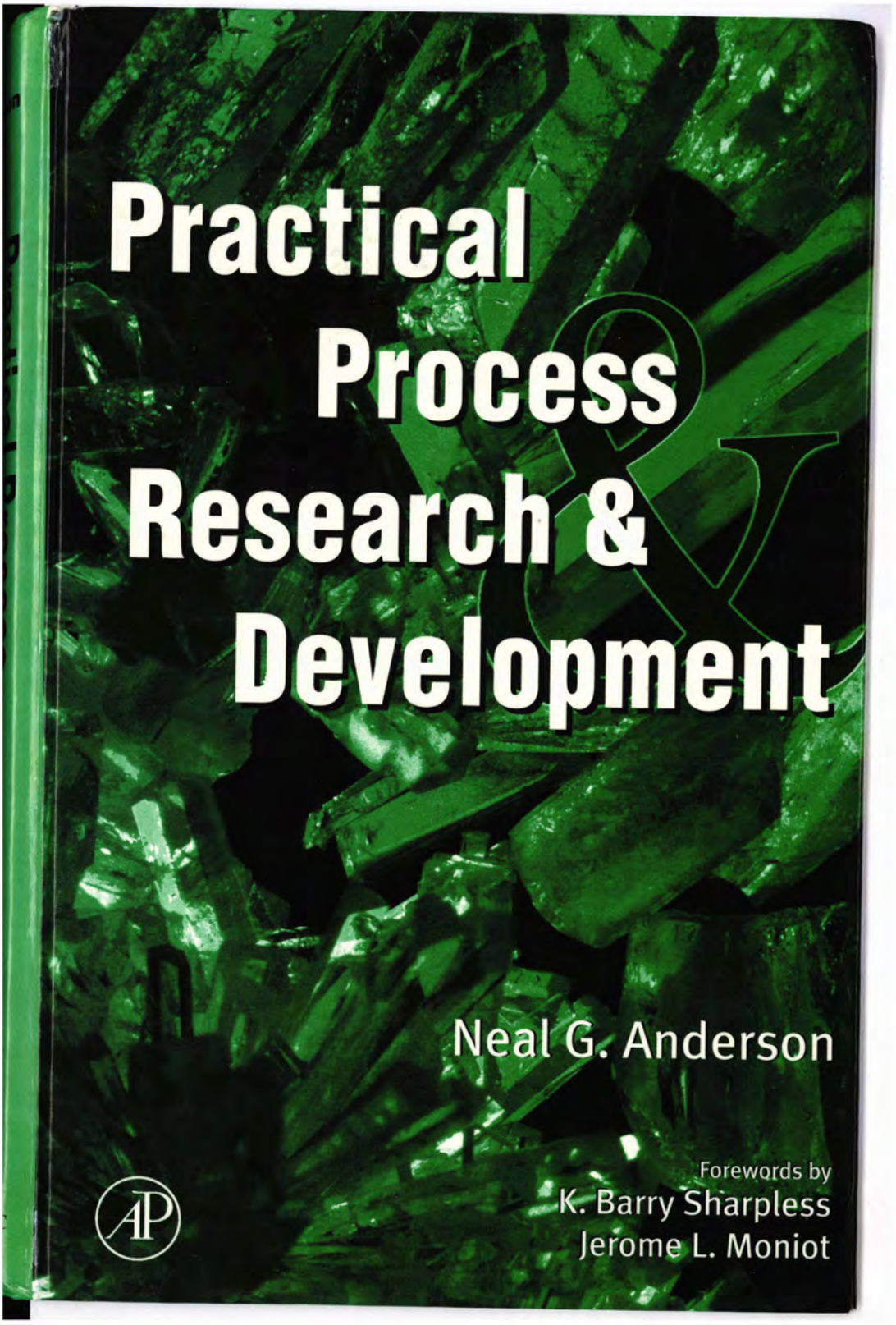

Practical
Process
Research &
Development
Neal G. Anderson
Forewords by
K. Barry Sharpless
Jerome L. Moniot


Anderson
Practical Process Research & Development
ACADEMIC PRESS

Alan J. Anderson, Ph.D.

Additional Praise for

Practical Process Research & Development

"This volume was clearly written by someone experienced with (a) the transition from being a classical organic chemist to being a process chemist and (b) taking laboratory chemical conversions into manufacturable chemical processes. Anderson's use of "tips," real-life examples, and summary tables makes this a must reference on every process chemist's (both the novice's and the experienced practitioner's) desk. This will be required reading by all new chemists, engineers, and analysts in my department."

—SEAN T. NUGENT, *Senior Director, Chemical Sciences, Searle Research and Development*

"Neal Anderson has assembled an immense amount of practical information that is absolutely essential to the design and execution of safe, reliable, and efficient large-scale syntheses. Critical facts once hidden in obscure sources or chemical folklore are now organized for ready access. Countless illustrative reactions and sequences from the latest literature are discussed lucidly, and impress upon the reader the scope and sophistication of modern organic process chemistry. This book is a must for beginners and old hands alike."

—RAYMOND CONROW, *Assistant Technical Director, Chemical Preparations Research, Alcon Laboratories*

"In writing this book, Anderson has done a great service to the chemical community, especially those chemists who are starting industrial R&D positions after their academic work. He has done a superb job of identifying the key elements of best practices in process R&D by providing a large number of judiciously chosen examples to illustrate these practices. In addition, plenty of useful data on key reagents, and practical suggestions on how to use these data in process chemistry, can be found throughout the book. Even though the book is primarily aimed at process chemists, others in academic laboratories as well as in pharmaceutical and agricultural discovery groups will find it immensely valuable. The new awareness that this book brings might even help to dispel some of our old inherently unsafe and environmentally questionable habits. To those of us who are in the teaching business, this book will serve as an eye-opener by showing the disparity between what we teach and what we practice. I predict that this book will also become a standard reference book used by synthetic chemists everywhere."

—T. V. RAJANBABU, *Professor of Chemistry, The Ohio State University*

Practical Process Research & Development

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Neal G. Anderson
Process Solutions L.L.C.
Nicasio, California

ACADEMIC PRESS
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To Hope
for all her love and support

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Foreword by K. Barry Sharpless

Process chemists are a breed apart. While their backgrounds may vary, they share a common preoccupation with understanding chemical reactivity. The best ones seem able to anticipate much of what can go wrong in a proposed reaction sequence, and thus avoid most of the traps, barriers, and dead ends that impede the rest of us. They gain profound satisfaction from being able to steer a complex reaction along one of many possible paths, creating the sense, albeit whimsical, of wielding "power over the molecules."

The process chemist's special sense for which reaction variables offer the most leverage in a given case is founded on the ability to absorb vast amounts of information about factors that affect reactivity and to sort them into a coherent and flexible "intuition." Information, both theoretical and empirical in nature, is continuously added and intuition is thus continuously refined. It is therefore virtually impossible for a young process chemist to avoid learning many crucial lessons the hard way. Whenever old-timers are in the mood for giving out "tips" (vide infra), I *always* pay attention.

Process chemists thus play a crucial role in advancing both basic and applied chemistry. Given that man-made chemical products would not exist without their skills, it is odd and unfortunate that they rarely have much say in selecting the molecular targets for which they must devise practical commercial syntheses. Nowhere is the exclusion of process chemists from the discovery process more unfortunate than in the pharmaceutical industry. Here discovery takes the form of a "sky's-the-limit" search, wherein chemistry that is feasible, let alone ideal, for application on a practical scale is all but ignored. The pharmaceutical industry therefore needs more process chemists than any other field, and the challenges they face are by far the most daunting of chemists in any area of pure or applied chemistry.

Neal Anderson, one of the outstanding practioners of pharmaceutical process research and development, has given us here the best text ever written on the

subject. This accomplishment is all the more impressive because the aforementioned "no holds barred" chemistry style favored by the discovery team means that the process chemist has to be ready and willing to deal with organic synthesis challenges reaching from simple to nearly impossible. "Everything you always wanted to know" about process research is here, and this monograph will no doubt be pored over carefully by all newcomers as well as afficionados of this subject. Readers will especially enjoy the many highlighted "tips," ranging from all manner of advice on experimental detail and procedures to general issues and trends concerning the process chemist's world. This desire to pass on the tricks of the craft for controlling and simplifying a reaction is the distinguishing trait shared by all "real" process chemists. In this way at least, I too fit the description: for the past several years, I have based my TSRI graduate course lectures on files accumulated over the years describing various "best" procedures, advice, tips, etc., on a wide and eclectic range of processes. These arise, in some guise or other, almost daily in the work of a process chemist.

