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# Asymmetric Catalysis: Rhodium-Catalyzed Hydrogenation for Tetrasubstituted Alkenes

Case Study

## About the client

A US-based pharmaceutical company that produces the key starting material for an API, which is currently in Phase II clinical trials for an autoimmune disease.

## Client objectives

While our client had been able to produce enough API for Phase I trials, one of the key challenges during the 5-step synthesis required for preparation of a key intermediate was the reduction of the α, β-unsaturated methyl ester 1 to give the hydrogenated product 2, containing two contiguous chiral centers, Figure 1. While this had been achieved by the client in good enantioselectivity with low loading through use of a Rhodium-DuPhos chiral catalyst, further optimization could realize improvements in yield and reproducibility.

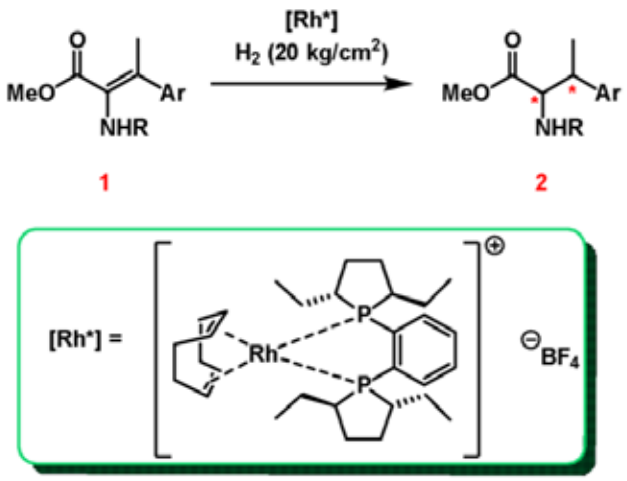


**Figure 1:** General scheme for asymmetric hydrogenation of the α,β-unsaturated methyl ester with the chiral Rh catalyst, Rh660.

Neuland scientists set out to optimize the process-scale reduction, provide proof-of-concept on a 3–5 kg batch and finally manufacture the material on 100 kg scale. In all cases, control of purity, yield and enantioselectivity was crucial.

## Key challenges: Large-scale enantioselective hydrogenation of tetrasubstituted alkenes

Asymmetric hydrogenation has long been a prevalent area of research, with the 2001 Nobel Prize for Chemistry awarded to Noyori and Knowles for utilizing Rh(I)- and Ru(II)-diphosphine chiral catalyst systems [1]. Due to these scientists' pioneering work, enantioselective reduction of alkenes has become a key method for preparing chiral materials, especially in the manufacture of pharmaceuticals and APIs, with key bioactive molecules utilizing Rh-mediated enantioselective hydrogenation [2] in synthesis including PCO371 [3], (S)-naproxen [4] and L-dopa [5].

While enantioselective hydrogenation of di- and tri-substituted alkenes is routine, selective reduction of tetrasubstituted olefins through hydrogenation is much more challenging. There are several ways to achieve this published in the literature, usually by exploitation of a transition metal catalyst such as rhodium, iridium, ruthenium and palladium, but the alkene substrates regularly suffer from low reactivity due to high steric congestion, leading to diminished yields and poor enantioexcesses [6]. To add to the

## Key outcomes

01 On 100 kg scale, the chiral product was isolated with excellent purity (>99%), enantioselectivity (>99%) and yield (>85%).

02 Reduction of hydrogen gas pressure also gave substantial safety gains.

03 These interventions meant low catalyst loadings (0.05 mol%) were possible, significantly reducing costs.

04 Nitrogen and hydrogen purge cycles were necessary to remove traces of dissolved oxygen from the reaction mass prior to addition of catalyst.

05 Exclusion of all oxygen and moisture during storage and weighing of the rhodium catalyst was crucial.

06 Cleaning and passivation between runs were key for excellent enantioselectivity and yield.

challenge, the transition metal catalysts required are not simple to work with; they are often highly sensitive to oxygen and moisture, and expensive. In addition, during the manufacture of pharmaceuticals the use of a transition metals can lead to contamination of APIs with residual metal, therefore low catalyst loadings and efficient purification are crucial, but this can add time and cost to a process, as well as harm environmental credentials.

## When considering the brief from the client, scientists at Neuland deduced that there were five main areas to address:

1. **Enantioselectivity:** >99% ee was the gold standard and had already been achieved by the customer, albeit on small scale with higher catalyst loadings than desired.

2. **Handing of the catalyst:** The Rh catalyst was highly sensitive to oxygen and moisture, with diminished yield and enantioexcess observed upon exposure to either.

