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#RESEARCHNEVERSTOPS

Use of DoE to increase process understanding of a de-bromination reaction

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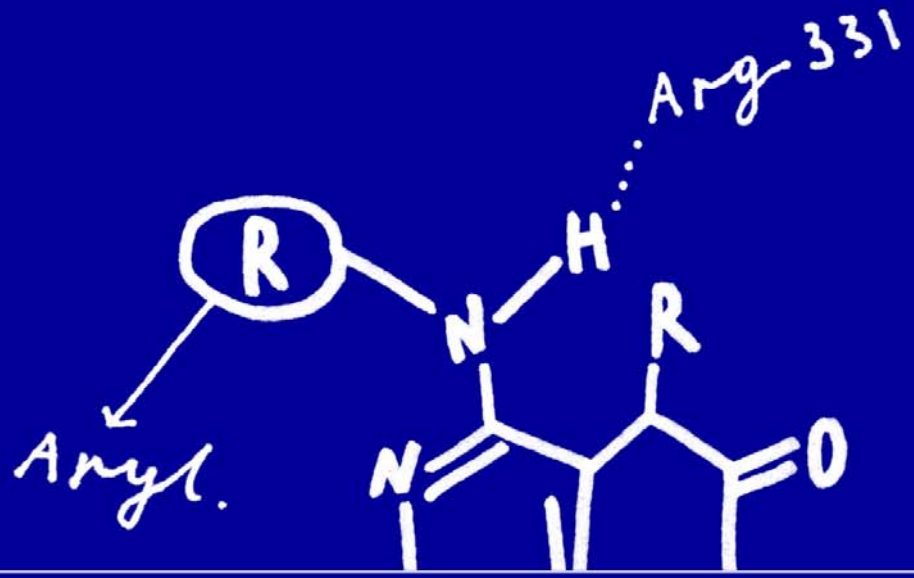
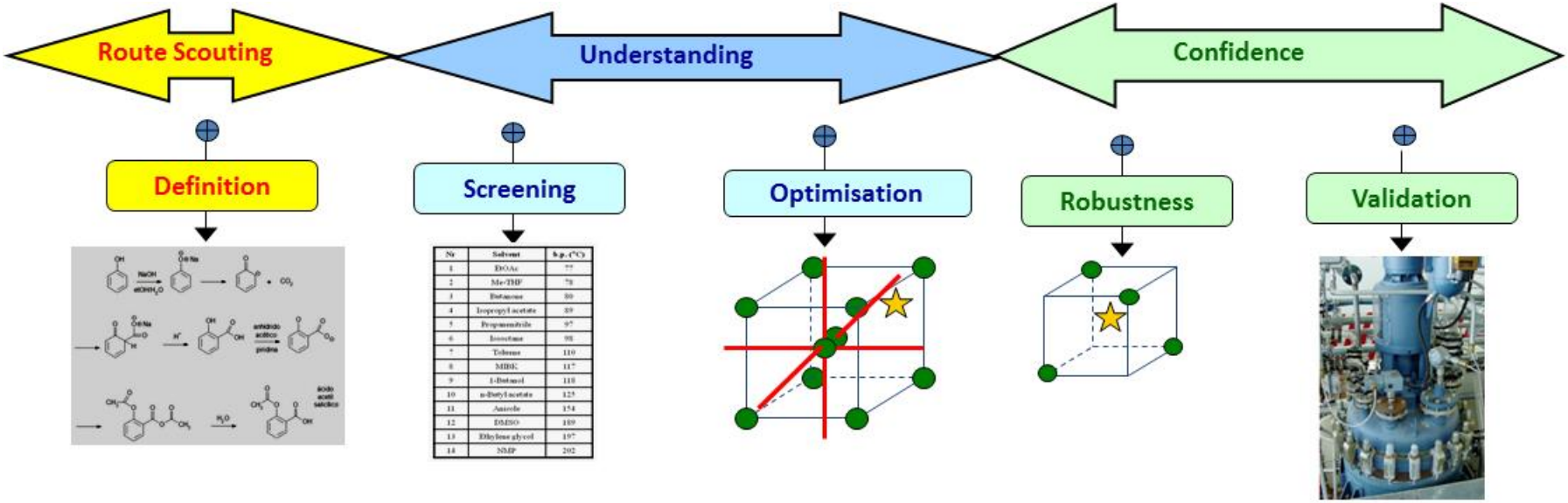


Development of a chemical process



Investigation and determination of the synthetic route

Definition of reagents, solvents, catalysts etc.