I first realized I was a process chemist after Seemon Pines invited me to the "Organic Reactions and Processes" Gordon Conference almost 30 years ago. This meeting has drawn the process chemistry faithful to New Hampshire for the past 40 summers. While the attendees bring with them a diverse range of experiences and specific interests, their differences are barely noticeable next to the main passion they all share, which is the discovery, development, and large-scale implementation of *useful* reactions and reaction sequences. Since the "discovery" part of the dream is fulfilled only on rare and unpredictable occasions (always in someone else's laboratory!), it is not a reliable generator of new material for presentation and discussion. Fortunately, process chemists are delighted by the more everyday "strategy/control" aspect of their field, and for good reason. Choosing the right sequence of reactions for a large-scale synthesis and then optimizing each of them demands many talents, with mechanistic acuity at the head of the list. Even a "simple" reaction step like acylation can misbehave and ruin an otherwise promising synthetic route. The very best process chemists seem to have built their reputations by repeatedly finding fixes for ailing reactions. These accomplishments, rarely as simple as they may appear after the fact, rely on an uncanny interplay of experience and mechanistic insight.

It is therefore fitting that whenever I've heard gifted process chemists like Merck's Edward Grabowski telling their favorite stories, it is clear that they too are proudest of these "all-or-nothing-at-all" quick "instinctive" fixes, more so because they chuckle about the trivial nature of the answer they found. The handful of people who are world class in pulling such "simple" solutions out of thin air bring to mind my two favorite quotes by scientists:

> The art of concluding from experience and observations consists in evaluating probabilities, in estimating if they are high or numerous enough to constitute proof. This type of calculation is more complicated than one might think.
>
> —Antoine Lavoisier

> Mediocre spirits demand of science the kind of certainty which it cannot give, a sort of religious satisfaction. Only the real, rare, true scientific minds can endure doubt, which is attached to all our knowledge."
>
> —Sigmund Freud

These insights of Lavoisier and Freud into the importance of welcoming doubt as the natural companion of all scientific inquiries seem apt in the present context. The process chemist is routinely asked to solve problems of great and often irreducible complexity. Since such ill-defined problems are encountered at nearly every stage in perfecting a reaction sequence that runs reliably at scale, it is not surprising that the best practitioners of the art relish working on the edge of chaos, fully expecting to find the trick(s) for taming a poorly understood reaction type. What really attracts them (and me) to these unpredictable systems is the awareness that here too lies the most fertile ground for stumbling on new reactivity, the origin of all useful new reactions.

> The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole.
>
> —Sir John Cornforth

Cornforth's old saw on the "perfect" industrial reaction reminds us how far we still have to go. This is especially so in the area of pharmaceutical manufacturing, which stands in stark contrast to the modern petrochemical industry. The latter has been on a much happier path since its birth, and, to the great benefit of humans, many of its workhorse reaction processes are already approaching perfection. Hence, the two biggest industrial applications for organic reactions and processes have evolved in nearly opposite directions.

Historically, the pharmaceutical industry has watched its drugs become progressively harder to synthesize, whereas the petrochemical industry, finding elegance and profit in simplicity, has moved steadily toward ever more direct and efficient processes. All petrochemical products depend on a handful of remarkably efficient gas-phase processes through which the abundant, but chemically uninteresting, fossil hydrocarbons are selectively transformed into about a dozen small, functionalized organic building blocks. The modular assembly of these few reactive blocks/monomers is then accomplished using a variety of unique processes and catalysts, each known to selectively and reliably catalyze a particular bonding pattern once the reacting block(s) is specified. This deceptively simple strategy of combining a few uniquely reactive blocks under the control of a few exquisitely selective catalysts is solely responsible for the astonishing productivity and versatility of the modern petrochemical industry. It has given us myriad new substances, with almost tunable properties, and often made on a massive scale.

Although on a tiny scale by comparison, the identical, small set of petrochemical-derived blocks (vide supra) is also the ultimate source of starting materials for about 90% of all the organic compounds used for any purpose by the pharmaceutical industry. However, the theme of gaining reliability and efficiency through a

modular synthetic strategy, so dominant in petrochemical organic synthesis and organic synthesis as practiced by living systems, has so far had negligible effect on the style of organic synthesis used to search for new medicines. But whatever else the future holds, to the extent that the insights and attitudes of process chemists become better inculcated in our students and better known throughout the synthetic community, new medicines should become easier to discover and to manufacture. Careful attention to this book will take us a long way down this highly desirable path.

Professor K. Barry Sharpless
Dreyfuss Professor of Chemistry and Molecular Biology
The Scripps Institute for Medical Research

Foreword by Jerome L. Moniot

The key role of process chemistry and process development in the economic success of the large-scale preparation of fine chemicals and the manufacture of pharmaceuticals in particular has frequently been underappreciated. In the pharmaceutical industry at large, organic chemists are employed in the discovery process to determine which molecules to make and also in the development/manufacturing role to determine how to make those selected molecules. Although organic chemistry is the common denominator in these functions, the discovery chemist is additionally focused on the biological activity and novel aspects of the compounds, while the development/manufacturing chemists are focused primarily on the practicality and elegance of the process to manufacture the compounds. The approaches to the use of organic chemistry may differ, but the goals of both groups of chemists are the same, namely, to enhance human life through new and effective medicines.

The evolution of a manufacturing process for an active pharmaceutical ingredient has several distinct phases of development. Beginning with the discovery or selection of the target molecule, the development of a practical route to full evaluation of toxicological and pharmacologic attributes is undertaken. Once the route is defined, initial scale-up development and the transition to process equipment proceed, followed by process optimization and refinement for manufacturing operations for each synthetic step through pilot trials.

Effective process development is an amalgam of synthetic organic methodology, physicochemical properties, purification technologies, chemical engineering principles, and practical mechanics orchestrated with a view toward safety, product quality, reproducibility, ruggedness, and cost efficiency. The simple translation of a description of a laboratory synthetic process into the series of sequential unit operations required to replicate the procedure in process equipment reveals the complexity involved. The numbers and sizes of vessels (head tanks for reagents, reactors, distillate receivers, phase splitting vessels, filtrate hold tanks, crystallizers,

etc.), as well as the numbers and types of filtration devices, product drying equipment, transfer lines, pumps, and valves, all need to be selected for chemical compatability and operational suitability. These determinations are frequently the focus of laboratory experimentation and safety hazard studies and involve close interactions with chemical engineers.

One development concern that is not immediately intuitive to laboratory-based organic chemists beginning development work is the effect of physical size on the progress and eventual outcome of an organic reaction, beyond those obvious effects due to the length of time required for operations. An example is surface addition of a reaction component. The design of a laboratory experiment to determine the effect of adding a reagent at the surface of a large-scale reaction is challenging. Rather than a few inches of mixture separating the surface of the reaction from the agitation device, the 6- to 12-foot separation in a mid-sized process vessel can lead to troublesome mixing gradients and localized stoichiometric imbalances (hot spots). As the text highlights, mixing is critical to the successful execution of an organic reaction and requires that process chemists and engineers work together closely to minimize difficulties with this aspect of process scale-up during development.

As Dr. Anderson points out, a key to many a successful process is the careful integration of physical phenomena, such as insolubility, preferential solvent phase distribution, and volatility, with control rates of desirable reactions or the rates of undesirable side reactions.

One of the thrusts of synthetic chemistry that distinguishes process development work is the emphasis on the postreaction workup and purification/isolation aspects of a process. Isolated intermediates must necessarily be filterable solids, and the tolerance of the chosen purification methods for impurities in the solution will have a profound effect on both yield and quality of the product.

Dr. Anderson has produced a very insightful and informative book for a process development team in pursuit of their ultimate goal. That goal can be summarized as the definition of a process that is characterized as being high throughput, safe, reproducible, and rugged and one in which a minimum number of different solvents are used to carry out the maximum amount of synthetic construction in the shortest amount of time, with the highest isolated yield of high-quality product, for the lowest cost per kilogram.

Dr. Anderson's text ably highlights many of the interrelations of the key facets of the development process, along with many practical reference tables to facilitate parameter selections for evaluation.

Dr. Jerome L. Moniot
Vice President of Technical Operations
Bristol–Meyers Squibb Co., Inc.

Preface

My goal with this book is to provide a comprehensive, step-by-step, hands-on approach to organic process research and development for the preparation of "small molecules." It should be useful to those in the pharmaceutical, fine chemical, and agricultural chemical industries and to those academicians who wish an insight into process R&D in these industries. I hope it will ease the transition for those who are entering industrial process R&D labs fresh from academia. More experienced readers may find some useful tips and ideas.

This book has been developed primarily from my experiences at Bristol–Myers Squibb. The principles discussed are illustrated by examples from the chemical literature, patents, and my personal experience in the laboratory, pilot plants, and manufacturing plants. Many of the guidelines for implementing processes on scale (Chapter 14) were developed by the New Brunswick staff of BMS, and the thoughts there represent many collective years of experience.

I have selected examples from the literature primarily through the middle of 1999. Some reaction schemes are used in several chapters because they provide insights into different areas of process development. The interested reader could consult many of the process papers mentioned in this book for additional examples of successful process R&D. Some tips are repeated in the hope that readers who examine chapters out of sequence will not miss valuable points.

