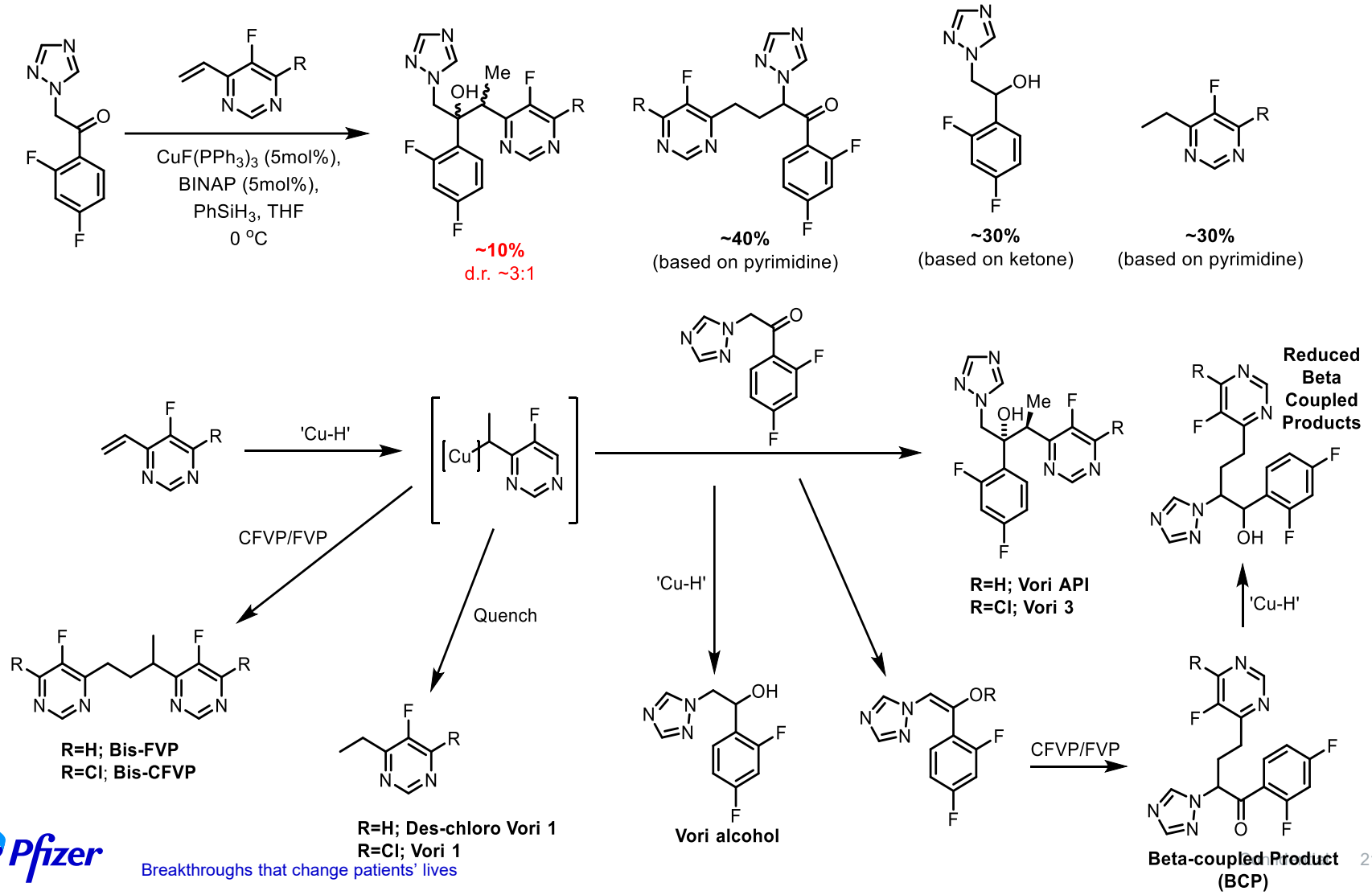


Proposed Mechanism

Shibasaki *et. al.,*
Tet. Lett, 2006, 1403

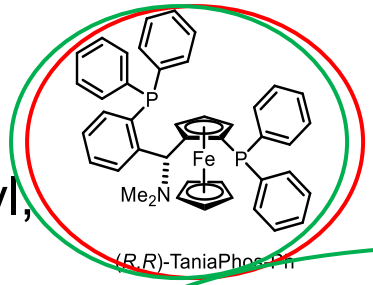
Origin of Impurities

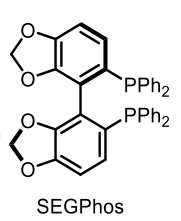
- Initial reactions conducted with $CuF(PPh_3)_3$.MeOH and BINAP

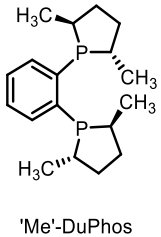


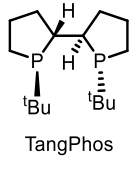
Choosing the Substrate: H or Cl?

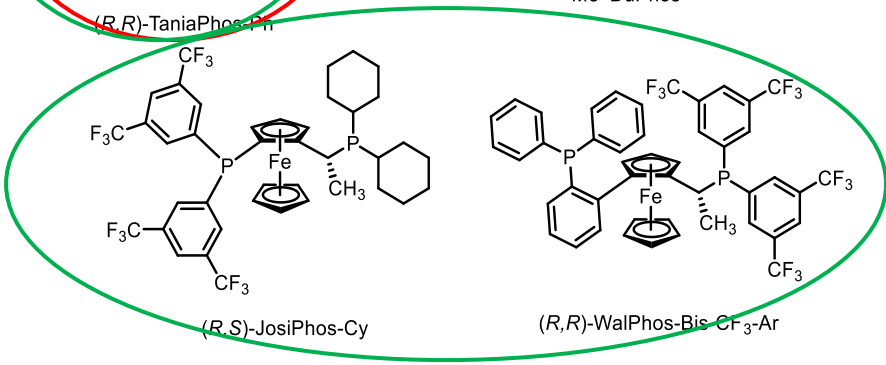
- Ligand screening conducted
  - Range of ligands including BINAPs, SEGPhos, DuPhos, P-chiral, ferrocenyl, monodentate