Identification of the best reaction conditions

Identification of the process critical parameters and reproducibility

Verification in Pilot plant

Ideal Synthetic Route

- ***Minimum number of steps***
- ***Fast and easy***
- ***Reagents commercially available and cheap***
- ***High yields***
- ***Minimum amount of by-products***
- ***Minimum amount of waste***
- ***Minimum quantity of solvents***
- ***Not expensive***
- ***Robust and Reproducible***
- ***Low risk of failure***
- ***No scale up issues***
- ***No chromatographic purifications***
- ***High purity of the final product***

Statistical methods

Some statistical tools (PCA, PLS and DoE) can be applied to each step of the development of the chemical route

Advantages:

- ***Lower number of reactions***
- ***Less time, especially if combined with parallel equipment***
- ***Better understanding of the chemical process***
- ***Higher precision in the determination of optimal values***
- ***Knowledge of the critical process parameters***
- ***Determination of the interactions among studied parameters***
- ***Evaluation of the robustness of the process***

Application of Statistical Tools to Chemistry

PCA-PLS: identify best Solvent/base/reagent combination

DoE Optimization: increase yield and reduce impurity formation

DoE Robustness: increase confidence of the process

Understanding

Confidence

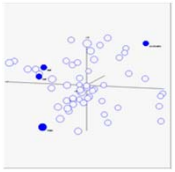
Screening

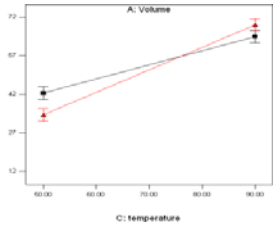
Optimization

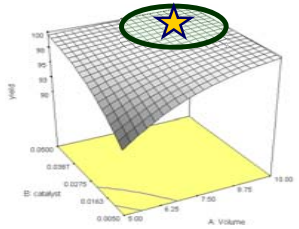
Robustness

Verification in Pilot Plant

Nr	Solvent	b.p. (°C)
1	EtOAc	77
2	Me-THF	78
3	Butanone	80
4	Isopropyl acetate	89
5	Propionitrile	97
6	Isooctane	98
7	Toluene	110
8	MIBK	117
9	1-Butanol	118
10	n-Butyl acetate	125
11	Anisole	154
12	DMSO	189
13	Ethylene glycol	197
14	NMP	202







Resistance to statistical tools

Despite these advantages, a high resistance to use statistical tools is encountered

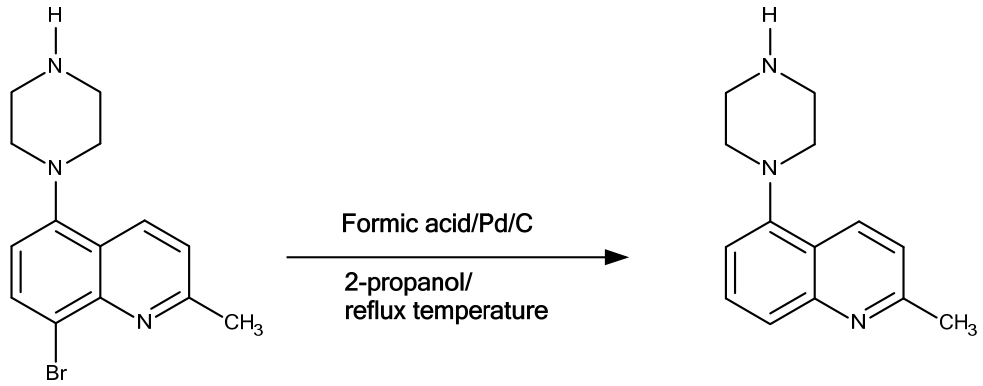
Main reasons:

- ***We don't have enough time to do it***
- ***We can understand everything with a reduced number of reactions***
- ***I can change one parameter at time and optimize the reaction***
- ***We don't need process understanding: if it works in lab, it will work in the pilot plant***
- ***I'm a chemist, not a statistic***

Case study

- *A case study will be presented where the DoE was applied successfully to a chemical reaction*
- *The reaction was previously tried in lab*
- *Some “a priori” considerations were applied to the chemistry*
- *No systematic study carried out*
- *Process understanding needed to reduce impurity formation*
- *Reproducibility and robustness not tested*
- *Used parallel equipment to reduce time*

De-bromination via catalytic transfer hydrogenation (CTH)

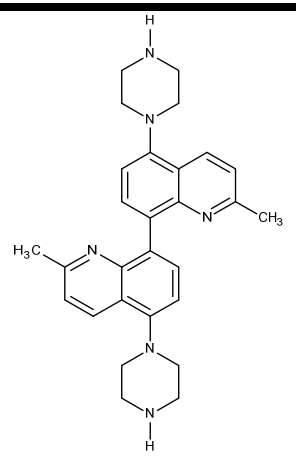


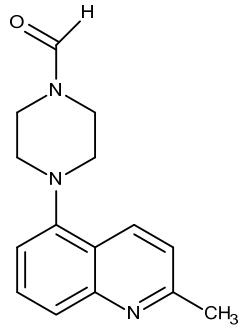
- *Catalyst: Pd/C 5% (0.3wt/wt)*
- *Hydrogen donor: formic acid (2eq)*
- *Solvent: 2-propanol*
- *Temperature: reflux (ca.82℃)*
- *Conversion: ca. 95%a/a after 3hrs*

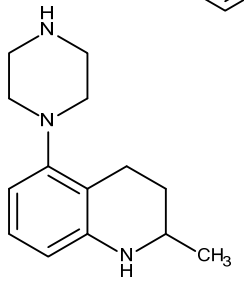
Main Issues

Formation of 3 main impurities

- *Dimer= ca.0.5%*
- *Formyl= ca.2% after 3hrs, ca.4% after 6hrs*
- *Tetrahydro= ca.2% after 3hrs, ca.6% after 6hrs*
- *Total Imps= ca.5% after 3hrs*
- *All impurities (except for the formyl) can react in the following step interfering with the precipitation of the API*
- *Final API obtained contaminated with the wrong crystalline form*







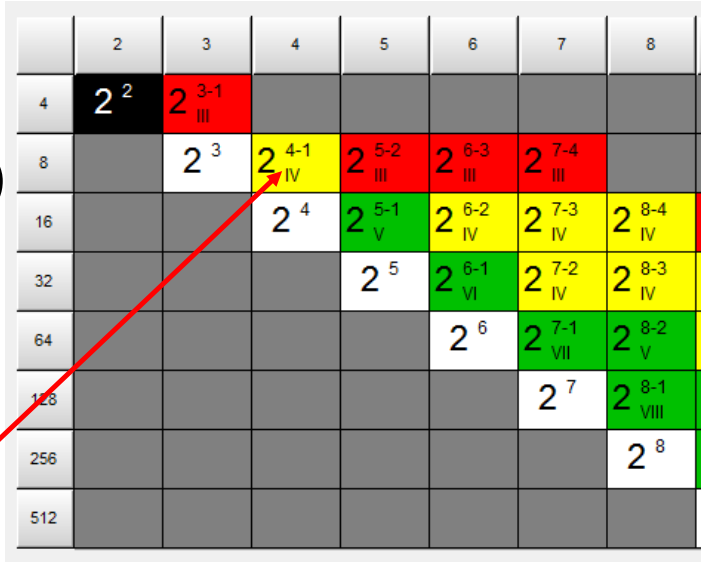
Initial information

- ***High quantity of formic acid used to generate the required amount of hydrogen***
- ***High quantity of catalyst needed to obtain a good conversion***
- ***High amount of formyl imp can be reduced by using a high amount of catalyst***
- ***High temperature to increase reaction rate***
- ***Reaction must be stopped after 3hrs to reduce impurity formation and degradation of final product***