3. **Catalyst loading:** The catalyst, Rh660, is expensive, therefore low catalyst loading was desirable. In addition, using larger quantities of catalyst means that traces of metal in the API precursor were more likely, with a 100 kg scale likely requiring multiple purification procedures, adding time and cost.

4. **Hydrogen pressure:** During process optimization by the client, hydrogen pressures of ~20 kg/cm2 were used, however this high pressure meant that there were significant issues surrounding safety.

5. **Oxygen:** It was noted that a stringently oxygen-free environment was essential for complete conversion, maintenance of catalytic turnover and high enantiomeric excess.

## Neuland's approach: drawing on key in-house expertise

### Cleanliness was crucial

Neuland has significant expertise in the use of transition metals for catalysis, especially those that are sensitive to oxygen and moisture [7]. During process optimization and preparation of demonstrative batches on 5 kg scale, it was rapidly realized that thorough cleaning and passivation between each run was required for effective hydrogenation and maintenance of catalytic efficiency.

### Work with reagents, not against them

The handling of the catalyst prior to reaction was key, with use of a glove box under nitrogen gas and exclusion of moisture when weighing the materials necessary to prevent water- and oxygen-mediated catalyst degradation, which caused lower yields and diminished enantioselectivity. In addition, sequential nitrogen and hydrogen purge cycles of the bulk reaction material to remove trace oxygen before the reaction proceeded were also required.

### High pressure isn't everything

Finally, while the client had optimized the process with hydrogen pressures of 20 kg/cm2, experiments by Neuland revealed that hydrogen pressures of only 7 kg/cm2 were required for complete reduction.

## Outcomes: Excellent enantioexcess with lower catalyst loadings on 100 kg scale

By considering the challenges to this reduction in a stepwise manner and ensuring protocols were in place to address them, Neuland scientists were able to successfully optimize the asymmetric hydrogenation process with successful scale-up from 5 kg to 100 kg achieved. In addition, catalyst loading was reduced to 0.05 mol%, reducing costs, and hydrogen pressure was reduced to 7 – 10 kg/cm2, improving safety. Importantly, through the scientists' diligence, excellent purity (>99%), enantioselectivity (>99%), and yield (>85%) were maintained, even at 100 kg throughput, Figure 2.

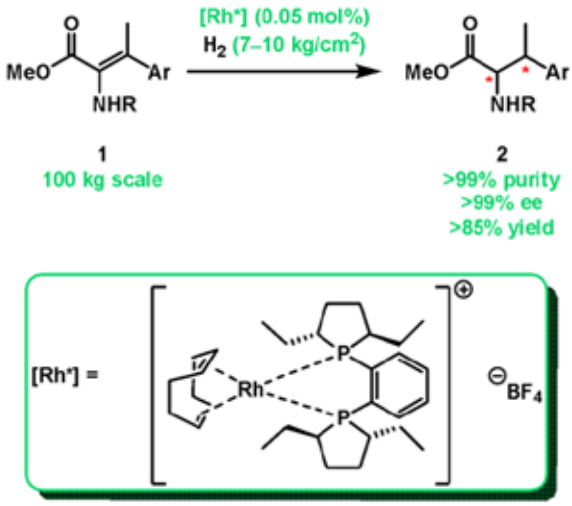


**Figure 2:** Neuland scientists prepared the required API precursor on 100 kg scale with excellent yield, purity and enantioexcess, reproducibly.

## Conclusion: Keep your experts close and your catalysts closer

Key to Neuland's success was understanding the limitations of the chiral rhodium reagent and the challenges surrounding asymmetric reduction of tetrasubstituted alkenes. Due to the nature of the substrate, alternative catalysts were not available, therefore optimization of procedures relied upon ensuring that the catalyst was working at maximum efficiency and that measures were in place to control exposure to oxygen and moisture, both during weighing and the hydrogenation itself. Reduction of the hydrogenation pressure is a key safety feature, and thorough cleaning and passivation between runs ensured that trace contaminants from previous runs were removed. It is this attention to detail and diligence during the process development that sets Neuland apart from the competition.

## About Neuland

A global CDMO, Neuland delivers success for biotechnology and pharmaceutical clients seeking complex APIs at all phases of the product life cycle. Their strength lies in overcoming complex chemistry challenges to advance drugs to market, having completed more than 150 NCE projects for custom APIs and developed more than 300 API processes. In business for more than 40 years, with 500+ clients in more than 80 countries, Neuland boasts an impeccable record of quality standards. Make Neuland your strategic partner for improved process efficiency, quality, and ultimately, faster time-to-market for your drug product.

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