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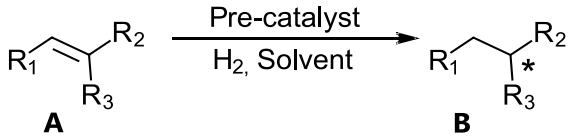
BEYOND PROCESS CHEMISTRY

Process Development Whitepaper
SCALE-UP
Optimisation of an Asymmetric Hydrogenation

INTRODUCTION

A key step in the production of an active pharmaceutical ingredient (API) required the installation of a **tertiary chiral centre** to afford the enantiomerically pure alkane **B**. While this could be obtained from the racemic alkane by a classical resolution, the overall yield for this resolution step was only 26%. Alternatively, the prospect of an **asymmetric hydrogenation** of tri-substituted alkene **A** to alkane **B** in high solution yield made this approach an attractive option. However, this transformation proved capricious, resulting in much variability, including poor conversions and low enantioselectivity.



PROJECT PLAN

In order to gain a **fuller understanding** of this catalytic reaction and precipitate the development of a manufacturing process, **key stress testing** and **robustness studies** were conducted taking advantage of our in-house Endeavor™ **parallel multi-reactor hydrogenator**. The following factors were studied, the impact of each of which is discussed below:

- Oxygen level
- Water content
- Catalyst loading
- Hold time
- Starting material quality
- Isolation

OXYGEN LEVEL

Studies on the effect of the **presence of oxygen** before and after the initiation of the catalytic cycle showed that the catalysis was completely inhibited when the active catalytic cycle was exposed to air. However, exposure of the pre-catalyst/reagent mixture to air prior to the initiation of the catalytic cycle had **no apparent adverse effect** on reaction, either in terms of conversion or enantioselectivity. Consequently, re-initiation of the catalytic cycle was possible with a charge of **fresh pre-catalyst** with minimal impact on reaction, including on the impurity profile.

WATER CONTENT

The robustness of the catalysis towards **water** was tested empirically by spiking experiments with different levels of water. Water was found to have **no detrimental effect** on the enantioselectivity. However, the reaction rate was significantly reduced with higher water levels such that over the standard reaction period of 16 hours conversion was significantly reduced (Table).

CATALYST LOADING

Catalyst loading was varied to determine the sensitivity to this key factor and the edge of failure. Screening experiments with different catalyst loadings (1-5 mol%) were performed in duplicate. These showed that a catalyst loading of 4-5 mol% gave excellent reaction performance and reliability (typically 96-97% conversion, 94-95% e.e.). A lower catalyst loading of 2-3 mol% was found to be possible in an alternative reaction solvent, but this solvent could not be used for a number of other reasons. Although a **5 mol% catalyst loading** was higher than desired, this was more than acceptable given the **significant improvement** in material yield obtained from this alternative process.

STARTING MATERIAL QUALITY

The success of this asymmetric hydrogenation was found to be heavily dependent on the **quality** of the input **starting material** alkene **A**. Variable results and poor performance were postulated to be due to inhibition of the catalysis by trace impurities and/or the high boiling alcohol solvent carried over from the previous step. Poisoning studies were thus conducted to determine the effect of residual alcohol (**Table**). It turned out that the reaction was unaffected when low levels of the alcohol were present (0.5 equivalents) but it suffered serious inhibition with a high level of the alcohol (5 equivalents).

Conditions	Conv. (%)	e.e. (%)
Control reaction	98	88
Water (0.4 w/w %)	93	85
Water (4 w/w %)	52	85
Catalyst loading (3 mol%)	43	91
Catalyst loading (5 mol%)	97	94
Alcohol (0.5 equiv.)	96	83
Alcohol (5 equiv.)	35	30
Optimised process	***100***	***95***

Table – standard reaction conditions: 5 mol% pre-catalyst, solvent, H_2 (7 bar), 50 °C, 16 h

The asymmetric hydrogenation of crude input alkene **A** resulted typically in both poor conversion and poor enantioselectivity (48-70% conversion, 6-23% e.e.), whereas purified **A** gave high conversion in good

enantiomeric excess reliably. This suggested that **removal** of residual alcohol and/or other **impurities** was **critical** to the success of the subsequent catalytic reaction.

ISOLATION

The original **isolation process** for alkene **A** was simply an **aqueous drown-out**. Improvements to this isolation process, first by slurry washing with an organic solvent, then followed by a crystallisation, resulted in gradually more reliable results. Finally, an optimised **crystallisation process** was developed, avoiding the drown-out and the slurry washing, delivering the requisite alkane **B** in an isolated yield of 77-80% in >98% purity. Purified alkene **A** from this isolation procedure reliably underwent the asymmetric hydrogenation reaction, resulting in **100% conversion and >95% e.e**. against targets of >99% conversion and >92% e.e.

CONCLUSIONS

Robustness and stress testing studies to explore the reaction space helped to establish the edge of failure for **several key reaction parameters** in this asymmetric hydrogenation. Of critical importance to the understanding of this process, controlling the input quality of the starting material proved to be the most significant to avoid poisoning the catalytic reaction. By identifying this factor, simple sequential improvements to the purification of starting material were made which enabled a **robust** and **high-yielding reaction** (100% conversion) to be developed with **high enantioselectivity** (>95% e.e.).

Overall, this **new asymmetric hydrogenation process**, in comparison to the more wasteful classical resolution, illustrates the great potential for beneficial impact in pharmaceutical manufacturing that can be uncovered through exploitation of **good catalysis** and **rigorous process research and development**.

Want to find out more?
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