There are many people to thank. Dave Burdick, Ed Delaney, Kumar Gadamasetti, Marc Halpern, Sean Nugent, Bob Polomski, Rob Waltermire, Steve Weissman, and especially Ray Conrow reviewed my draft chapters and gave me insightful technical comments. Alice McKee, Phyllis Minicuci, Donna Gibson, Charlee Sevenski, Marion Morgan, and Cindie Good were very kind to let me use the New Brunswick Bristol–Myers Squibb library. Julie Arnheim and her staff at the Princeton University Chemistry Library were very helpful. I have had many illuminating discussions with Barbara Ciaramella, Bill Ferguson, David Kacsur, San Kiang, Atul Kotnis, Ken Morris, Larry Parker, J. D. Pipkin, Larry Steele,

Steve Taylor, Ajit Thakur, Bill Winter, and other past and current employees of Bristol–Myers Squibb. Professor Rich Lawton and John R. Carson taught me so much and allowed me room to learn. Jerry Moniot first mentioned to me the concept of snapshot, and we have spent many hours discussing problem-solving and details of process development. Barry Sharpless kindly gave his thoughts on this work. Don Doell and Christine Williams provided useful information on process reactors. Colleen Saggese supported me in the crunch and helped me marshal the details to complete the manuscript. David Packer at Academic Press had faith in this project. Gail Savage made my manuscript much more powerful and readable, and I appreciate her writing lessons. Linda Gustafson was very responsive with the production of the pages. Participants in my courses have given me valuable feedback and encouragement. Many, many thanks to all these people.

I also must thank Bristol–Myers Squibb for many rewarding years. BMS provided world-class laboratories for learning about technology and people.

Discerning readers will undoubtedly find some exceptions to the general guidelines offered here. I welcome comments on the book and will appreciate mention of the inevitable errors.

Neal G. Anderson

About the Author



Neal G. Anderson, Ph.D., has worked for over 20 years in chemical process R&D in the pharmaceutical industry. He earned a B.S. from the University of Illinois and a Ph.D. in medicinal chemistry from the University of Michigan and completed postdoctoral studies at McNeil Laboratories. With almost 18 years in process R&D at Bristol–Myers Squibb Co. in New Brunswick, New Jersey, Dr. Anderson has extensive hands-on experience in laboratory, pilot plant, and manufacturing facilities. He has made key contributions to processes for the manufacture of four major drug substances, including captopril, has participated in 12 manufacturing start-ups, and has successfully introduced many processes to pilot plants. He received the Bristol–Myers Squibb President's Award and spot awards, and his final position was Principal Scientist.

In 1997, Dr. Anderson established Process Solutions L.L.C., a consulting firm offering practical guidance on developing and implementing processes for bulk pharmaceuticals and fine chemicals. As part of these consulting services, he presents courses on selected aspects of practical process R&D. He also practices chemistry in the kitchen, by home-brewing beer.

CHAPTER 1

Approaches to Process Development

"It is well-known that there are no technical optima in industry, only economic optima. . . ." [1]

I. INTRODUCTION

The cost and pace of developing active compounds for the pharmaceutical and agricultural industries is dramatically increasing. The estimated average cost of developing a drug has risen from $350 million in 1997 [2] to $500 million in 1999 [3]. Combinatorial chemistry and high-throughput screening increase the rates of identifying new lead compounds [3–6]. New screens are being considered to aid in selecting compounds with desired biopharmaceutical properties [7]. Pressures to produce are increasing as companies set ambitious goals to transform active leads into approved, revenue-producing agents. Efficient development of processes to prepare kilogram quantities of drug candidates and active ingredients is necessary to sustain the pace of drug development and recoup the expenses of development. As part of development efforts, those involved in process research and development (process R & D) must keep pace by developing processes for large amounts of drug candidates and drug substances.

Devising and implementing a reliable manufacturing process in a timely fashion are keys to maximizing profits from a drug or chemical within the exclusive marketing period allowed by a patent. Gone are the days when most drugs could

be prepared in as few as four relatively simple steps. Today's typical "small molecule" (generally a compound with molecular weight no more than 750 daltons) requires 10–15 reactions, some of which are likely to be fairly complex. One error during the process of preparing the drug substance (active pharmaceutical ingredient, or API; sometimes known as bulk drug substance, or BDS) or intermediates can have tremendous financial impact by delaying key toxicology studies, clinical trials, or delivery of the drug to pharmacists' shelves [8]. The urgency commonly felt in the pharmaceutical industry weighs heavily on process research and development: for instance, for a drug selling at $400 million annually, a one-day delay in the approval or delivery of the drug substances can cost $1 million! The timely implementation of reliable processes is key to the continued financial health of pharmaceutical companies. As may be seen in Table 1.1, the cost of drug development provides tremendous pressure to reduce development time [2], and the pressures to decrease development time are ever-increasing.

The role of process R & D is to ensure that high-quality material is provided in a timely fashion to fill the needs of developing a compound. The process chemist must satisfy two groups of clients: those who use the drug substance (primarily toxicologists and pharmaceutical chemists) and those who use the processes (scale-up operations, manufacturing, and suppliers for outsourcing). The criteria of the first group are that a high-quality drug substance be prepared in the desired physical form and that the expected amount be delivered in a timely manner. This group is rarely concerned with how the drug substance is prepared. The second group, those who use the processes, want reliable procedures to prepare the drug substance and intermediates. How smoothly the operations proceed determines whether the organization can meet goals of supplying material to users. Those involved in process R & D must evaluate and evolve processes to meet current

TABLE 1.1. Assessing the Costs of Drug Development[a,b]

Development cost (average)	$350 million–$500 million
Development time (average)	12–15 years
Hourly development cost	$2660–$4750 (for each hour during the development years)
Period allowed by patents for exclusive marketing	Varies according to country (20 years for U. S. patent)
Actual sales period for exclusive marketing	Patent life less the development time
Cost of delaying introduction to market *by one day* for drug expected to sell $400 million annually	Loss of ca. $1 million per day

[a]C. M. Cimarusti, contributed talk at The Third International Conference on Process Development Chemistry, Amelia Island, FL, March 26, 1997.

[b]C. Littlehales, "The Price of a Pill." *Modern Drug Discovery* **1999**, *2(1)*, 21.

and future needs. By incorporating the approaches of those who develop processes for large-scale production early in the development of a drug candidate, one can compress the development cycle.

The emphases of process R & D change as a compound is developed (Table 1.2) [2]. In the early stages of a drug development, discovery chemists use expedient routes to prepare compounds. Quantities as small as 10 mg, prepared in the laboratory, allow for *in vitro* screening. Once a promising compound has been identified, the kilo laboratory may prepare more material to fuel additional studies, including toxicological studies, formulation studies, and perhaps early testing in humans (Phase I). The key is to prepare enough material to enable the scheduled studies. The discovery route is often employed, so any changes that are made are aimed at making larger-scale preparation more practical. For full-scale development, efficient routes are developed in the laboratory and tested in the pilot plant. Material prepared through pilot plant runs will be used for further studies in humans (Phase II and III) and to develop optimal formulations of the active ingredient into dosage forms. For full-scale manufacturing the optimal route is ideally used. This route considers all factors involved in preparing the drug substance by the most cost-effective means possible.

The appreciation for process R & D is changing. Decades ago the prevailing thought was that large amounts of material could be generated by a process used in the laboratory to produce gram amounts of product, and it was necessary only to use larger equipment. This notion is lampooned in Figure 1.1. Process chemistry was viewed as dull compared to drug discovery. More recently pharmaceutical companies are placing some of their best minds into process R & D efforts, as the significant financial benefits of developing efficient processes are recognized. There is also growing recognition that successful process R & D requires different equipment and different approaches from those used in conventional laboratory work for discovery of active compounds.

TABLE 1.2. Process R & D Requirements during Phases of Development[a]

	Discovery	Early development	Full development	Launch
Amount of compound/batch	10 mg–10 g	10 g–10 kg	10 kg–100 kg	100 kg and more
Type of synthesis	Expedient	Practical	Efficient	Optimal
Site for preparation	Laboratory	Kilo laboratory	Pilot plant	Plant
Number of batches	1–5	1–10	10–100	10–1000

[a]C. M. Cimarusti, contributed talk at The Third International Conference on Process Development Chemistry, Amelia Island, FL, March 26, 1997.

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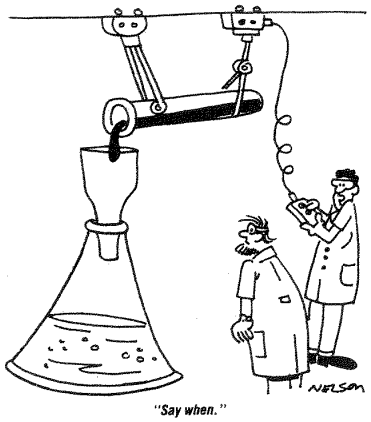


FIGURE 1.1 Scaling up a chemical process
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TIP: As an analogy to the layman, one may consider the process of baking bread. When more loaves are made from a single batch, efficient mixing of the dough takes longer and may require specialized, powerful equipment. Baking more loaves may require more time and perhaps higher temperatures than that prescribed in a cookbook. For overall baking efficiency, it is not enough to simply buy more loaf pans!

