

# Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective in Chemical Process

## Research and Development

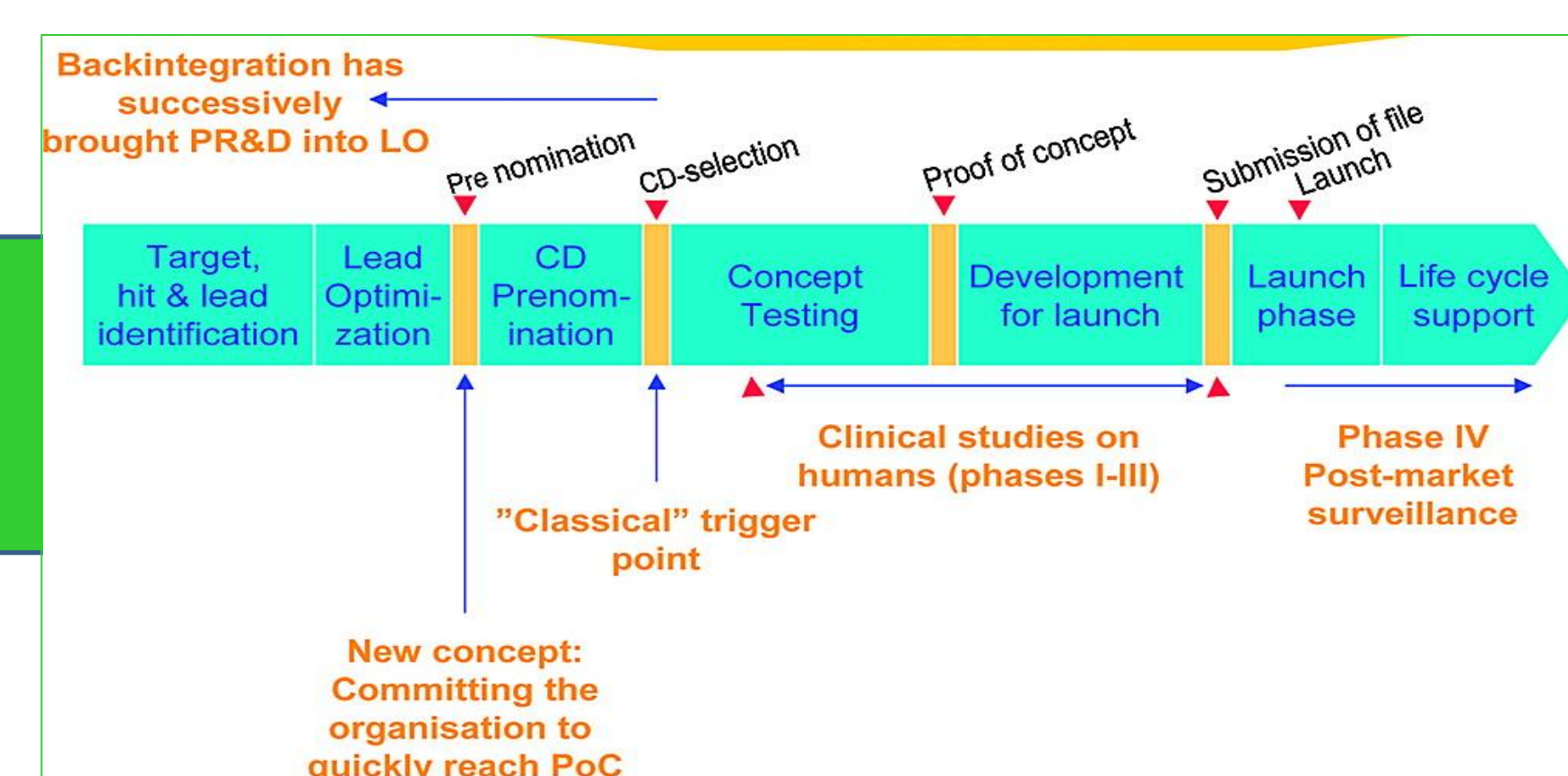
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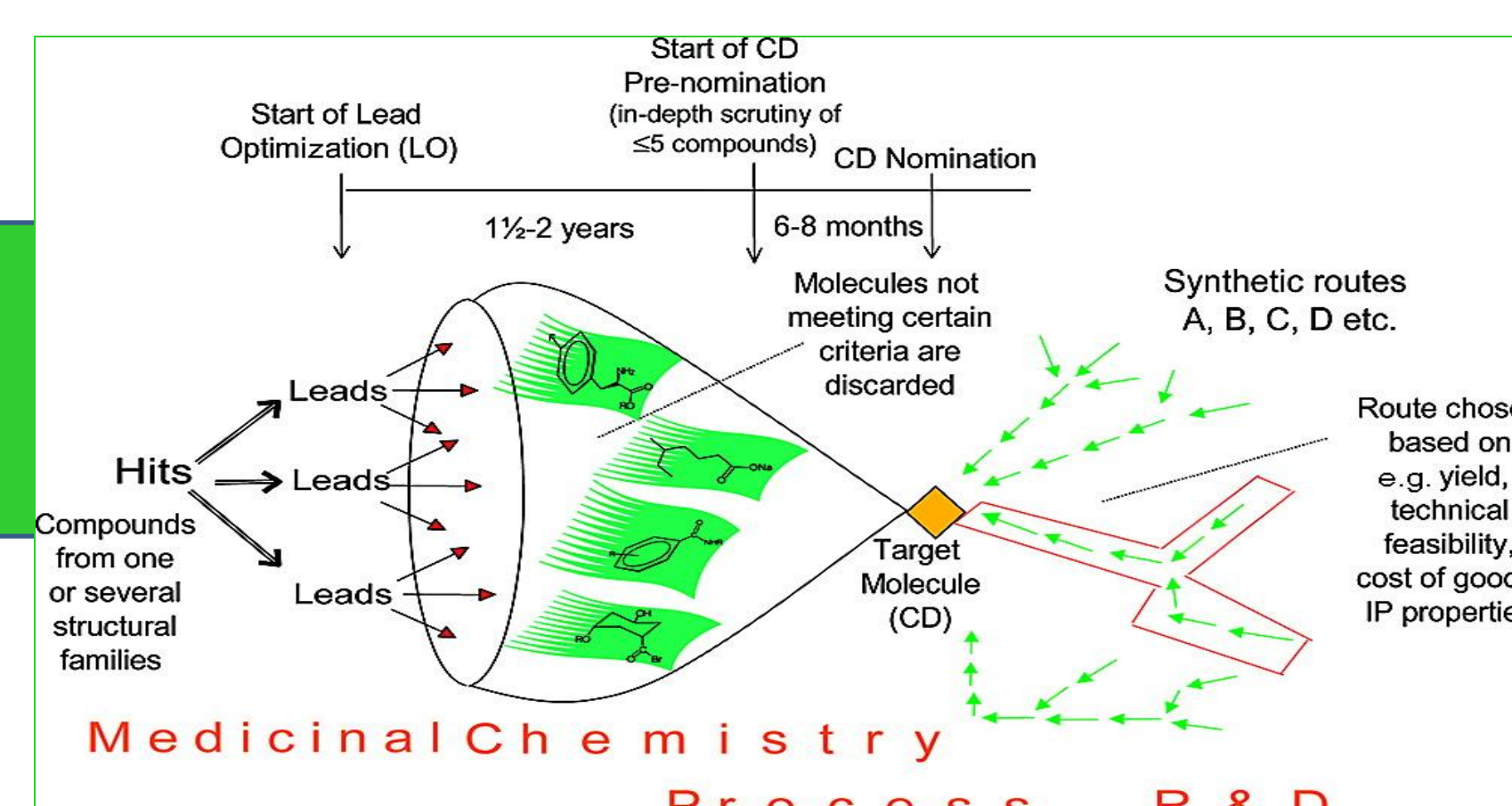
Process research and development focuses on organic synthesis, analytical chemistry, engineering, safety, operation, and application as disciplines in a wide scale production. The pharmaceutical industry must comply with regulations and take into account these disciplines as well as all aspects surrounding the methods of applying research for development of an effective product. A small scale operation can have strong results after taking time to develop these effective products. To generate this into a larger scale operation, factors that may have been overlooked come into play. Safety of the operation as well as impact from the operation is huge factors to take into account. The availability of starting materials and any hazards and impacts on the environment from the same small scale processes now become concerns in a larger scale operation to produce commercially. For the companies in the industry, cost can cause previous work done to need changes and become irrelevant when operations are taken to a higher scale. Now as complexity in pharmaceuticals becomes more and more challenging, demand grows for process knowledge. The whole operation is not given time to research and develop which route is best for further operation, making moving their work to a larger scale to could cause regulations and disciplines to possibly not be met. The timeline from an idea to the launch of a drug years later is met with decisions on what molecules can be used effectively both in a small and large scale, and the quality, time, and cost of projects under this timeline.