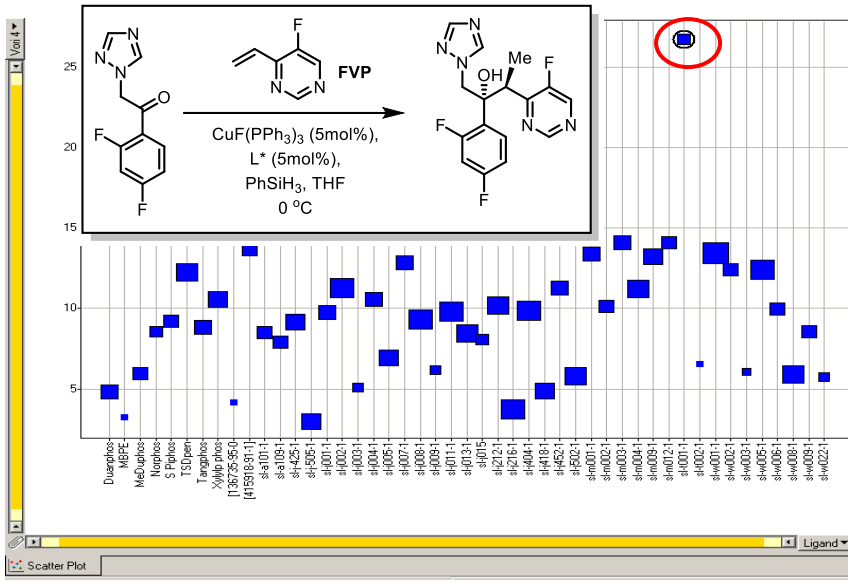


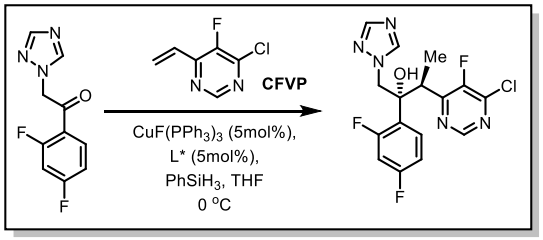




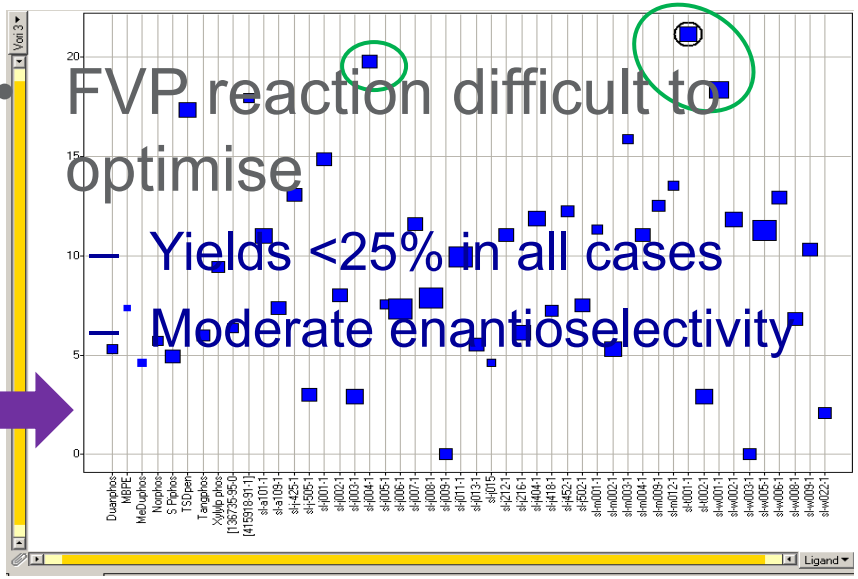






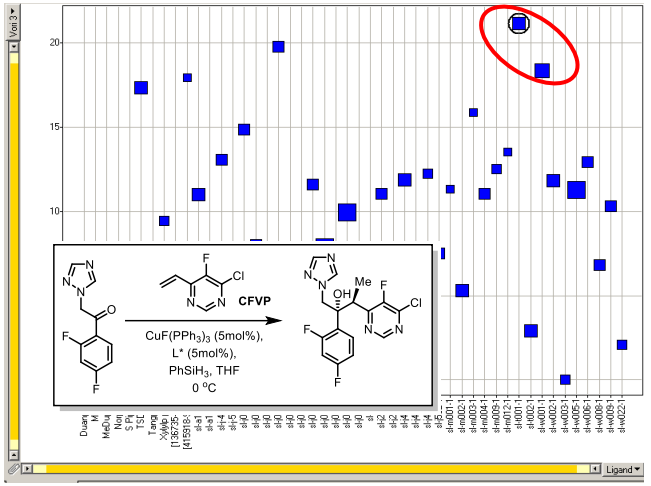


- FVP reaction difficult to optimise
  - Yields <25% in all cases
  - Moderate enantioselectivity

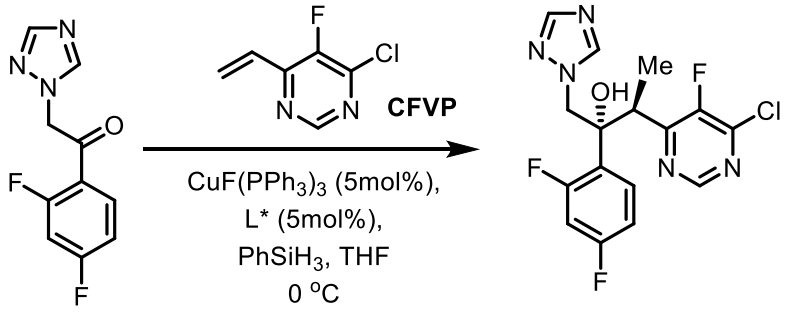


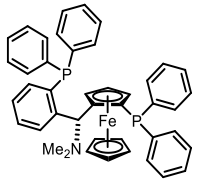
Ligand Screening

- Ligand screening conducted
  - Range of ligands including BINAPs, SEGPhos, DuPhos, P-chiral, ferrocenyl, monodentate
  - Reactions with FVP less tunable by ligand
  - TaniaPhos & WalPhos brought into 2nd round of screening

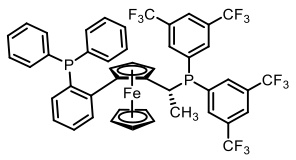


- Under similar conditions:
  - (*R*,*R*)-TaniaPhos-Ph **63% e.e.**
  - (*R*,*R*)-WalPhos-$(CF_3)_2$ **-91% e.e.**
  - (*S*,*S*)-WalPhos-$(CF_3)_2$ **87% e.e.**