Thorough science is the basis of high-quality process research and development. Practical processes must be developed to reap the rewards of basic research, and without down-to-earth applied research there will be no sustained basic research [9]. For the successful practitioner of applied research, rewards come from the satisfaction of thoroughly understanding a process, successfully carrying out a large-scale operation, and preparing a compound that has been identified as having potential benefits for humankind.

The pharmaceutical industry serves two purposes: to prepare medicinal agents that reliably serve consumers, and to return a financial reward for the investor. Thus pharmaceutical companies operate from a mixture of altruism and pragmatism.

Financial reward is the underlying pressure for today's research in the pharmaceutical industry. Many considerations can have significant impact by acting indirectly through this pressure. For instance, the development of RU 486 by major pharmaceutical companies in the United States was discontinued due to political opposition to the "morning-after pill" [10]. Major pharmaceutical companies

have resisted pressure to market birth-control pills to prevent pregnancy as many as three days after unprotected sex [11]. Vociferous outcries by ACTUP and other groups may have hastened the development of AIDS treatments. A 5-year, $100 million grant to treat AIDS in Africa speaks of altruism—and some feel a desire to develop long-term business contacts [12]. Merck has given away millions of dollars of ivermectin to treat river blindness in Africa [13]. Environmental impacts of chemicals and resulting legislation have curbed the use of solvents and reagents [14]. Continually developing resistance of bacteria to existing medicines promotes the development of new antibiotics [13]. Improving production yields of manufactured products by only a few percent results in significant cost savings. On a more personal level, companies apply various performance pressures, through promotions, raises, bonuses, awards, and perquisites. These pressures are felt down the managerial ladders. Cost-motivated considerations are key in all phases of process research and development.

Productivity during scale-up is therefore a major concern for efficiently getting an active compound to market. In scale-up operations, productivity is related to throughput, the amount of product that can be made per reactor volume per day. Sometimes this is referred to as space-time yield or volume efficiency [15]. To increase productivity, conditions are developed to minimize reaction times, streamline operations, and simplify processing.

II. THE IMPORTANCE OF SIMPLE SCALE-UP OPERATIONS

The reliability of scale-up operations can have a significant impact on cost of the drug substances, and process conditions must be chosen wisely. Processes must provide suitable amounts of high-quality drug substances by or before the prescribed deadlines. If quality is not sufficiently high, additional time and drug substances will be lost through rework, thus increasing cost overall. A rugged or robust process must include three qualities: high-quality product must be prepared within the expected time cycle; the process must accommodate relatively broad purity ranges for the inputs, whether prepared or purchased; and the process must operate within parameter ranges, e.g., temperature and pH, which are readily obtainable during the expected process time cycle. Unless the process is rugged, additional time is incurred, and the quality of the drug substances may be jeopardized. Appropriate in-process controls (IPC) are necessary to maintain low operating costs. Processes must be as simple as possible, but superficially simple (simplistic) processes may be eventually prone to errors.

TIP: In developing processes, process chemists seek elegance in simplicity.

Some operations routinely performed in an academic laboratory are avoided on scale due to their time-consuming and often redundant nature. Including such operations in a process extends processing times and drives up operating costs. Additional steps present risks of physical losses, decreased yields, and the possibility of increased worker exposure to dangerous conditions and chemicals. In addition, with more steps there is an increased chance of contaminating batches, which poses increased difficulties for making material in compliance with current good manufacturing practice (cGMP). Managers of production facilities always seek to eliminate unnecessary steps in order to minimize manpower costs and optimize productivity.

The example most often posed to the beginning process chemist is to avoid using solid desiccants, e.g., Na_2SO_4 and $MgSO_4$, to remove water from solutions in organic solvents. This operation may actually be unnecessary if the solvent being used has suitable azeotropic capabilities to remove water and subsequent processing requires concentrating the rich solution. A considerable amount of time is needed to carry out this drying operation on scale (see Table 1.3).

The total of 16 operator-hours (two operators for one 8-hour day) for drying an extract over Na_2SO_4 is actually conservative. This estimate assumes no processing difficulties arise extending the operations, and no supervision of steps. If two

TABLE 1.3. Estimated Processing Time on Scale for a Na_2SO_4 Drying Operation

Operation	Estimated operator hours
Set up and test filter [a]	2
Charge Na_2SO_4 [b]	0.5
Stir suspension	2
Filter off solids	2
Deliver rinse to site	0.5
Apply rinse to solids	0.5
Suction dry solids	0.5
Pack up solids for disposal	0.5
Rinse equipment for "safe to clean"	0.5
Clean reactors and equipment train [c]	4
Demonstrate reactor and train are clean	2
Store equipment	1
	16 hr total

[a]Not including any additional time for using a filter aid, e.g., diatomaceous earth.

[b]Since Na_2SO_4-associated solids are often dense and $MgSO_4$-associated solids are sometimes flocculent, these drying operations pose different problems in thorough transfer from reactors to filters.

[c]Including agitation vessel, filter, filtrate receiver, and transfer lines.

operators are required for each operation, the total number of operator-hours may double. Not all of these steps would extend the processing times to prepare drug substance, as many of these operations can be performed simultaneously with more critical processing.

In a plant operating at full capacity, 2 operator-days are very valuable. The actual cost is as high as the value of material that could have been processed in that equipment during that time, which can be as much as $10,000–$100,000. In a pilot plant setting, the cost of performing an unnecessary step can also be considered the loss of processing information that could have been learned during that time. Thus opportunity cost (opportunity lost) in using a redundant step is very high.

In addition to the financial burden of incorporating an unnecessary step such as drying over a solid desiccant, there are increased opportunities for physical losses and contamination. Transfer lines, couplings, and reactors ("kettles") can leak, especially if the bottom valve was inadvertently left open. Using a filter and a filtrate receiver afford the chance for contamination. One should always question whether any step is a necessary operation.

TIP: Azeotropic drying may not always be appropriate, especially if the reaction product is heat-sensitive. Some solvents have relatively poor abilities to remove water, and azeotropic drying would require that large amounts of solvents be used or recycled (see Chapter 4). Some solvents do not form an azeotrope with water. In such cases drying solutions by using solid desiccants or molecular sieves may be appropriate.

At the end of a development cycle, the process chemist must have an exquisitely thorough knowledge of the process. Unnecessary steps will have been purged from earlier iterations of the process. For instance, the process chemist will know when further extractions are unnecessary. Also known will be the points at which a process can be held in processing equipment without affecting quality and yield.

Developing a suitably simple process and thoroughly explaining it are very important when transferring a process to another site (technology transfer). After the process has been successfully demonstrated at a manufacturing site and the lead chemists and engineers have gone home, the process may be stressed in ways never anticipated by those who developed it. A simple process will afford fewer opportunities for unwelcome changes, permitting the steady production of active ingredient.

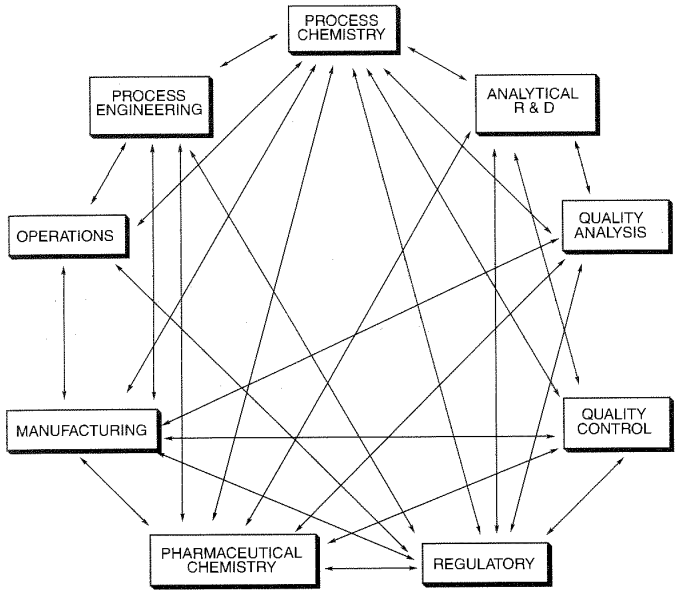
III. THE IMPORTANCE OF TEAMWORK

The process chemist must interact with people of many other disciplines and training levels in order to prepare the drug substances and ingredients effectively on scale. Some of the interactions are shown in Figure 1.2. Communication and assistance must go in each direction. Good teamwork is crucial. No one person should be expected to anticipate and solve all of the problems. For devising pragmatic, cost-effective processes, the chemist is well advised to consult engineers and those who are responsible for preparing drug substances on scale [16]. Operators should never be considered just "a pair of hands." Their input is very valuable, because they often are the only ones who see all operating details. Operators also can bring a practical approach to carrying out processes, especially when using equipment that is familiar to them. The process chemist should explain processes to the analysts, so that methods can be developed to assay for anticipated impurities. Analytical chemists in Analytical R & D and Quality Control often detect new impurities, which can lead to alterations in the process. Other interactions may be inferred from Figure 1.2.