### Process Research and Design



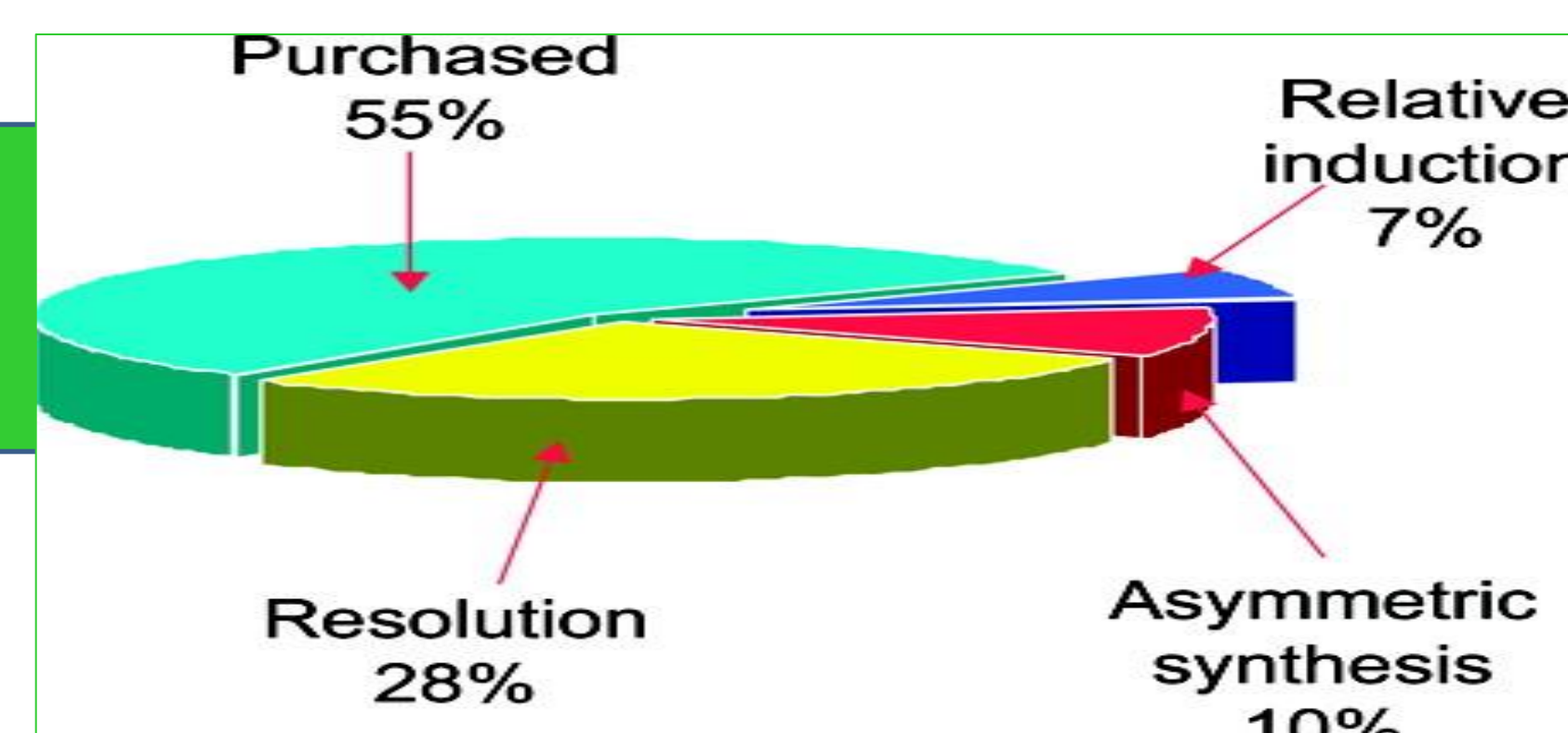
This timeline illustrates key activities critical to research and development. Milestones are indicated alongside the timeline emphasizing the process in pharmaceutical research and development. This may start with an idea of how a disease can be handled and ends with a manufactured drug years later after all criteria in the project are met.