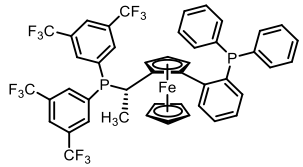




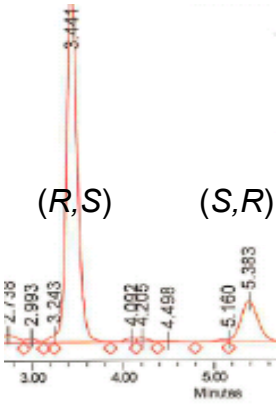
(*R*,*R*)-TaniaPhos-Ph

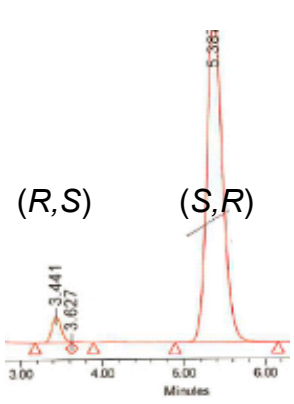


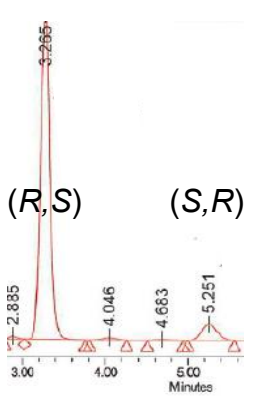
(*R*,*R*)-WalPhos-Bis-CF_3-Ar



(*S*,*S*)-WalPhos-Bis-CF_3-Ar

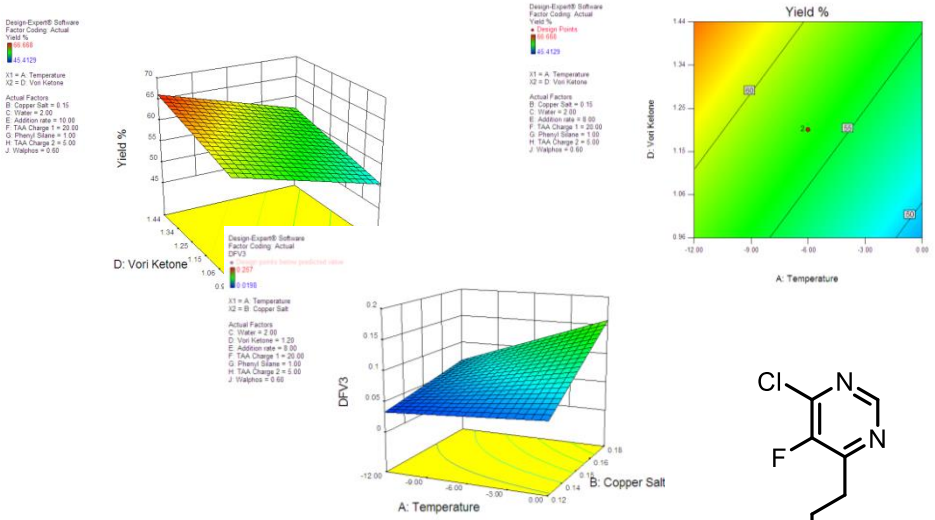


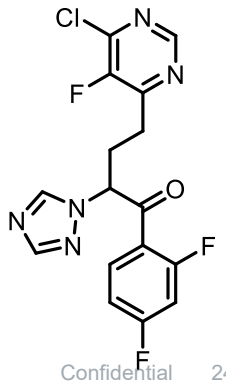




Optimisation

- Initial reactions conducted in THF (at 60 mL/g CFVP)
- 1st solvent screen conducted:
  - Broad screening (ether, ester, alcohol solvents) – limited by solubility
- 2nd round of screening combined with Design of Experiment (DoE)
  - Ligand & Catalyst:Ligand ratio
  - Solvent
  - Temperature
  - Reagent equivalents
  - Concentration

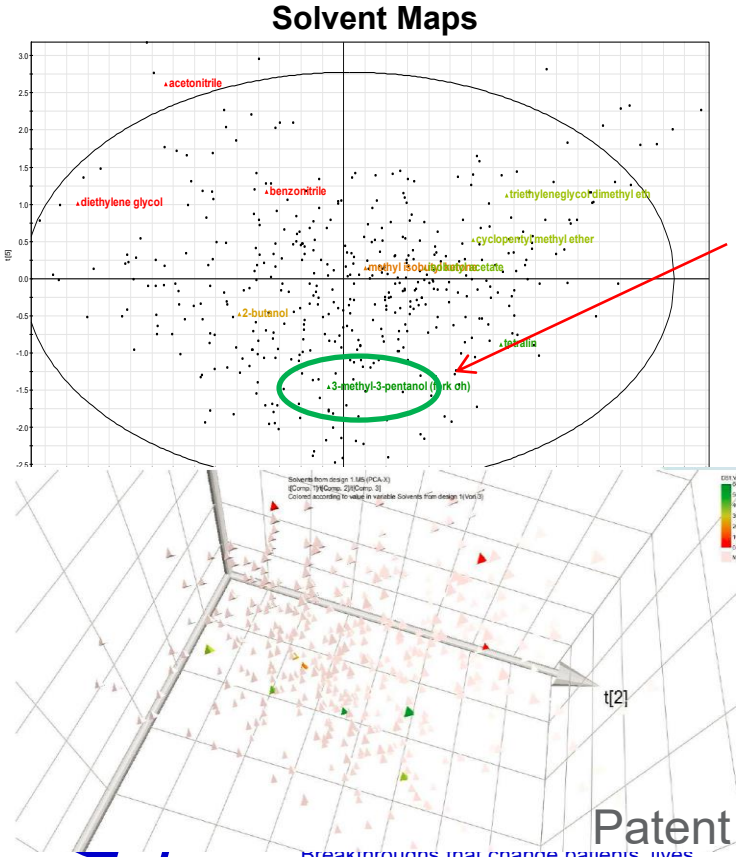


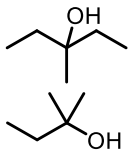


- Water shown to have large effect on reaction time…
  - Slow reactions gave increase in beta-coupled product
  - Water increased turnover

Solvent Selection 2

- Principal Component Analysis (PCA) combined with DoE:
  - Mulitvariate data analysis tool, reducing complexity in large data sets
  - Way of describing discrete parameters according to properties to allow use in DoE
  - Map of ‘chemical space’: solvents behaving similarly closer to each other