IV. DETERMINING OPERATIONS THAT CAN AND CANNOT READILY BE USED ON SCALE

Most of the reactors used for scale-up operations are chosen for flexibility in running different processes. This is particularly true for pilot plants and plants where equipment may be used to manufacture more than one product. A standard reactor for the chemical processing industry is shown in Figure 1.3.

Examination of Figure 1.3 reveals several features important for scale-up considerations. The contents of the vessel are viewed through the sight glass in the manway; formation of a cloud in the headspace above the reaction, as may occur by mixing NH_3 and HCl, may preclude examining the batch without opening the manway. Instrumental, not visual, endpoints are generally preferred for in-process monitoring. Manual access to the vessel during operations is limited through the manway, making physical manipulation of a batch cumbersome, especially on the bottom of the vessel farthest away from the manway. The agitator (impeller) is raised above the bottom of the vessel, and the ratio of the impeller radius to the internal tank radius is 0.4–0.5:1.0. The minimum agitation volume is about 10% of the nominal volume of the vessel. The maximum tank volume is usually 90–105% of nominal tank volume, depending on the stirring and any foaming from the batch. Liquids can be added to the reactor through the nozzles and openings in the dome of the reactor. Vertical elements called baffles minimize vortexing and allow for more even distribution of the contents. Baffles can also



Department	Key Responsibilities
Process Chemistry	To initially develop a chemical process
Process Engineering	To identify practical considerations needed for effective scale-up
Operations	To carry out scale-up experiments and prepare large quantities of material
Manufacturing	To manufacture drug substance
Pharmaceutical Chemistry	To formulate drug substance into drug product
Regulatory	To interface with FDA and other regulatory authorities
Quality Control	To ensure that the quality of drug product destined for human use is maintained
Quality Analysis	To ensure that high-quality materials are used to prepare drug substance and key intermediates
Analytical R& D	To critically analyze materials produced by Process Chemistry, Process Engineers, Operations, and others

FIGURE 1.2 Departmental interactions for process scale-up

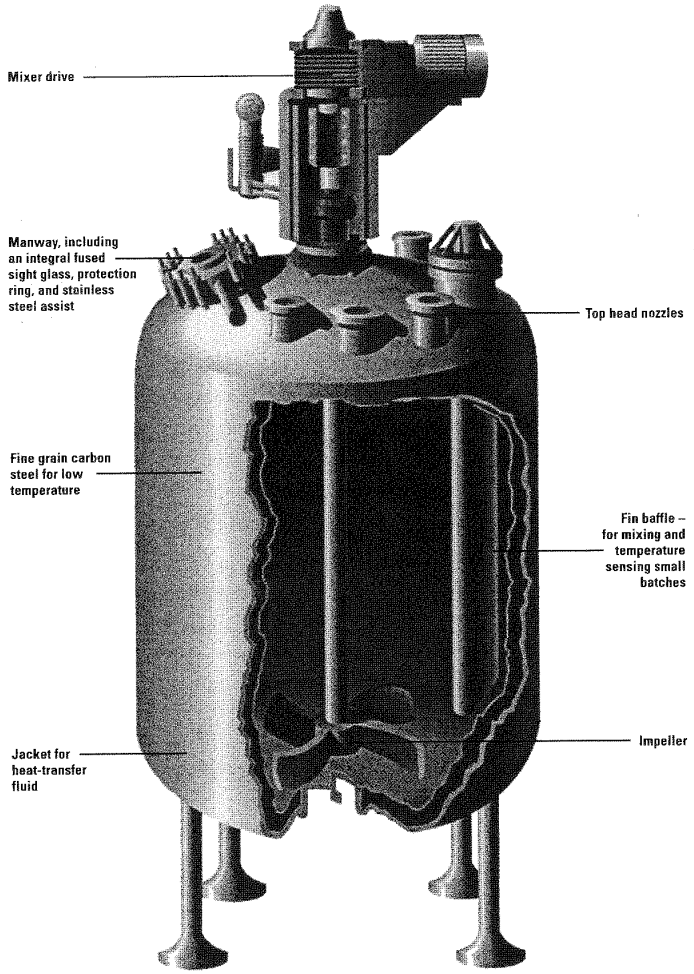


FIGURE 1.3 Standard reactor used for scale-up in the chemical industry
Used with permission of Pfaudler, Inc.

provide support for addition lines and monitoring devices such as thermocouples. The immobility, size, and physical constraints of scale-up vessels can determine how operations are carried out on scale.

Many operations can be performed more easily and reliably on large scale than on small scale in the laboratory; other operations are very difficult to scale up. In

this context, "large-scale" reactions are those that are conducted in stationary vessels with volumes of 50 liters or more, where access to the vessel contents is limited through an opening which is proportionately small relative to that of laboratory glassware. (Reactions which are run in 22-liter or even 50-liter glassware can often be conducted similarly to those run on a gram scale.) A comparison of common processes is shown in Table 1.4. It must be stressed that any scale-up operation can be modeled in the lab with the purchase of suitable control equipment. Similarly, equipment can be purchased and used to carry out on scale any operation developed in the laboratory. However, for rapid developing processes for scale-up, the chemist usually modifies processes to allow the use of existing equipment.

TIP: Any operation used in the laboratory can be used on scale, provided that there are enough time and money available.

IV.A. Rotary Evaporation

Concentrating a large amount of a solution or a solid to dryness requires considerable time and is inefficient on a large scale. Commercial equipment is available for rotary evaporation of solutions in 100-liter flasks, but a half-filled 22-liter round-bottom flask is as much as most individuals can conveniently and safely handle without external support of the flask. On scale there is no immediate analogy to a rotary evaporator. Most concentrations are carried out in stirred vessels.

IV.B. Concentrating to Dryness

As a residual solid or viscous liquid is concentrated to dryness, stirring becomes difficult, especially in an immobile vessel. Due to the small surface area-to-volume ratio of large equipment, heat transfer and distillation take longer than similar operations in the laboratory. Decomposition may occur with extended heating, especially if there is uneven heat distribution. Complete removal of residual solids and viscous liquids is difficult from vessels with access limited through manways. Residual solvents may be removed ("stripped") from liquids using specialized stills, e.g., wiped film evaporators, in which the mobile liquid flows over a heated zone. Only rarely are extracts concentrated to dryness.

TABLE 1.4. Comparisons of Operations in the Laboratory and On Scale

	In the laboratory		On scale[a]	
Operation	Commonly used	Easy to effect	Commonly used	Easy to effect[b]
Rotary evaporation	X	X		
Concentrating to dryness	X	X		
Triturating	X	X		
Use of highly flammable solvents (e.g., Et_2O, pentane)	X	X		
Decanting	X	X		
Siphoning	X	X		X
Column chromatography for purification	X	X		X
Drying over solid drying agents (e.g., Na_2SO_4, $MgSO_4$)	X	X		X
Azeotropic drying		X	X	X
Addition of dangerous reagents (e.g., *n*BuLi, CH_3I)	X	X	X	X
Extended additions		X	X	X
Maintaining cryogenic temperature	X	X		X
Fine control of heating / cooling	X	X	X	X
Maintaining constant pH	X	X	X	X
Efficient mixing of heterogeneous systems	X	X	X	X
Tubular flow reactors				X
Rapid quench / transfers	X	X		X
Distillation	X	X	X	X
Solvent displacement by distillation (solvent chasing)		X	X	X
Reslurry		X	X	X
Charcoal treatment	X	X		X
Suction filtration	X	X	X	X
Centrifuge filtration			X	X
Spray drying				X
Tray drying	X	X	X	X
Lyophilization			X	X

[a]"On scale" refers to a reaction run in fixed, immobile vessels of 50 liters or larger size.
[b]Many scale-up operations are easy to effect once the suitable equipment has been commissioned.

IV.C. Triturating

Physically mixing a residue with a solvent, or triturating, is an old means of effecting some purification. Usually the residue is a viscous oil or a solid, and the mixing is performed by hand with a spatula in lab glassware. If the residue cannot be

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readily dispersed in the solvent, attempts to triturate on scale will be difficult to carry out. Recrystallization and reslurrying solids are effective alternatives (Chapter 11).

IV.D. Flammable Solvents

Using highly flammable solvents on scale requires considerable planning for safe operations. Equipment must be grounded to prevent static discharge and induction of fires. To avoid accumulation of volatilized solvents, the head space of equipment must be swept with inert gases. Personnel and operating areas often must be monitored to avoid accumulation of and exposure to dangerous solvents. Such extensive precautions often delay or preclude use of solvents such as pentane and Et_2O. Alternative solvents include heptane and methyl *t*-butyl ether (MTBE) (Chapter 4).