DoE on the CTH

A DoE was carried out to define better reaction conditions and increase robustness

- ***Objectives:***
  1. ***Increase the yield up to 97%***
  2. ***Reduce each impurity below 0.5% (Formyl<1%)***



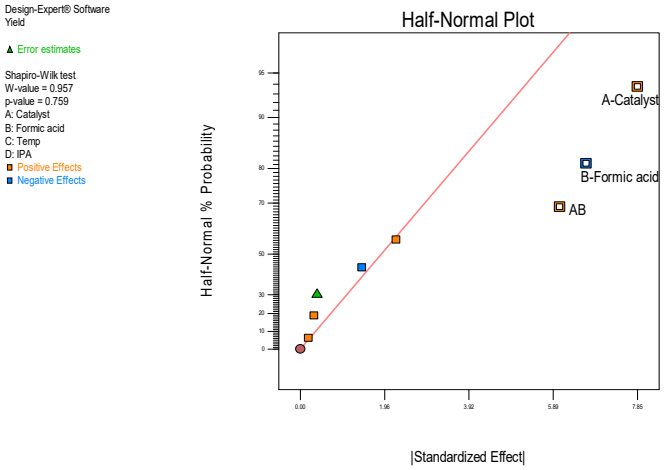
Four factors considered

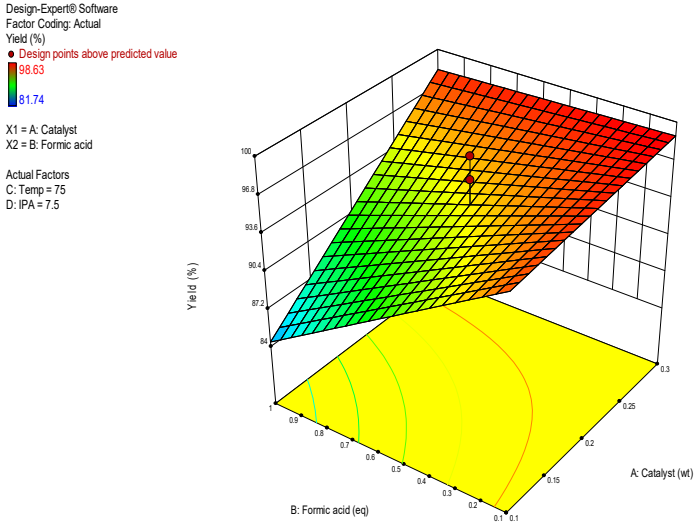
1. ***Quantity of catalyst***
2. ***Quantity of formic acid***
3. ***Temperature***
4. ***Concentration***

A yellow Fractional Factorial Design was selected to identify main factors and interactions when not aliased

Ten reactions were carried out using parallel equipment (1block, two center points)

Yield



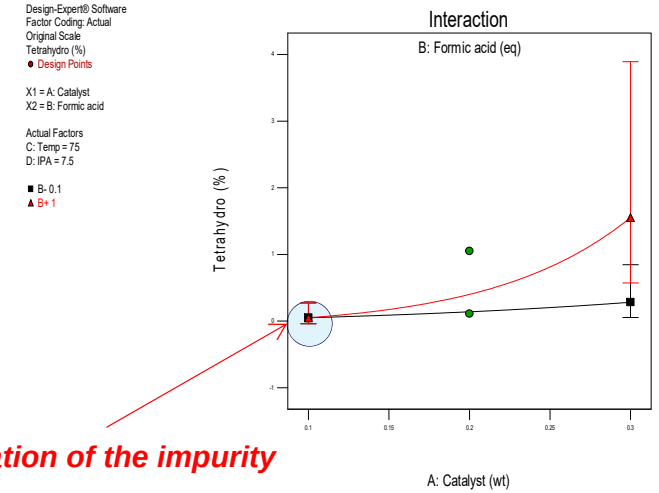


Response range between 81.7 and 98.6%
Factors affecting the yield:

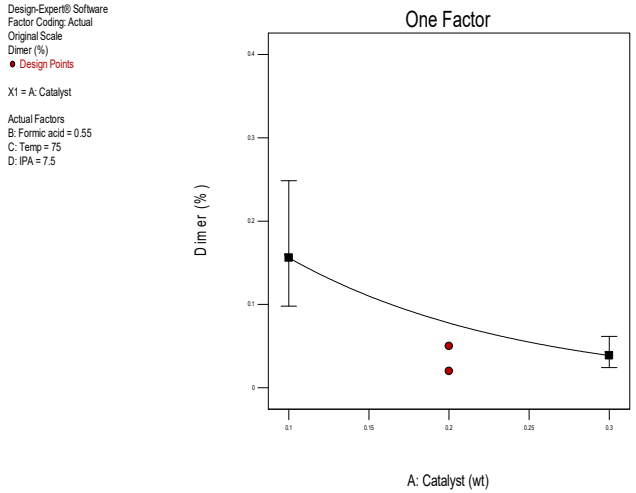
A) Catalyst
B) Formic acid
AB) Interaction Pd-HCOOH

High conversions: low quantities of formic acid and high quantities of catalyst
Effect of the catalyst highly reduced when using a low quantity of acid

Tetrahydro and Dimer Impurities



No formation of the impurity



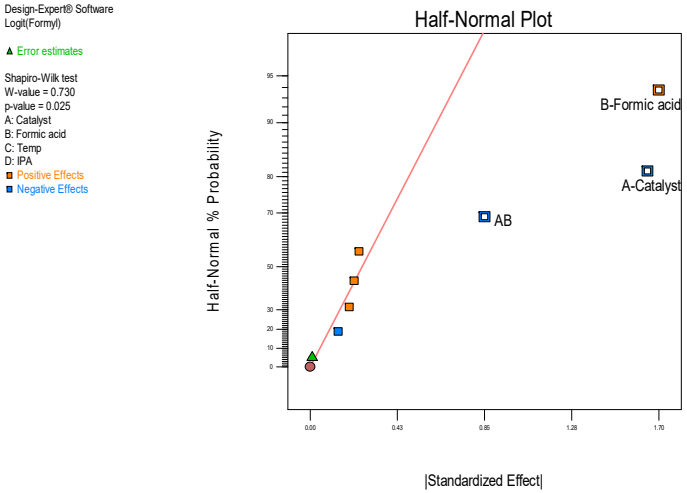
Tetrahydro (range from 0 to 2.2%)

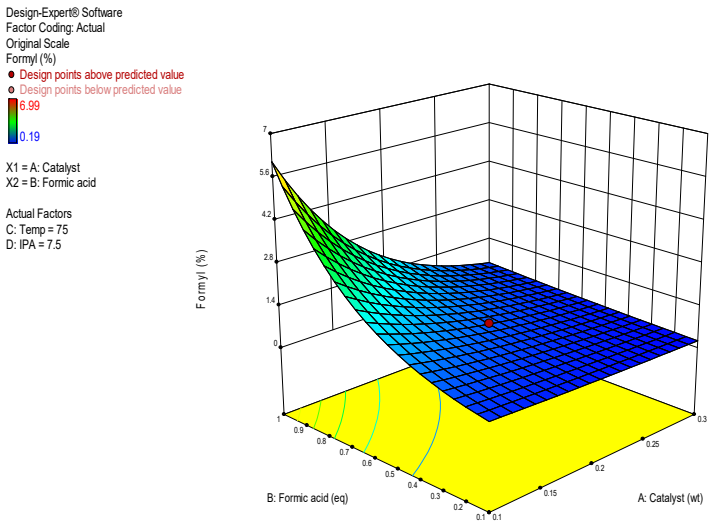
- ***A) Catalyst***
- ***AB) Interaction Pd-HCOOH***
- ***B) Quantity of formic acid***

Dimer (range from 0.02 to 0.33%:

- ***A) Catalyst***

Formyl Impurity





Response range between 0.19 and 6.9%

Factors affecting the formation of the Formyl Impurity:

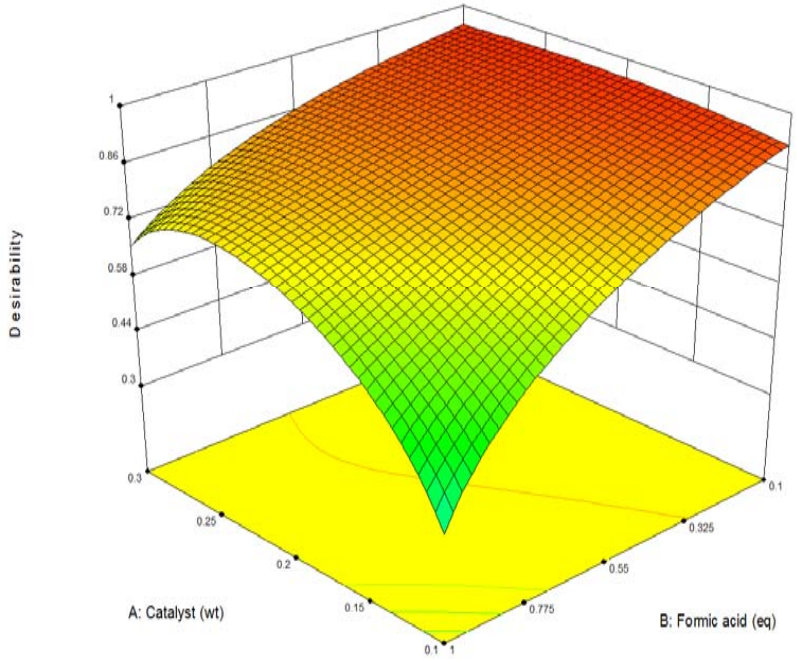
A) Catalyst

B) Formic acid

AB) Interaction Pd-HCOOH

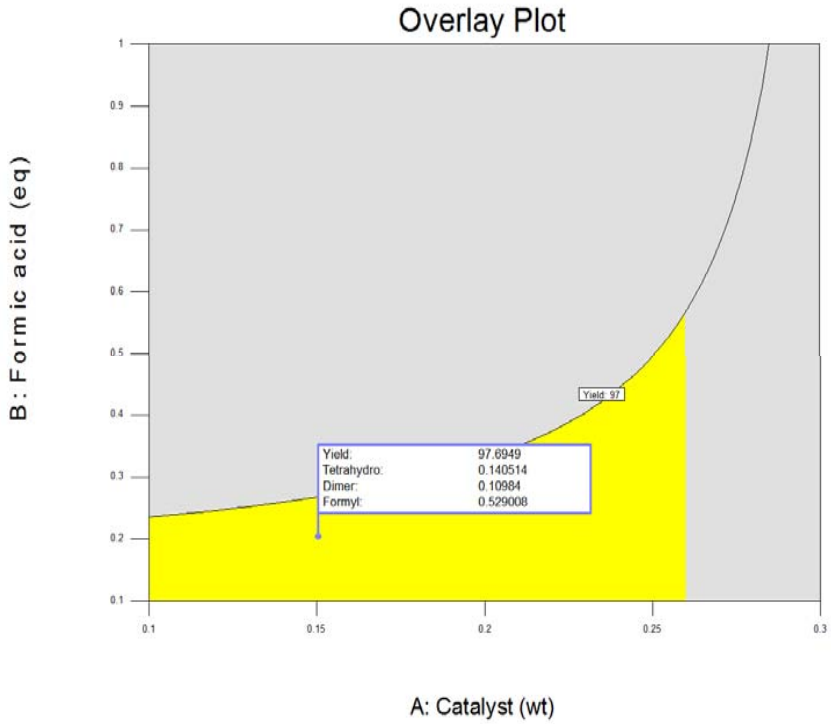
DoE results: Summary

- ***A strong interaction between formic acid and catalyst was highlighted***
- ***The quantity of formic acid was reduced improving the impurity profile, but without affecting the yield***
- ***Thanks to the interaction, expensive Palladium was reduced***
- ***Solvent didn't affect the responses, so was reduced, increasing the capacity of the reactor***