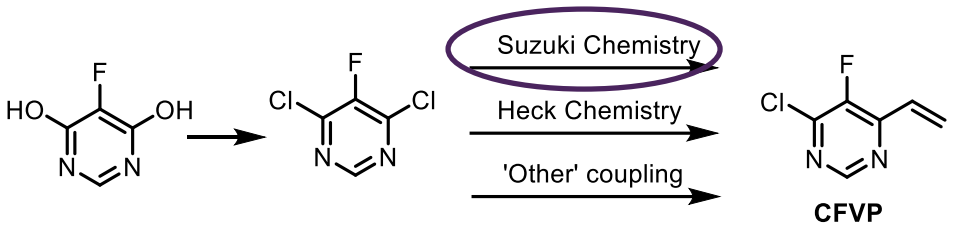




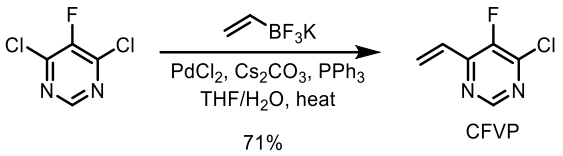
- Key findings:
  - ‘Greasy’ alcohols increase product yield
    - 3-methyl-3-butanol ($$$)
    - 2-methyl-2-butanol (*tert*-amyl alcohol) ($)
  - Increase in enantioselectivity using TAA compared to iPrOAc:
    - 63% ee to 81% e.e. using TaniaPhos
    - 87% ee to **94% e.e.** using WalPhos
  - Reduction in solvent volumes (60 to 12.5 vol)
  - Reduction in cat. & ligand loading
  - Yield increase: from ~10% to 30% to **65%**

Patent Reference: WO2014060900

Making the vinyl pyrimidine 1

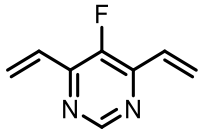


Suzuki-Miyaura chemistry

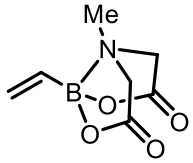


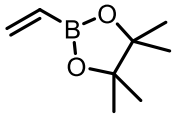
J. Org. Chem., 2006, **71**, 9681

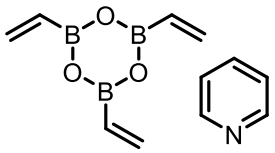
- Suzuki chemistry
  - Divinyl impurity difficult to purge
  - DoE/PCA approach with solvent, addition, concentration, catalyst (and loading), vinyl source, equivalents
  - Difficult to find conditions to minimise di-addition
  - And high cost of Pd cat. and vinyl reagent(s)

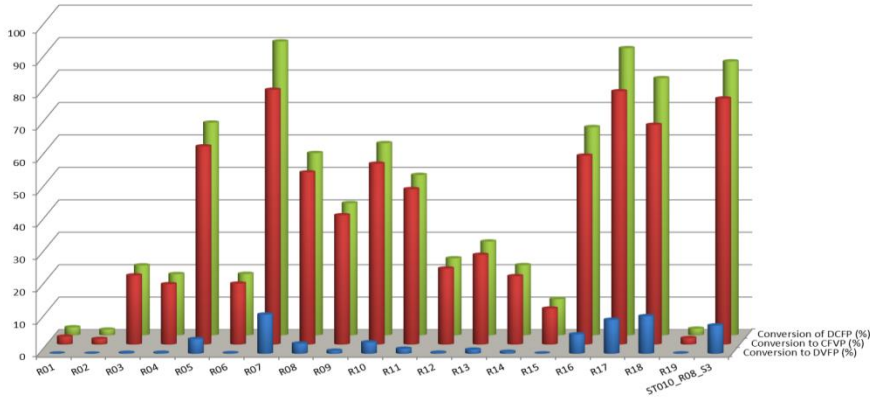


5-fluoro-4,6-divinylpyrimidine

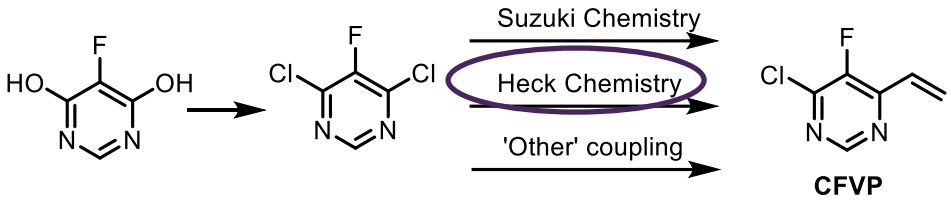




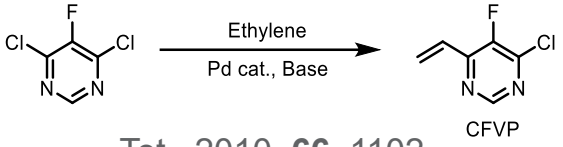




Making the vinyl pyrimidine 2

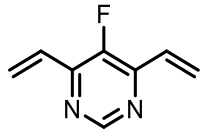


Heck-Mizoroki chemistry

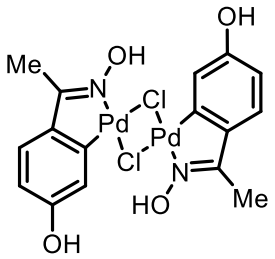


Tet., 2010, **66**, 1102

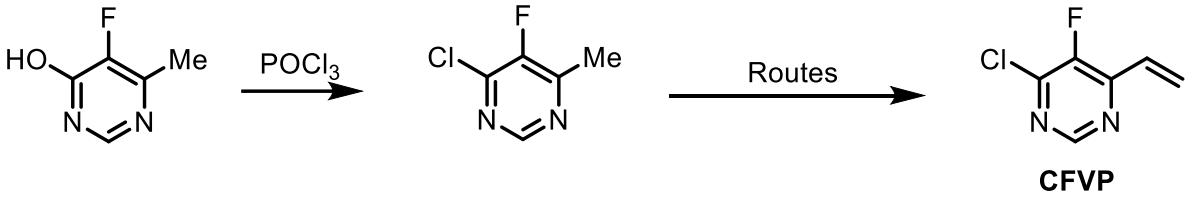
- Heck Chemistry:
  - Initial screen to scope out chemistry: catalyst, base and solvent:
    - Low conversion, with some divinyl impurity
  - 2nd screen: narrower catalyst scope, higher temperature, base
    - Higher temp important for conversion; KOAc/Najera palladacycle best results – but max 60% yield