### Lead Optimization and Prenomination Phase



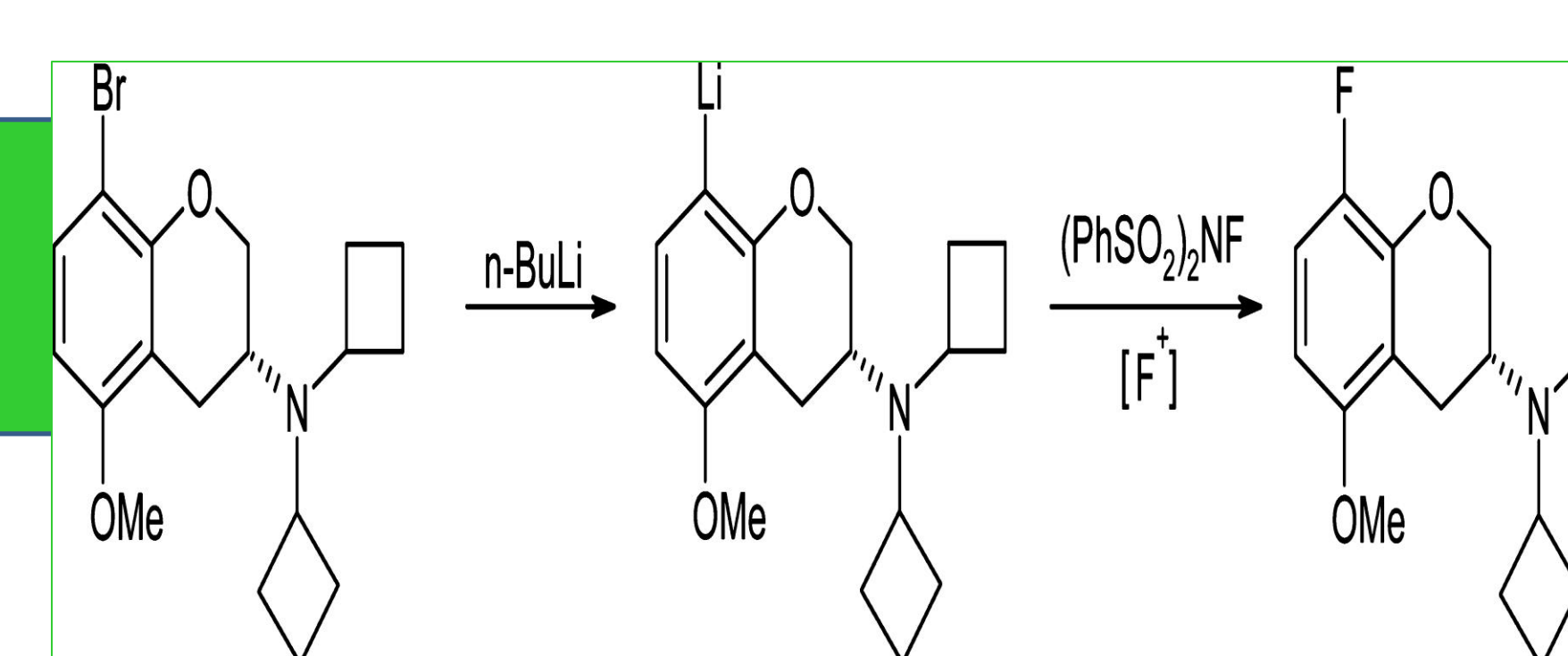
Early interactions enable chemists to decide further studies and routes of potential candidate drugs. These early processes are not fully developed, but reduces time taken to nominate a desired compound drastically. Further experimental work can then be taken along with looking for alternative routes, assessing hazards, and order and processes of starting materials.