IV.E. Decanting and Siphoning

Heavy, unwieldy, or stationary equipment cannot be manipulated to pour off supernatants. A better alternative is siphoning. Removing a supernatant by siphoning often is unwieldy on scale, because controlled manipulation of the suction hose becomes difficult as the liquid level nears the top of the suspended solids. Siphoning is often easier to carry out in conical vessels or in those with a high height-to-diameter ratio, and such vessels are not commonly used for scale-up operations. It may be advisable to invest time in developing a protocol for siphoning if the process is to be run repeatedly in dedicated equipment.

IV.F. Column Chromatography for Purification

Chromatography is very labor-intensive, considering the time spent in packing the column, applying the crude mixture to the sorbent, eluting with relatively large volumes of solvents, and concentrating the rich fractions for further processing. Time and resources are spent in developing a practical method for large-scale operations, recovering solvents and reconditioning the solid phase. The difficulty of effecting purification by chromatography on scale encourages the process chemist to devise routes with crystalline intermediates, to upgrade quality by recrystallizing. Consequently chromatography is used on scale when other forms of purification are ineffective. Products purified by chromatography have relatively low production volume and high value after processing, and they usually display biological activity at very low dosages. Considerations for chromatography on scale are discussed in Chapter 11.

IV.G. Drying over Solid Desiccants

As discussed earlier in this chapter, drying solutions over Na_2SO_4, $MgSO_4$, or molecular sieves is an operation rarely used on scale, with azeotropic drying being preferred. A fixed bed of molecular sieves may be used if the solute is heat-sensitive or if other considerations such as the time and processing costs of a heated distillation preclude drying by azeotropic distillation.

IV.H. Drying Solutions by Azeotropic Distillation

Solvents with dissimilar polarities often form a minimum-boiling azeotrope upon heating to distill. This operation can be used to remove dissolved or suspended water from some solvents and solutions. Details on azeotropic drying may be found in Chapter 4.

IV.I. Addition of Dangerous Reagents

Setting up safe reaction conditions under which to use toxic reagents is relatively easy in the controlled environment of fume hoods, but considerable thought must be given to using such materials on scale. Once suitable conditions have been put in place for operating on scale, it is often easy and quite safe to effect such reactions. For example, simvastatin is manufactured by alkylation with neurotoxic, volatile CH_3I (Figure 1.4) [17]. This reagent is transferred to the reactor through inert, leak-free lines with permanent connections. (Such plumbing is called "hard-piping.") Thorough analysis of operating conditions is necessary to protect the operators, the plant, and the community.

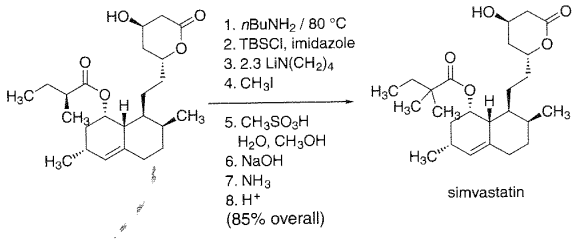


FIGURE 1.4 Preparation of simvastatin using CH_3I

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IV.J. Extended Additions

In most academic settings, addition times are rarely extended unless high dilution is known to be advantageous, e.g., for macrolactonization. Syringe pumps are often used for this operation in the lab, and this equipment is a wise addition to the process lab. On scale it is not uncommon for an addition to require 30 minutes to 3 hours or longer in order to maintain the desired reaction rate, temperature, or ratio of catalyst to substrate. Addition rates are easy to control on scale by using metering pumps or metering valves.

IV.K. Maintaining Cryogenic Temperature

"Cryogenic" temperatures are those of about −50°C and colder. In the lab, reactions are readily cooled by immersing a reaction vessel in a dry ice–solvent bath. For longer reactions or those requiring close control of the reaction temperature, the reactor may be cooled by solvent from a recirculating cooling bath. If the available coolant cannot chill a reactor to the desired temperature, a system may be improvised by cooling a solvent in a kettle with dry ice and pumping the solvent through the reactor jacket. Direct injection of liquid nitrogen into a reaction can afford another alternative. For efficient operations at temperature ranges about −70°C, metal reactors are preferred: commonly used glassed-steel reactors are relatively poor heat conductors, and glass linings may crack at low temperatures due to different thermal contraction of glass and metal.

> **TIP:** It is important to ascertain that expensive metal reactors will not be corroded by reaction mixtures!

IV.L. Fine Control of Heating and Cooling

Once the considerable mass of a large reactor and the solution it contains have reached the desired temperature range, maintaining a reaction temperature can be relatively easy. However, if the reaction is moderately exothermic, removing heat from the mass will require additional time due to the decreased surface area-to-volume ratio on scale (see Chapter 13), and additions may take longer while maintaining the desired temperature range. Repeated operations on scale may

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justify the installation of equipment to monitor and control the temperature and the addition of critical components, thus simplifying operations. Fine control of heating and cooling (±2°C) may be necessary for reproducible crystallizations on scale.

IV.M. Maintaining Constant pH

In the lab and on scale, reactions can be readily controlled using a pH stat, a pH meter with an automatic titrator that maintains the desired pH range by delivering a suitable reagent, e.g., aqueous NH_3. For reactions with enzymes, tight control of pH may be important not only for the desired transformation, but also to avoid degrading the enzyme. Rugged pH probes are available for large-scale operations.

IV.N. Efficient Mixing of Heterogeneous Systems

Mixing is primarily studied by chemical engineers. On scale, baffles and agitators affect mixing in both horizontal and vertical planes by a pumping action. Chemists should consult chemical engineers on how to scale down agitation to simulate large-scale mixing in the laboratory. Since considerable time and labor are needed to change an agitator in a large vessel, changing an agitator is not usually entertained prior to pilot plant batches.

> **TIP:** For routine use, process research and development labs should include powerful overhead stirrers, driven by electric motors or air.

IV.O. Tubular Flow Reactors

When a reaction is passed through small tubular reactors, only small portions of a batch are subjected to conditions of extreme heating or cooling. This process alternative is suitable for reactions of short duration; for slower reactions, multiple passes through the reactor may be necessary. Continuous flow reactors can afford safer conditions than conventional batch operations, as only a small amount of the reaction is subjected to reactive conditions at any moment. Examples of continuous flow reactors are discussed in Chapter 13.

IV.P. Rapid Quench and Transfers

Reaction mixtures can be transferred in the laboratory in the span of minutes or even seconds, but extensive planning is needed to carry out extremely rapid transfers on scale. The rate-limiting step in transferring a liquid is passage through the smallest diameter opening, such as a drop valve of a vessel, a metering valve, or a hose. If the transfer rate is crucial for good yields or quality in the lab, attention should be paid to this aspect for scale-up; continuous reactors may be a suitable alternative.

IV.Q. Distillation

Most solvents can be removed readily from process streams by distillation on scale. Distillation of a product can be very labor-intensive and may require specialized equipment. Once suitable equipment has been installed and commissioned, processing can be relatively trouble-free, especially if the appropriate control equipment is used. Many high-molecular weight molecules are too unstable to distill, making crystalline intermediates and products necessary for convenient operations.

IV.R. Solvent Displacement by Distillation (Solvent Chasing)

To replace a lower-boiling solvent with a higher-boiling solvent on scale, usually the process stream is concentrated and the higher-boiling solvent is added to the concentrate. Then distillation is continued, with the second solvent "chasing" the first.

IV.S. Reslurry

Solids may be stirred in a solvent and recovered by filtration, without ever effecting complete dissolution. Reslurrying can be an effective purification, by removing impurities adsorbed to the surface of the crystals. Reslurrying can also change the morphic state of solids (see Chapter 11).

IV.T. Charcoal Treatment

Cleaning charcoal from laboratory glassware is a trivial undertaking, but days may be required to remove all charcoal from an immobile vessel with access

constrained through a small handhole. On scale, charcoal treatments are done after suitable justification and agreement has been reached with all the affected parties. Often dedicated equipment is used for charcoal treatments, or a solution may be passed through a filter or in-line filter containing charcoal. Additional considerations may be found in Chapter 10.

IV.U. Filtration of Solid Products

Suction filters that are similar to Buchner funnels are often used in pilot plants. These filters may be used in many operations on a small scale. With relatively thick filter cakes, extended filtration times occur. To speed the removal of liquids (deliquoring) from the filter cakes, operations may use other types of filters, such as Nutsche filters, filter presses, and centrifuges [18]. Centrifuges are often used in manufacturing operations for the efficient isolation of solids. Laboratory centrifuges are available for studies before committing a process to scale-up.