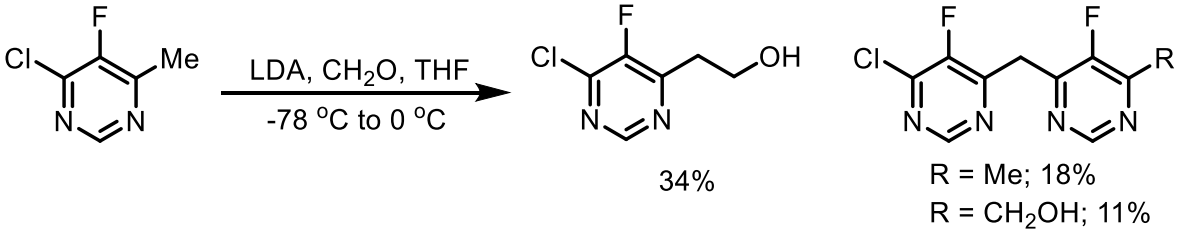
5-fluoro-4,6-divinylpyrimidine



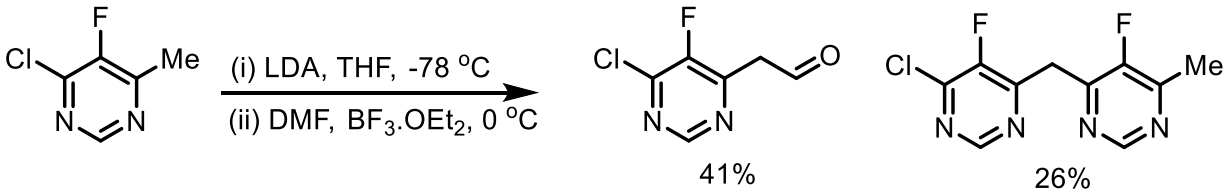
Making the vinyl pyrimidine -

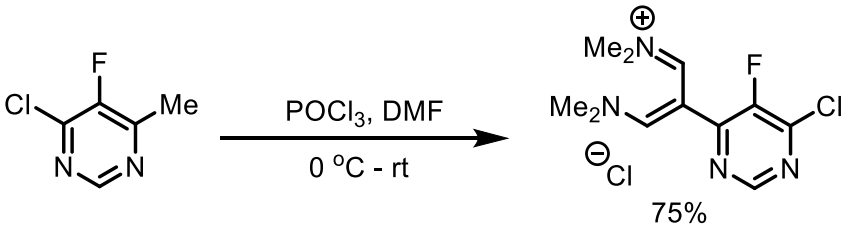


- Hydroxymethylation:



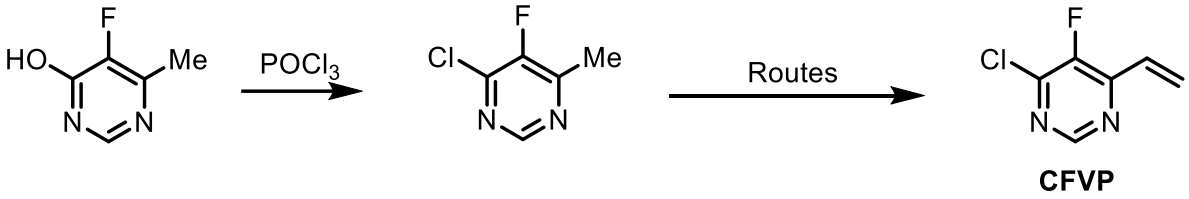
- Formylation:



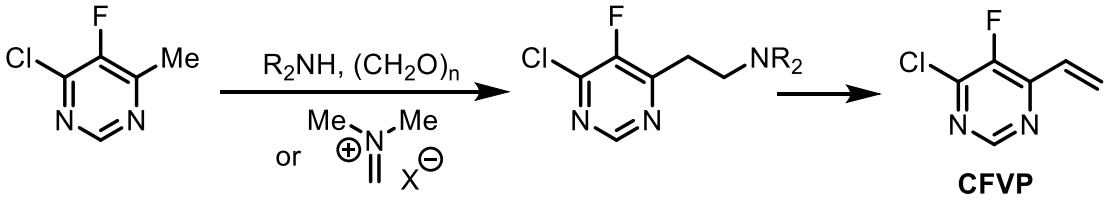


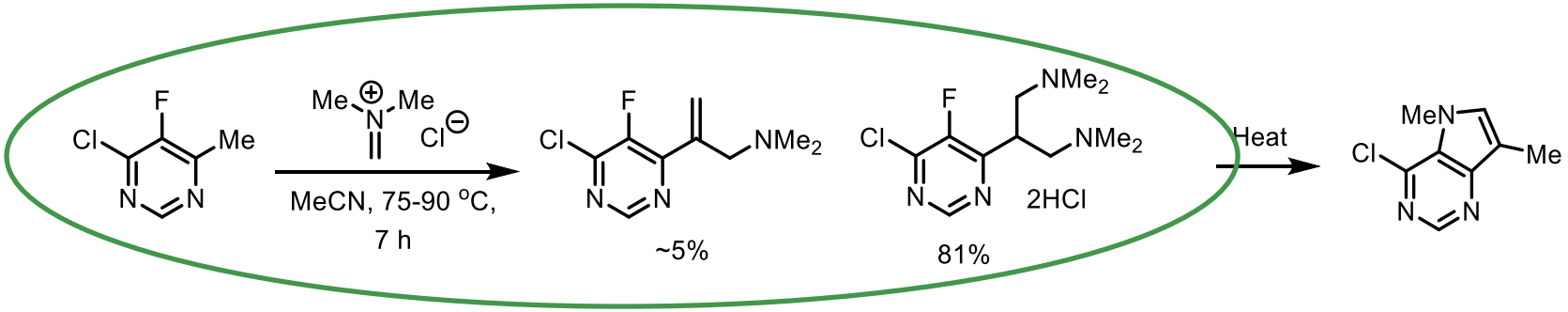
Patent Reference: WO2014060900

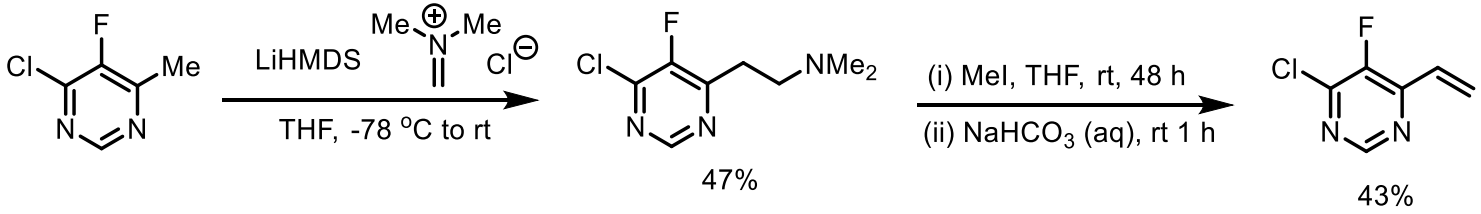
Making the vinyl pyrimidine – Mannich Routes