### Ways Stereogenic Centers Are Installed



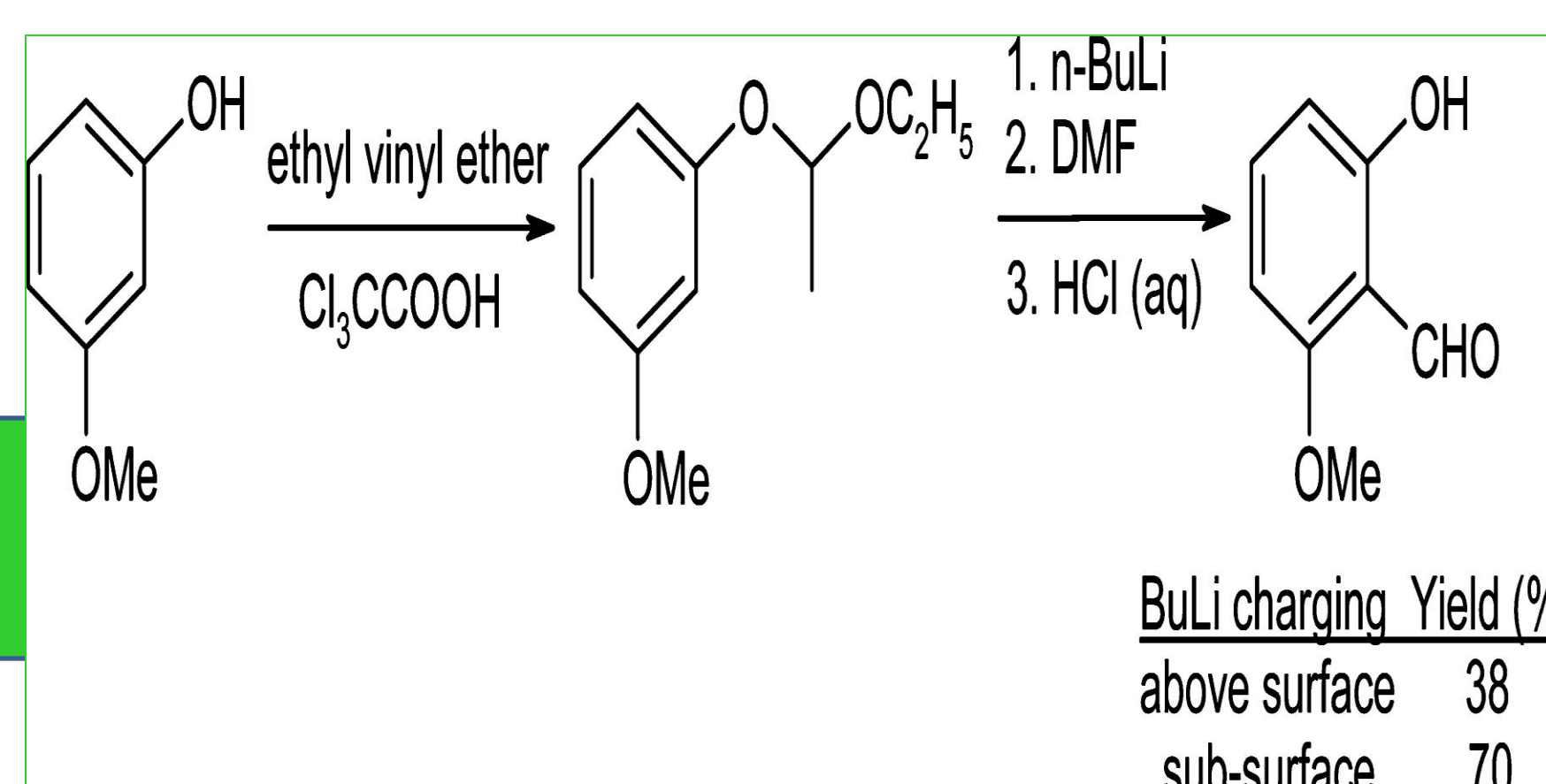
Stereochemically defined building blocks are necessary, and are relied on in pharmaceutical industry. The supply is from external sources however, and is shown to be relied on in 55 percent of cases. The cases involving the above methods and necessities were based on studies from 128 synthetic sequences, with 1039 discrete transformations. The resolution is a more classic method that has been applied over many years, giving it reliability and experience for the industry to use. Asymmetric synthesis is known to be prestigious, but is complex and somewhat uncertain in outcomes.

### Route of Production More Effective



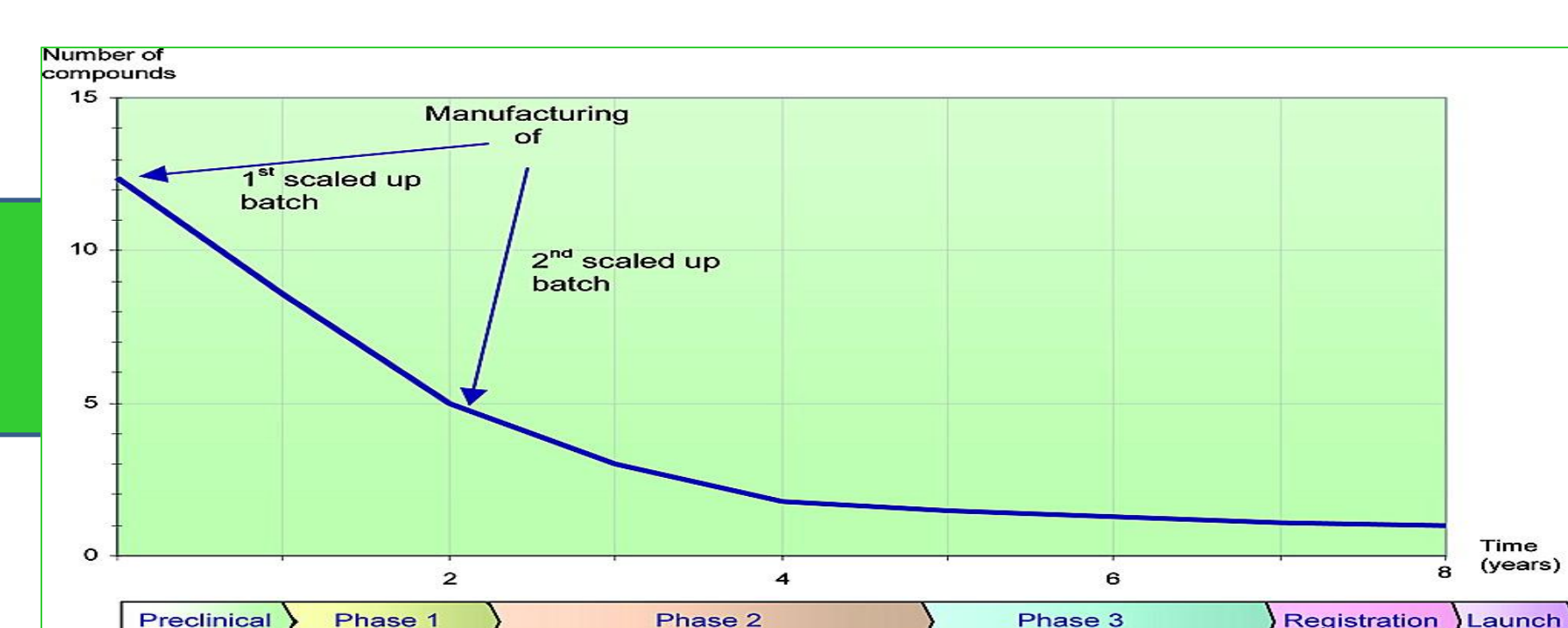
Intermediates used in reactions such as these result in a product that utilizes only about seven percent of the molecular weight. This reaction, however, is an optimized procedure that avoids complexity and danger from the risk of corrosion from fluorination. Steps required in a reaction often relates to the quality of the product. Though not always, fewer steps like this create a more efficient product.