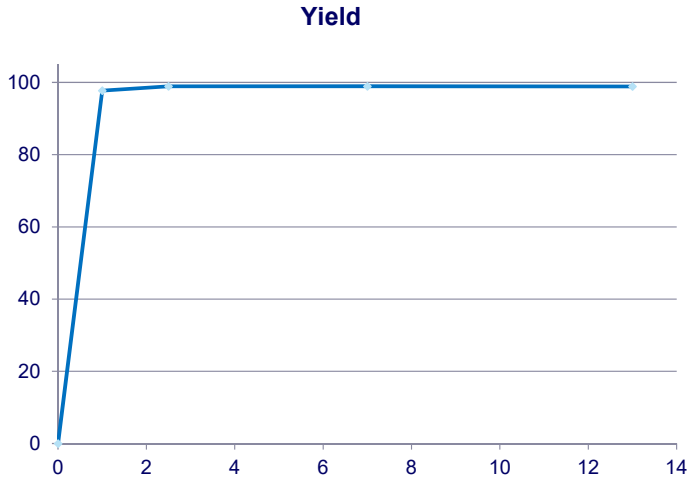


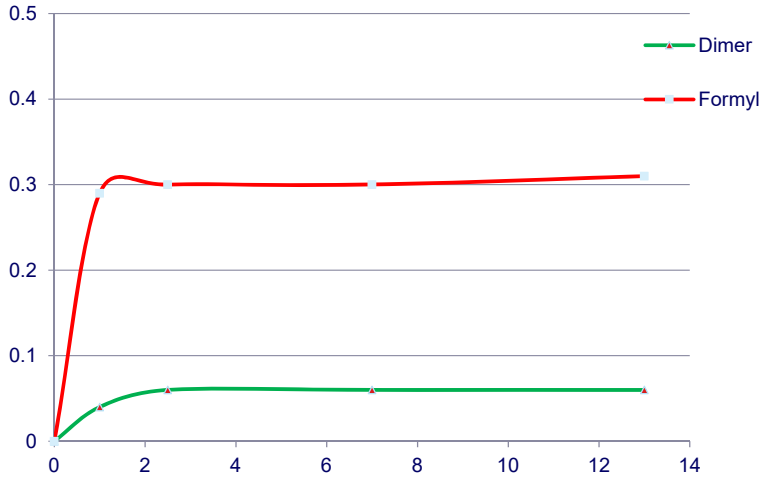
Robustness

- *New conditions were moved towards a more robust region*
- *Pd reduced from 0.3 to 0.15wt/wt*
- *Formic acid from 2 to 1.2eq*
- *New conditions tested on a small scale in lab*
- *Results after 2.5hrs:*
  - *Yield=98.9%*
  - *Tetrahydro imp=n.d.*
  - *Dimer=0.06%a/a*
  - *Formyl imp=0.3%a/a*



Reaction and impurity kinetic





- ***Reaction fast: almost complete conversion after 1hr***
- ***Reaction stable with time***
- ***No formation of the two impurities after 2.5hrs (effect of reduced formic acid)***

Reaction scale up

- *Reaction tested in the JLR (kilo-labo) giving very good results*
- *Scale up in the Pilot Plant Verona*
- *Obtained 11.3kg of solid product*
- *Yield= ca.75% including crystallization*
- *Assay= 99.75%a/a*
- *Product used to test following steps*
- *Final API obtained with good assay (99.2%w/w) and suitable solid form*
- *No major issues observed*

Conclusions

The DoE was applied successfully to a chemical reaction, reaching the following targets:

- ***Process understanding***
- ***Interactions between parameters identified***
- ***Yield increased***
- ***Impurities reduced***
- ***Expensive catalyst loading reduced***
- ***Robust region identified***
- ***Ca. 1 week work***
- ***Reaction moved to Pilot Plant obtaining expected results***

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QUESTIONS AND ANSWERS