- Mannich Reaction:

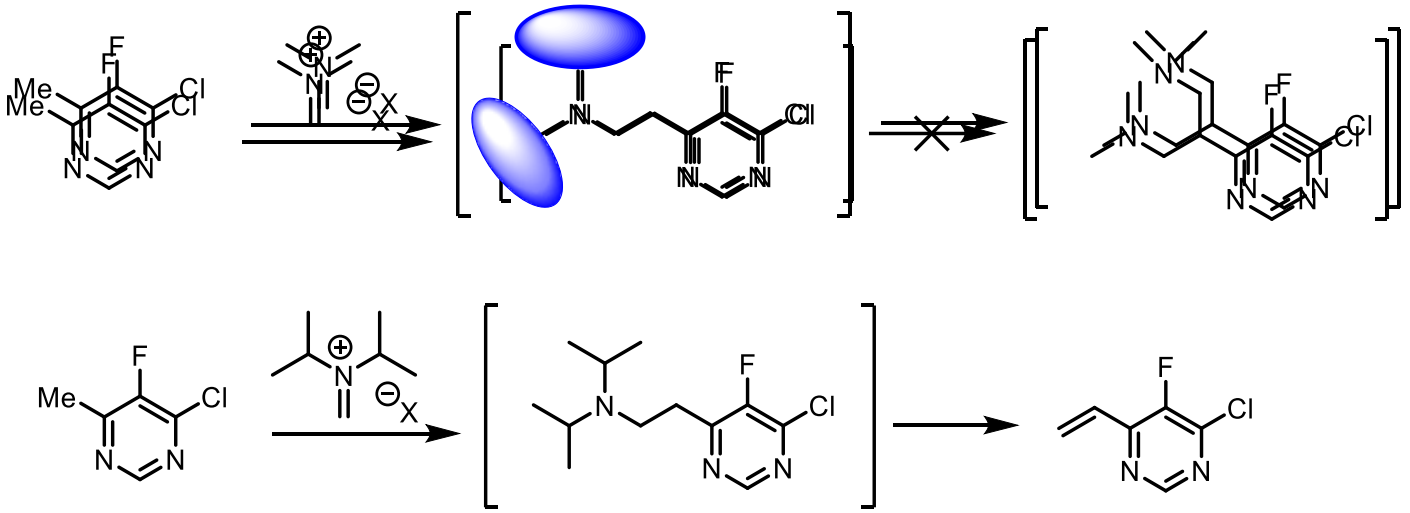




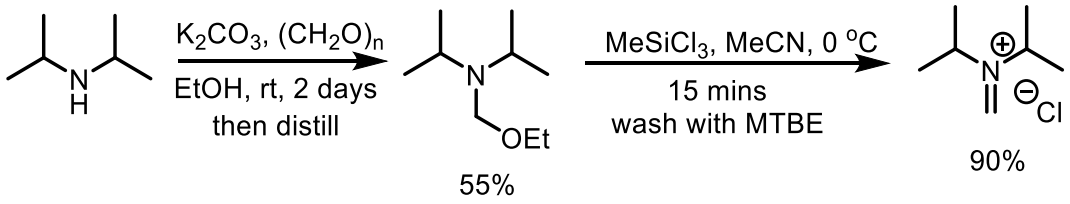


Patent Reference: WO2014060900

Optimised Mannich



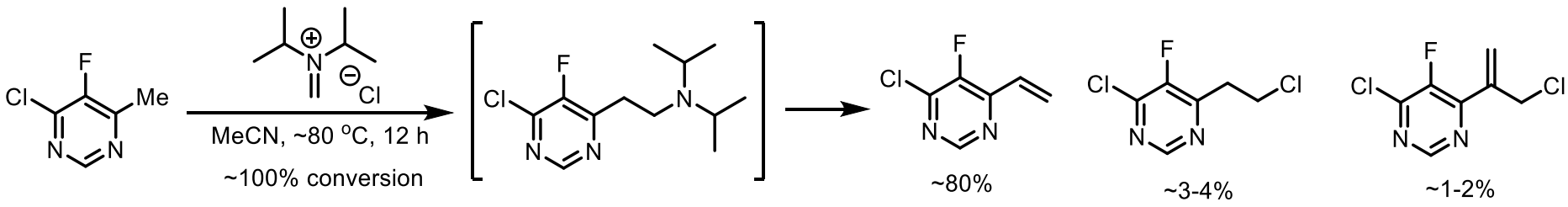
- Synthesis of ‘diisopropyl’ Eschenmoser salt