### Effect on Yield in Reaction Setup



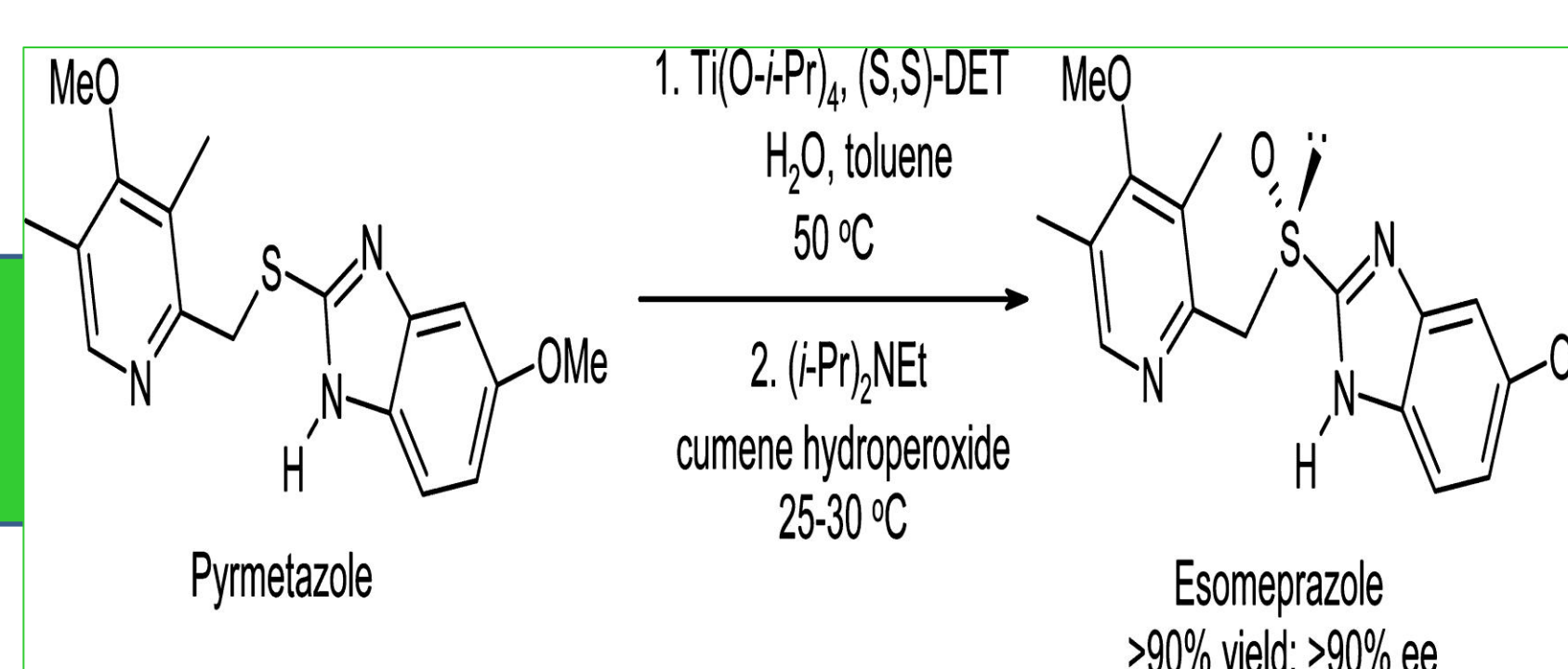
The following reaction is a Lithium-mediated formylation. This first step was conducted in both the lab and using a plant method on a larger scale. The hexane solution (BuLi), entered the vessel in the plant above the surface of the reaction solution. Laboratory production of this same procedure resulted in a greater than 70% yield of the desired aldehyde. However, this procedure generated only 38% of the desired aldehyde. This poor result was traced back to the reaction mixture, and devising a solution to enter the BuLi reagent from beneath the surface. This avoided formation of byproduct, thus a more efficient reaction.