IV.V. Drying Solids

Vacuum tray drying, which is analogous to laboratory oven drying to remove solvents from solids, is not efficient for drying batches produced on very large scale, such as 100 kg. For rapid evaporation of solvents, the wet solids must be applied in thin layers, requiring significant amounts of operator time to load and unload dryer trays with product. A variety of dryers are available to mix solids during drying and allow for more rapid and even drying. Difficulties will arise if the solids partially melt or expand in volume (foam up) upon drying. Most scale-up sites have only a few types of dryers, and due to equipment costs optimal dryers may be chosen only for the manufacturing of marketed products. Discussions of dryers may be found in chemical engineering texts [19].

An alternative is spray drying, in which volatile solvents are rapidly removed from an atomized solution. A high-quality feedstock is necessary, as spray drying affords little opportunity for purifying by crystallization.

IV.W. Lyophilization

Lyophilization (freeze drying) may be used to prepare a dosage form that is to be reconstituted for injection. The solution to be concentrated is distributed into small vials, and specialized equipment is employed to freeze the samples and remove the solvent. For other purposes lyophilization is impractical on scale.

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V. SAFETY CONSIDERATIONS

Good processes are safe for the operators, the environment, and the consumer. OSHA has proposed exposure limits for many compounds, and worker safety considerations will only become more stringent with time. An out-of-control, runaway reaction can lead to fatal consequences and to spills and emissions that are injurious to the environment. Environmental emissions standards are posed and regulated by agencies at the federal (EPA), state, and local levels. "Green chemistry" is becoming more important. The consumer is protected by the effective process controls filed with the FDA, so that the purity and impurity levels of the API are held within specified ranges.

At some stage in the development of a process, the reaction hazards need to be characterized. If the reaction is dangerously exothermic, alternative conditions must be sought. Quantifying the exothermic nature of a reaction permits the assessment of the cooling needed, which may dictate the equipment chosen or even encourage the development of alternative operations. The best approach is to have a hazard assessment lab on site for immediate assistance; contract labs can also provide this service.

> **TIP:** Most chemicals are dangerous. Chemicals should be handled with respect and from a position of knowledge; the chemist who is scared of chemicals should move from the bench! One must be familiar with the material safety data sheets (MSDS) for the compounds in use. All wise chemists plan for emergency operations.

The wise practitioner of process development tries to stay informed of unexpected, hazardous reactions, which are often published as letters in *Chemical & Engineering News* and other publications. Even transfer and storage operations should be considered. For instance, transferring a distillate of $SOCl_2$ and EtOAc to drums that had contained $SOCl_2$ seemed a safe method for short-term storage of the distillate. However, this storage led to pressure buildup and violent eruption, probably due to contact of the distillate with elemental zinc in the drum liners [20].

Toxicological properties of intermediates and impurities often dictate safe handling considerations on scale, as routine laboratory safety techniques may not transfer easily to the pilot plant and larger scales. Information on the safety of purchased chemicals may be found in the relevant MSDS. Intermediates prepared during processing may be hazardous to operators, and special handling may be

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necessary (see Chapter 2, Section III.E.). New intermediates should be routinely tested for adverse toxicological effects. A toxicology expert should be consulted before materials are committed to scale-up operations. Some guidelines for anticipating hazardous behavior of some compounds are discussed in Chapter 3.

TIP: For the purposes of minimizing worker exposure and contamination of batches, portable hoods or even small rooms can be set up on the floor of scale-up facilities.

VI. TAKING ADVANTAGE OF SERENDIPITY AND GOOD OBSERVATIONS

All successful scientists look for unexpected results. What at first seems to be a negative result may afford a ready solution to problems if exploited. The classic example is Fleming's discovery of penicillin from a petri dish that had been contaminated by penicillin spores [21]. By exploiting and developing anomalies, four major herbicides were produced with combined sales of over $600 million in 1994 [22]. Workers in the Sharpless laboratory found that charging 10 times the intended amount of pyridine led to a successful oxidation and isolation of acid-sensitive epoxides, which were stabilized by the additional pyridine (Figure 1.5) [23]. Catalysis by copper was detected when old syringe needles were found to be necessary for effective aryl ether formation (Figure 1.6) [24], and a successful process was developed. The unexpectedly easy removal of the normally troublesome by-product triphenylphosphine oxide allowed for ready development of a

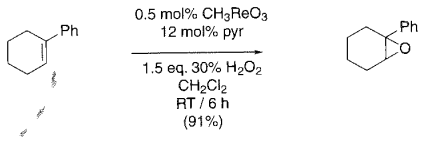


FIGURE 1.5 MTO-mediated epoxidation

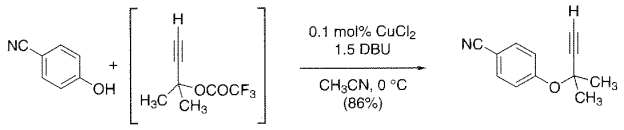


FIGURE 1.6 Copper-catalyzed aryl ether formation

Mitsunobu reaction on a manufacturing scale (Figure 1.7) [25]. Even in these days of urgent development pressures, some room for pursuing anomalies and creativity is still essential. The prepared chemist notices the unexpected and exploits nature to best advantage.

VII. DEFINE THE TIME AVAILABLE FOR PROCESS OPTIMIZATION

Different phases of developing a drug substance require different amounts of optimization, time, and money. Researchers must know how much optimization is needed for each aspect. For the person preparing material for a toxicology study in a kilo lab, drying an extract over Na_2SO_4 may be a well-established step, and investigating an azeotropic drying operation may not be a good use of time. Often one has responsibilities for several phases of a project simultaneously. For

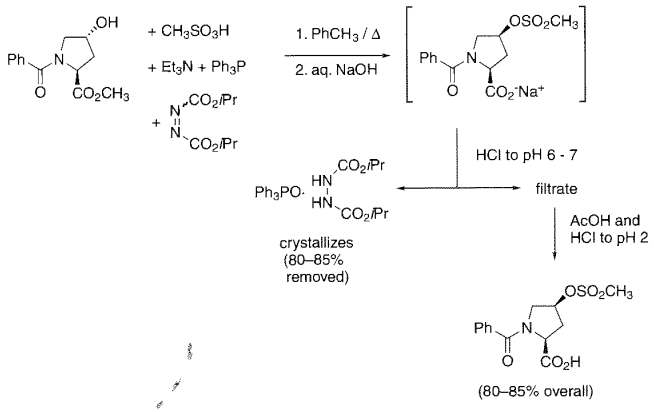


FIGURE 1.7 Preparation of a Mitsunobu product by first crystallizing and removing by-products

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instance, in preparing for a pending pilot plant run, one may identify potential changes in operations that could ease processing. It may be difficult to determine whether the pending batches should be postponed in order to develop a process modification, or if fine-tuning the process should be postponed until the pending campaign has been completed. As another example, one may be preparing a batch for toxicological testing while investigating possible optimization for scale-up to the pilot plant. The former requires close attention to product isolation, while the latter may require more attention to the details of operations. Since aspects of a project often overlap, it is important to know the amount of optimization required for each phase. The amounts of optimization justifiable for several phases of a project are shown in Table 1.5.

One of the goals of successful process development is to design and introduce a smooth-running manufacturing process. Effective laboratory effort prior to scale-up, e.g., pilot plant trials, will pay off by establishing a manufacturing process

TABLE 1.5. Focus of Efforts for Preparing Batches

Reference compound	Use the most expeditious route. Minimal optimization justifiable. Use chromatographic purification if needed.
Kilo lab batches	Cost of raw materials may be fairly high. Invest time to decrease risk of poor yields. Meeting the deadline is primary concern.
Toxicology batches (drug candidate)	Meeting deadline is primary concern, to reach go/no go decision points during API development. Note that animals may be grown in advance of such studies. Invest time to determine and prepare desired final form (salt, polymorph). Prepare high-quality material, but not ultra-pure. If tox studies are conducted on material of an unrealistically high purity, subsequent tox studies will be needed to qualify batches of lower quality.
Pilot plant batches	Expensive to occupy equipment, so optimize for reasonably smooth processing. Cost of raw materials may be significant, so optimize to obtain expected yields. Poor yields and quality impact campaigns to prepare intermediates and API. Preferable to solve any processing problems in lab.
Manufacturing	High cost and value of raw materials and intermediates. Small change in yield or quality has a major financial impact. Extensive efforts to fine-tune processes are readily justified.

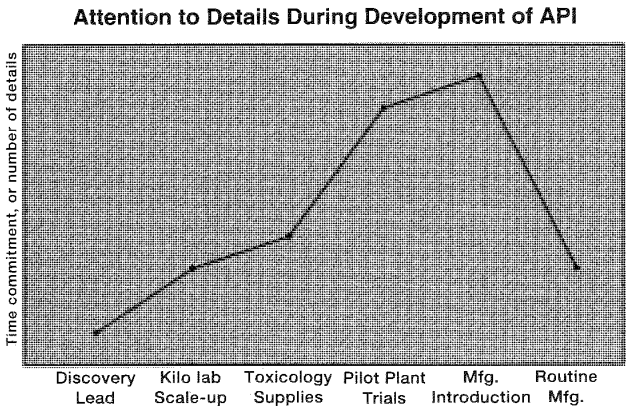


FIGURE 1.8 Attention to details during development of a final product

that provides high-quality material in a timely fashion, with attention to only the necessary details. A graphical depiction is shown in Figure 1.8. In manufacturing operations, even small changes can have a major financial impact; efforts should be focused for optimal understanding and control of a process at this scale.