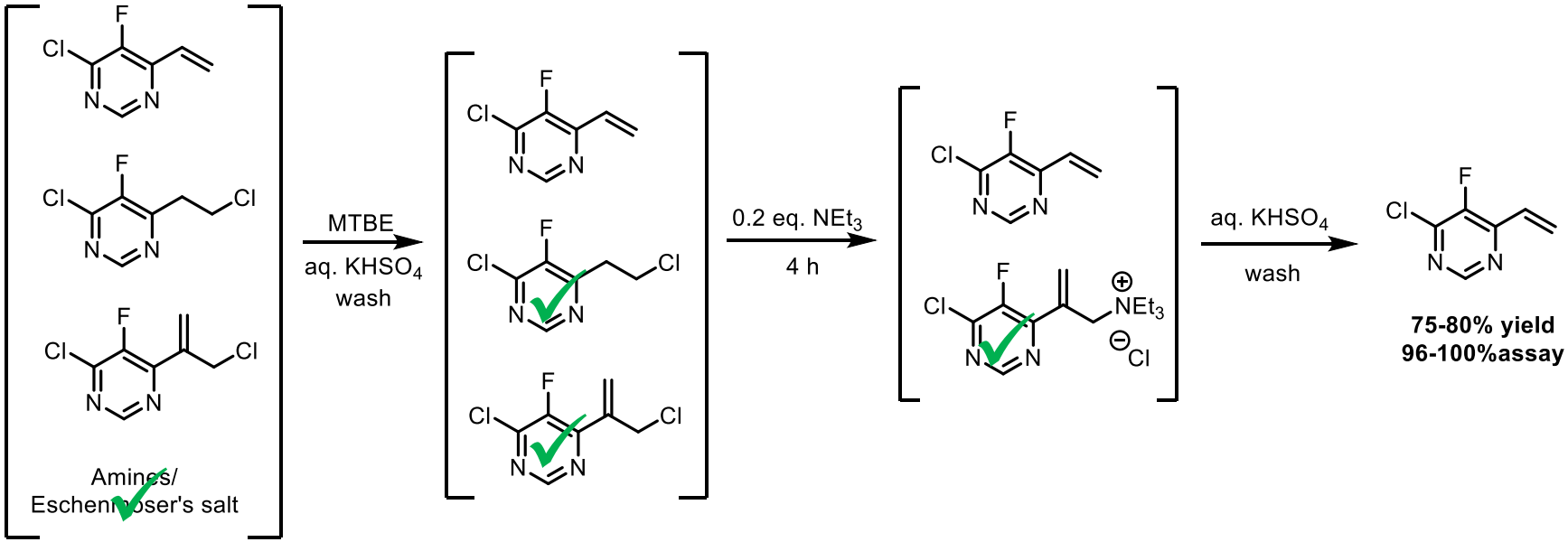
Tet. Lett, 1988, **29**, 2377

Optimised CFVP Synthesis

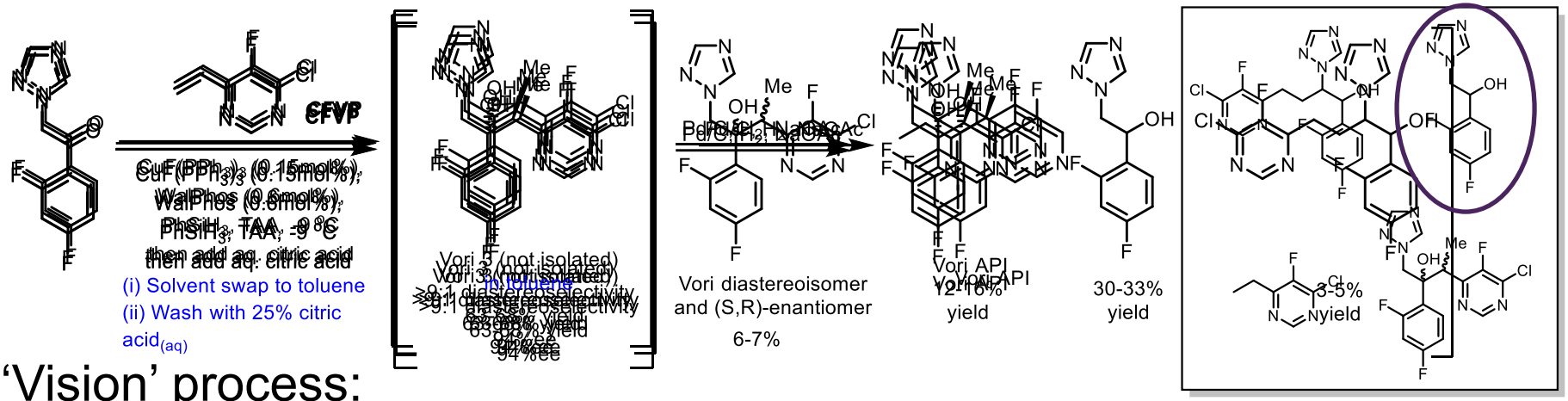
- Revised Mannich reaction:



- Reaction work up:



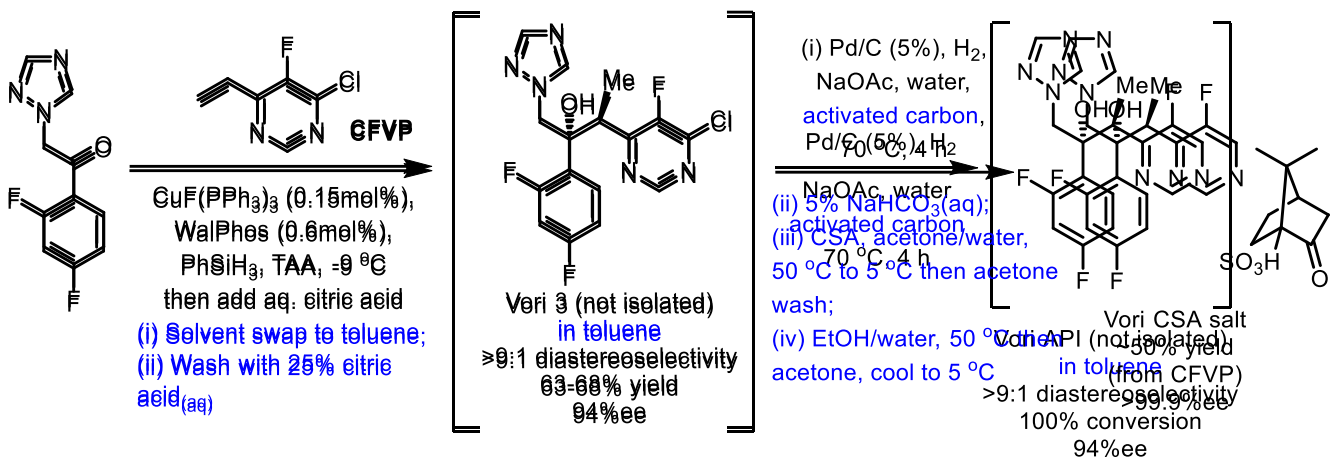
Overall Process Design 1

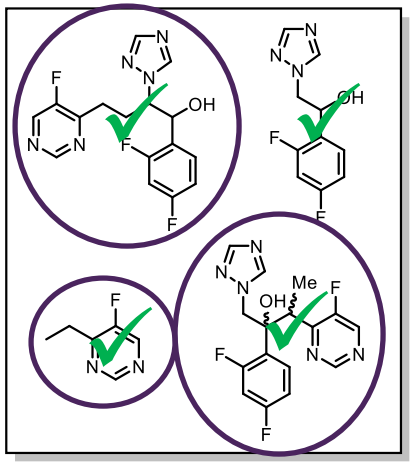


- 'Vision' process:
  - Reductive aldol reaction with direct telescope into hydrogenation
  - Isolation of API directly
- Hydrogenation very slow and concerns about impurity purge
- Clean up options considered:
  1. Aqueous washes directly post reaction troublesome
  2. Salt screen conducted for Vori 3
  3. Solvent swap to toluene plus aq citric acid excellent purge of key impurity (94% removal in 2 washes)