### Attrition in Preclinical Phases Through Human Studies



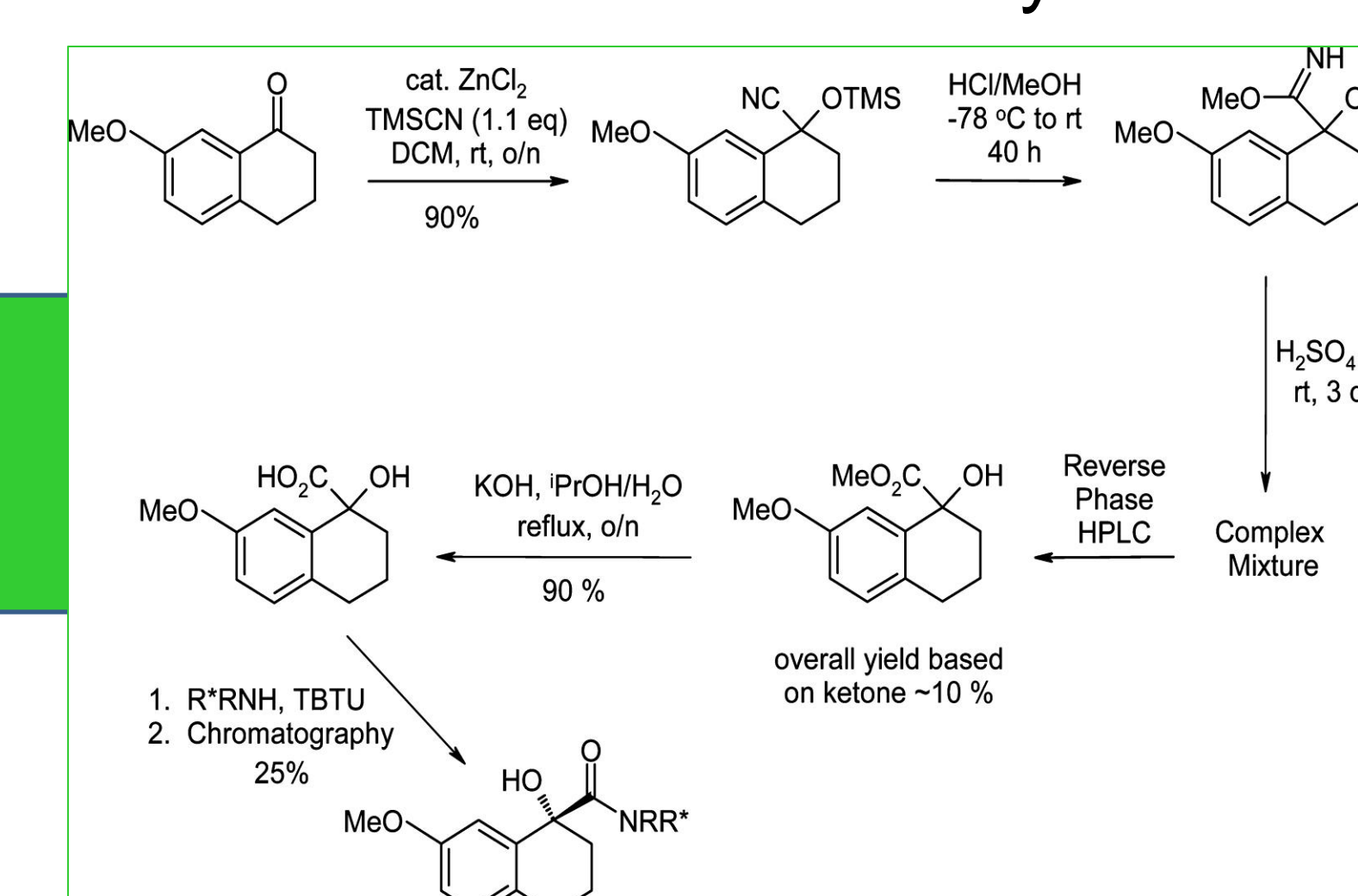
By focusing on products that initially survive and have a high success rate and opportunity, the process research and development over time allows for a fully optimized product. Based on importance, and safety, health, and environment criteria early on, projects can be prioritized, though this makes for a failure rate of one of three compounds. The development of chosen projects over time is shown through attrition of molecules and compounds in the graph.

### Example of a Transition Metal Catalyst to Conduct Selective Transformations

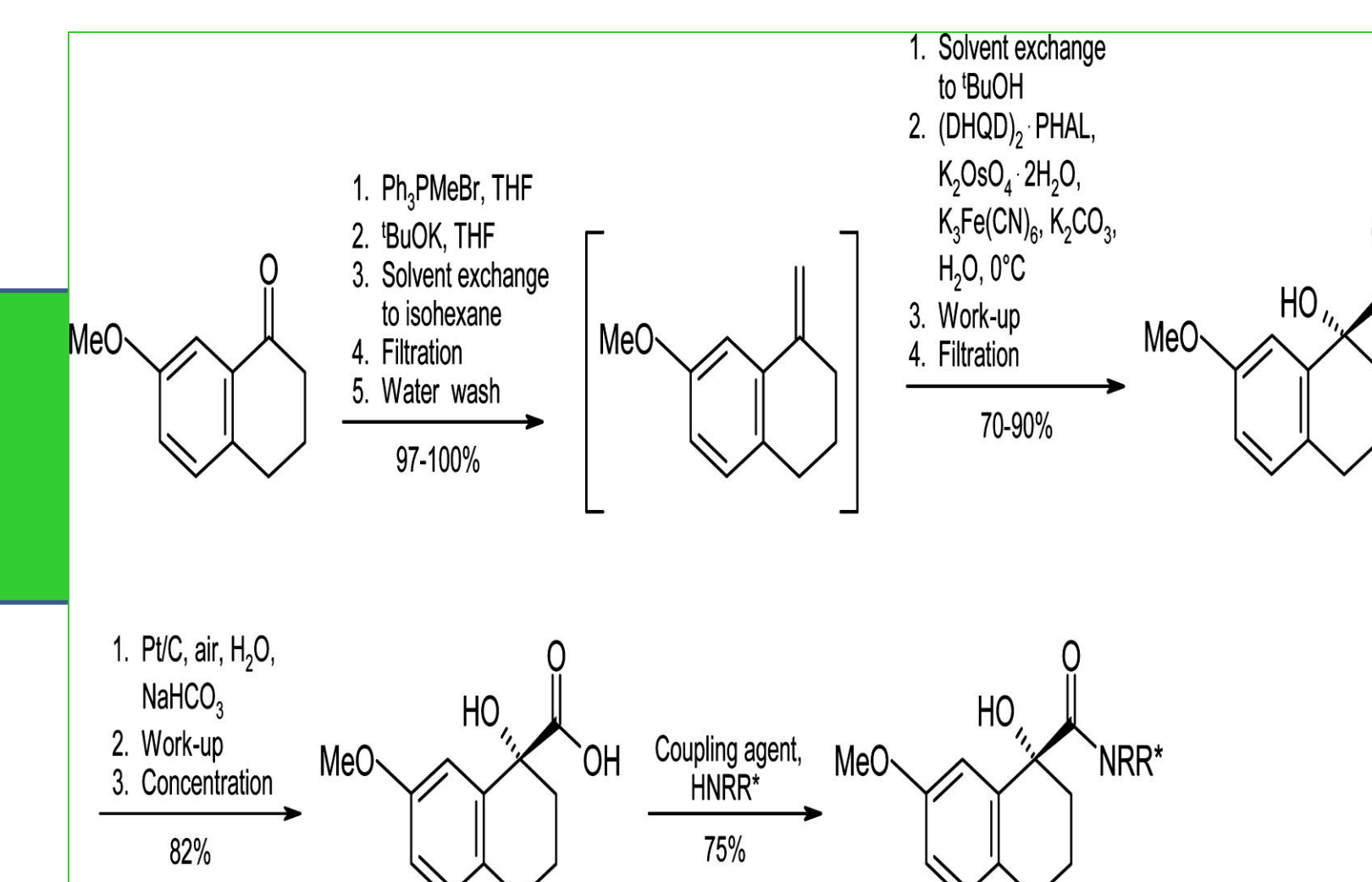


An example of using transition metal catalyzed stereoselective synthesis in a production scale process. This example uses Titanium catalyzed asymmetric sulfide oxidation. Esomeprazole yields very high as it is a very significant drug in Nexium. Catalysts used in productions like this are ready and are numerous, allowing selective transformations to result very positively.

### Synthetic Route Devised by Medicinal Chemistry

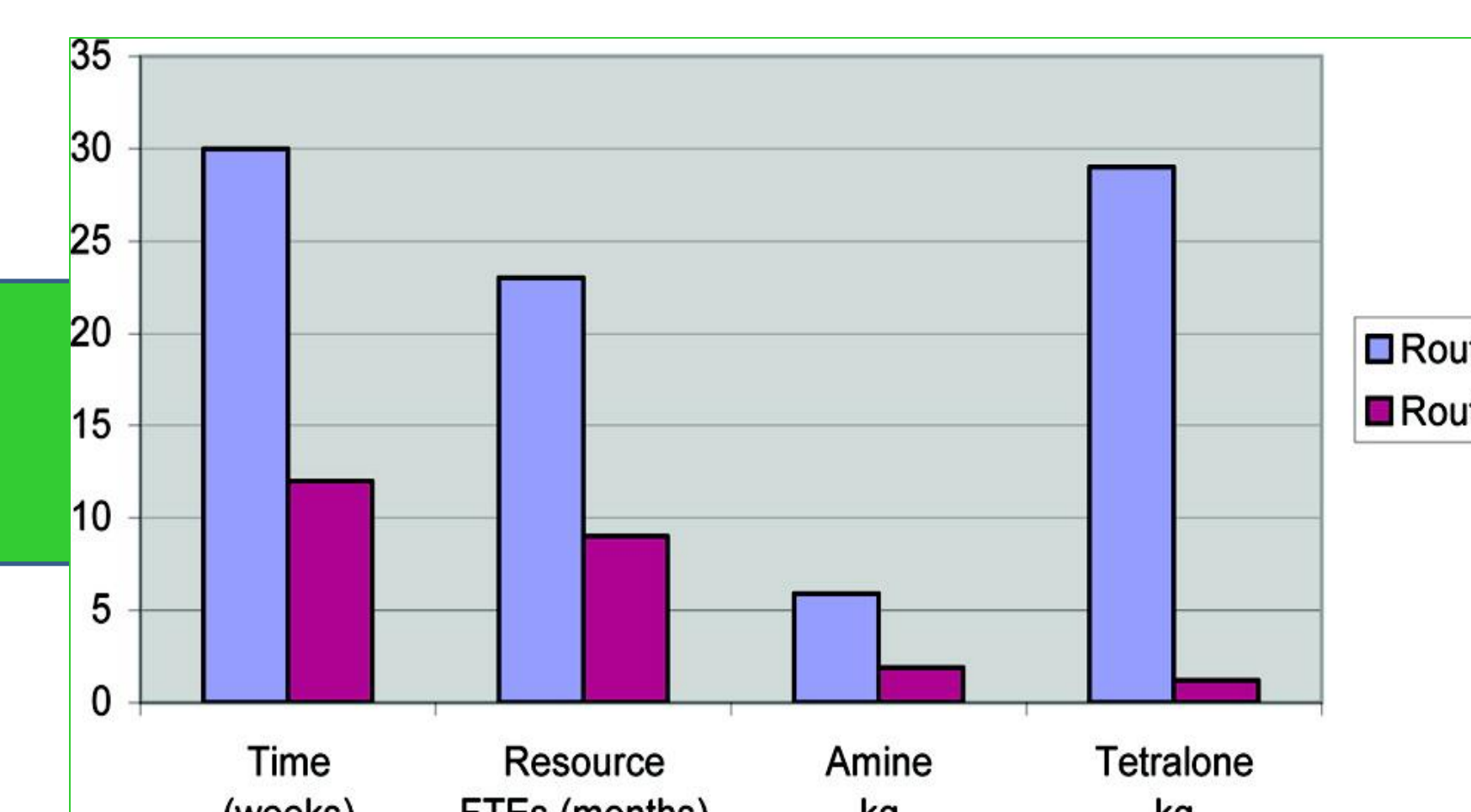


### Improved Process Based on Asymmetric Dihydroxylation



This graph shows the comparison of the reaction shown in producing alpha-Hydroxy Carboxamides. Route A is the medicinal route in a previous slide and route B the improved process. The initial route involved chromatography and resulted in a barely two percent overall yield. The time and cost needed an alternative, along the low availability of reagents in bulk. Originally the process was the same but it then diverges, resulting in the asymmetric dihydroxylation for the correct stereochemistry, then oxidation to result in an overall 42-55 percent yield. This process cut out the time spent on chromatography, as well as cost of resources and materials.