Patent Reference: WO2014060900

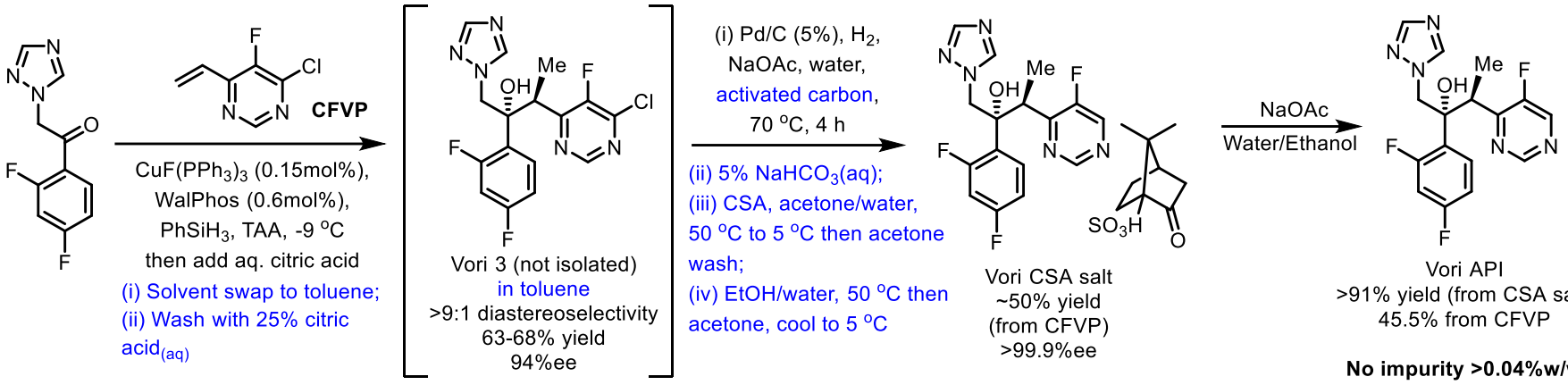
Overall Process Design 2



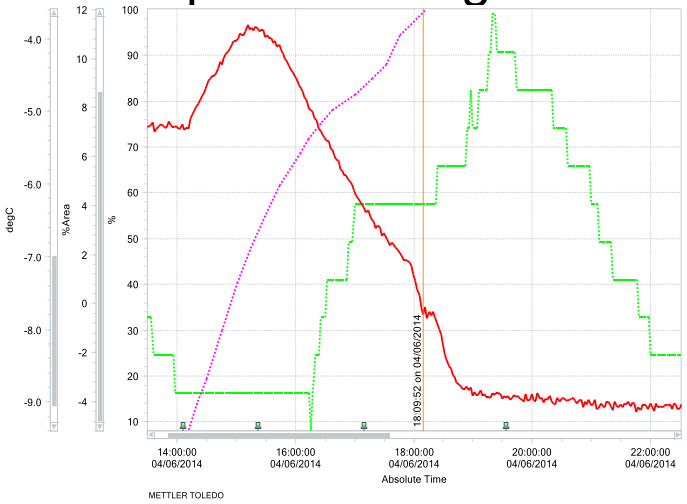


- Hydrogenation of Vori 3 in toluene (telescope)
- Direct precipitation of Vori API from reaction mixture not feasible
  - Quality upgrade required
- Isolation of CSA salt (as per 1st generation process)
  - Work up developed to remove salts (aq. $NaHCO_3$)
  - Precipitation of CSA salt from toluene (CSA in acetone/water)
  - Recrystallisation of CSA salt from aq. EtOH/acetone

Overall Process Design 3

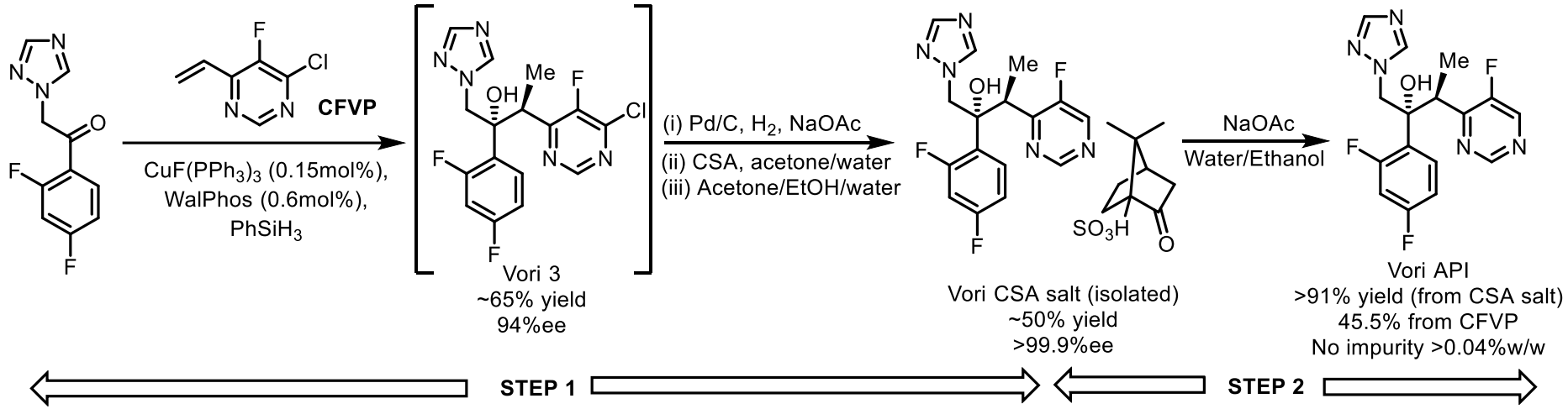


- Final step – salt break
  - As per 6th step in 1st generation process – minimise impact on Drug Product (e.g. tablet)
  - Excellent API quality obtained
- Now is Commercial Process:
  - Similar reaction profile and yield obtained
  - Monitor reaction using PAT (midIR)



Patent Reference: WO2014060900

Summary



- Successful development of route which meets targets
  - Quality: No new impurities >0.04%w/w
  - Cost: API cost <50% of current manufacturing route
  - Capacity: Less than 1st generation route
  - Supply base for new RSM (regulatory starting material) established
  - New IP for Pfizer
- Two isolation process
  - Overall yield >40% (vs <21% 1st gen)
  - Process validation successful ➔ filed as commercial process

Patent Reference: WO2014060900

Acknowledgements

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John Dillon
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Ringaskiddy API

Vori team

CRD

Alan Pettman
Adam Scott
Stuart Field
Alan Happe
Robert Singer

Procurement

David Nolan
Stephen Galvin

Pfizer gCMC

Consultants

Adesis

CatScI

Almac

Peakdale

LIOS

Thank You