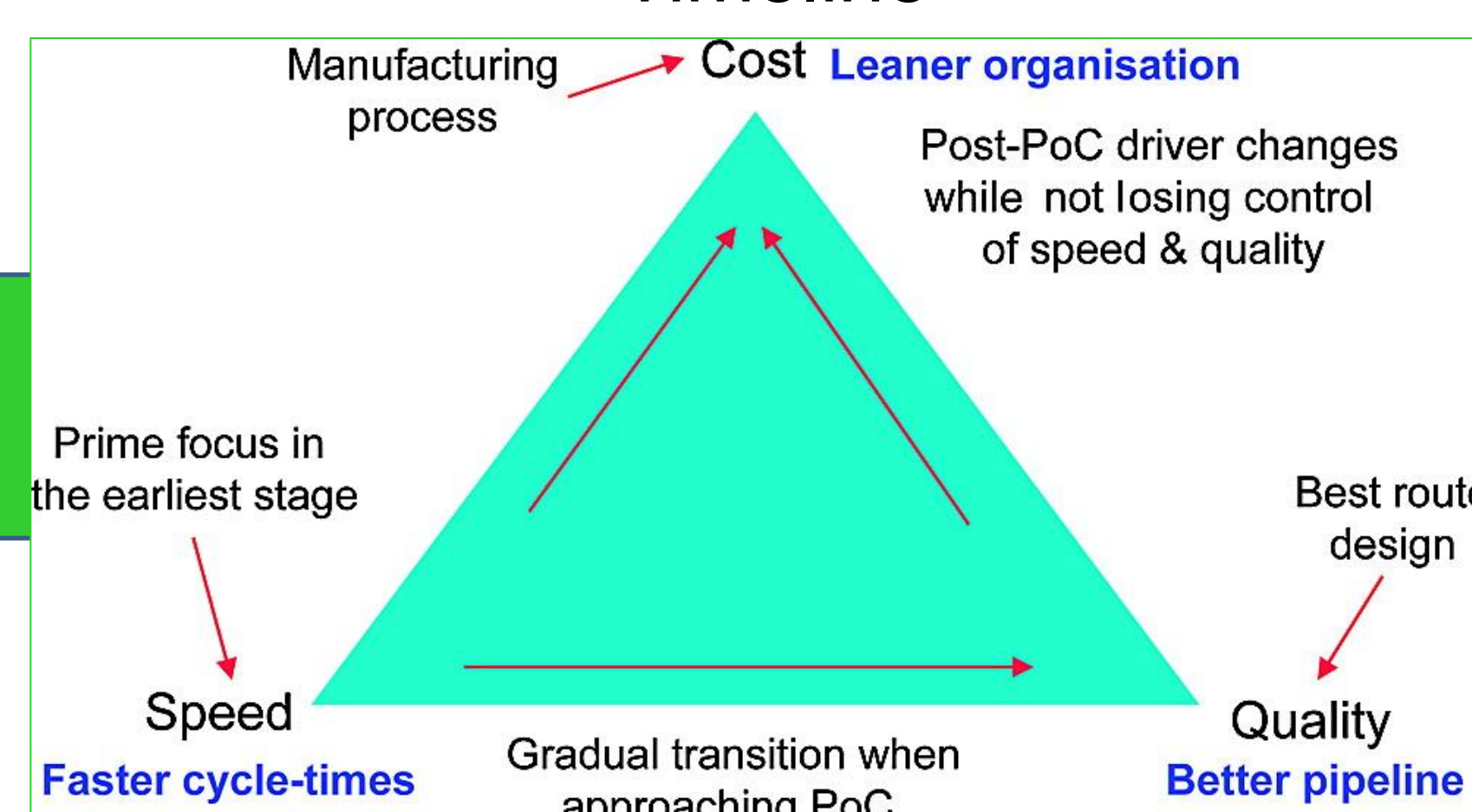
### Comparison of Routes Taken for Same Product



### Conclusion

Process research and development in the pharmaceutical industry changes not only as new products are created, but within a single project itself. The synthesis and events to create a desired product rely on numerous aspects in the industry. They also may not even need to meet criteria such as cost or safety on a large scale because the experiment may not even reach it past an original preclinical phase into any kind of production. The research and development are mostly pressured by time now. Many drug projects can over time create a very efficient drug, but finding the desired result with one or two decisions determines now if the project will make it. This research and development is the forefront of later decisions relating to overall cost or efficiency. Improvement and continuing progress in methods used demands more and more work to keep up with the demands of just one project in the pharmaceutical industry. Safety and regulations are always taken into account and are aspects that will not change as the industry demands change. Technology and capabilities continue to innovate this demand for efficiency, and help the challenge of restrictions on time. The whole production of a drug in the pharmaceutical industry cannot really be perfected or automated because of the chemical process, but these developments in improving and rationalizing the production is promising and continues to push forward.

### Speed-Cost-Quality Triangle Along Timeline



Relating the Speed, Cost, and Quality to decide where to put main efforts into as a drug project progresses. The speed is something that initially needs to be focused on, since small scale experiments that take time will not be wanted in a large production scale of the reaction. Quality is something that is focused on to reduce time, if the route is originally a long one, since a shorter route results in a more efficient product, and something that can drastically change when moving a project to a large scale. The cost of a project is more imminent when producing on a large scale, and can be a main reason to look for alternatives.