Within the range of process R & D considerations, different companies may set up groups or divisions to address various aspects of development (Figure 1.9). In some firms, those who develop the initial processes to scale up and prepare material for toxicological studies also are responsible for developing and introducing processes to pilot plant and manufacturing facilities. At the other end of the process R & D continuum, companies may have separate groups for process research, kilo lab operations, scale-up and introduction to pilot plant facilities, scale-up and introduction to manufacturing facilities, and further gradations. Someone involved only with kilo lab operations may choose to pay less attention to details of process development that pertain to further scale-up. Therefore defining the scope of one's responsibilities is important for efficient process development.

TIP: Since very few compounds survive initial screening, the time spent to optimize processes may not be repaid! Targets for process development must be carefully chosen.

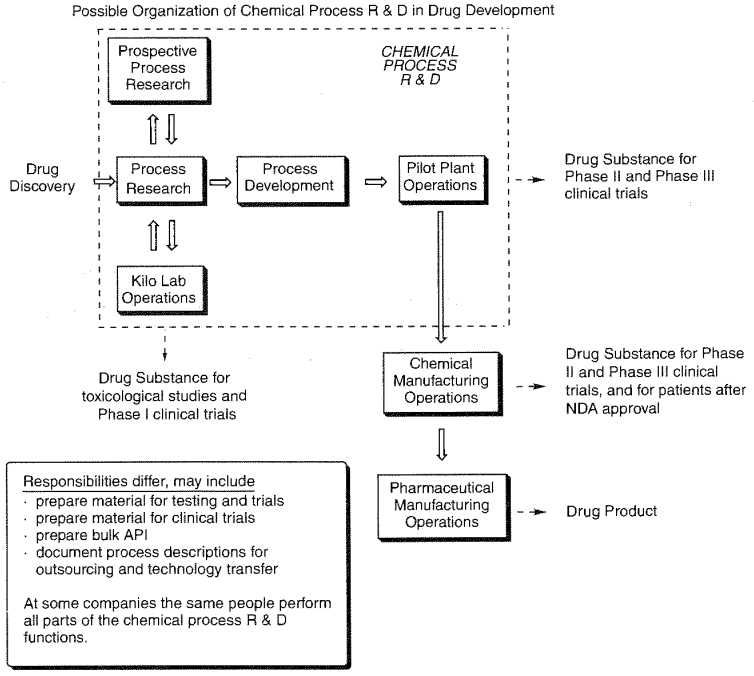


FIGURE 1.9 Possible organization of chemical process R&D in drug development

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CHAPTER 2

Route Selection

I. INTRODUCTION

Routes to pharmaceuticals and fine chemicals can be characterized by two extremes: expedient routes, and optimal routes. Expedient routes are employed early in the development of a drug candidate to expedite the preparation of material that is required for initial testing. Making this material in a timely fashion is necessary to promptly assess the feasibility of developing the compound. Often the initial route used to prepare gram amounts of material is scaled up by numerical factors, with only minimal development efforts. Chromatographic purification and other labor-intensive steps may be incorporated in deference to the goal of preparing the desired amount of drug candidate by the deadline. Preparing large amounts of product using an "expedient" route can be a grueling exercise. Such routes are rarely incorporated into a final manufacturing process.

Optimal routes are developed to manufacture inexpensive bulk drug substance or final product over the lifetime of a patent or longer. The development of these cost-effective routes can justify the expense of many years of work. Laboratory processes are developed and examined on scale, and they evolve into optimal routes that are cost-effective, rugged, and forgiving. The optimal routes are filed with the FDA but may not be disclosed elsewhere.

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Once a compound has been identified as a promising drug candidate, process research investigations are made to develop a practical route to for preparing larger amounts of material that cannot readily be made in a kilo laboratory. Research may occur simultaneously to develop routes that are practical enough to make the kilogram amounts of product and to develop more optimal routes. Personnel efforts may be delicately balanced in order to provide suitable process optimization for scale-up while not delaying the timely preparation of material needed.

The discussion in this chapter and in most of this book focuses on developing an optimal route. By developing early processes that incorporate approaches readily usable on scale, the full-scale development of optimal processes can be compressed. Table 2.1 summarizes characteristics of expedient and optimal routes, which are discussed on the following pages.

II. CHARACTERISTICS OF EXPEDIENT ROUTES

II.A. Familiarity

Routes and reagents may be selected on the basis of an established route, the chemist's familiarity in working with particular reagents, or even the ease of obtaining a reagent from the stockroom. Expensive reagents may be used, and the short-term availability of suitable amounts of specialized reagents may become a key consideration. Intermediates may be outsourced from custom manufacturing houses when the ability to supply material in a timely fashion is more critical than cost or quality.

II.B. Technical Feasibility

Confidence is needed in order to justify risking precious starting materials, reagents, and research time. Researchers may spend long hours faithfully reproducing a narrow set of conditions known to work on smaller scale. Point-type reaction conditions, i.e., those in which a small change affords a dramatic drop in product yield or quality [1], can be tolerated for a few runs when the goal is to immediately provide key amounts of material.

II.C. Availability of Suitable Equipment

The availability of equipment will influence route selection. For instance, if hydrogenation equipment cannot readily be used for scale-up purposes, a route that does not require removal of a protecting group by hydrogenolysis may be selected.

TABLE 2.1 Summary of Route Characteristics

Criteria	Time-efficient Route	Cost-effective Route	Comments
Expediency	X		Appropriate early in drug development
Familiarity	X	X	Familiarity developed during scale-up
Fits equipment	X	X	Practicality is key
Expensive reagents	X		Availability?
Long-term reagent availability		X	Sources may be natural products/biotechnology
Optimized work-up		X	Optimize productivity
Chromatographic purification	X		Tedious on scale
Convergency		X	Less mass of intermediates needed; smaller batches can be made; early intermediates less precious
Telescopic work-ups		X	Isolations are tedious; avoid unless significant purification effected
Protecting groups	X		Minimize number and size (cost and throughput considerations)
Minimized number of steps		X	Optimize productivity
No change in oxidation state		X	Redox reactions burden plants
Incorporate rearrangements/ isomerizations	X	X	Optimize productivity
Stereospecific		X	Chapter 16
Enantiospecific		X	Chapter 16
High overall yield		X	May include statistical optimization
Technically feasible	X	X	Reliability on scale necessary
Point vs. plateau conditions	Point ok	Plateau preferred	Point conditions may be readily controlled on scale
Minimize excess reagents		X	Chapter 5
Outsource intermediates	X	X	Ideal to have more than one supplier
Process research directed to fixed, key late intermediates		X	"Freeze" the final step
Facile rework for final product and key intermediates		X	Key because chromatography not cost-effective
Patent exclusivity	X	X	Optimized process may be patented
Low environmental impact		X	Impact increasing

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TIP: For those reactions not requiring high-pressure reactors to contain hydrogen, transfer hydrogenations can be conducted in equipment routinely used for other purposes [2]. Suitable monitors should be in place to detect levels of hydrogen and oxygen.

III. CHARACTERISTICS OF COST-EFFECTIVE ROUTES

Optimal routes usually require appreciable time to develop. All of the following should be considered as an overall picture.

III.A. Technical Feasibility

Confidence in a large-scale route is usually earned after studies in a pilot plant setting. One goal for scale-up operations is to develop and demonstrate rugged and forgiving processes. A rugged process is one that is understood well enough to produce reproducible quality and yields without resorting to unexpected problem-solving. In a rugged process, critical processing parameters have been identified, and the ranges that are known to be acceptable may be relatively narrow. Plateau-type conditions, where yield and quality are not affected by deviating from the optimal conditions, are preferred [1]. Parameters to be considered include quality of input materials, addition times, reaction times, temperatures, undercharging and overcharging chemicals, pH during reaction and work-up, extended processing, and interrupted processing. A forgiving or robust process is one that will provide the expected quality and yield of product over a wide range of operating conditions. The better a process is understood, the greater the technical feasibility.

In a pilot plant or manufacturing facility, controls can be put into place in order to effect fine adjustment of processes. Processes requiring point-type conditions can be accommodated and must be controlled. For instance, the yield of 3-hydroxy-4-methoxypyrimidine (**1**, Figure 2.1) is sharply decreased by crystallization under conditions more acidic or more basic than pH 5.3, probably due to the amphoteric nature of this compound [3]. Reproducible yields were obtained on scale because the isolation conditions could be tightly controlled.

III.B. Availability of Suitable Equipment

Often routes are chosen in order to use existing large-scale equipment because of the great costs of buying and installing new equipment (and plants). Purchasing

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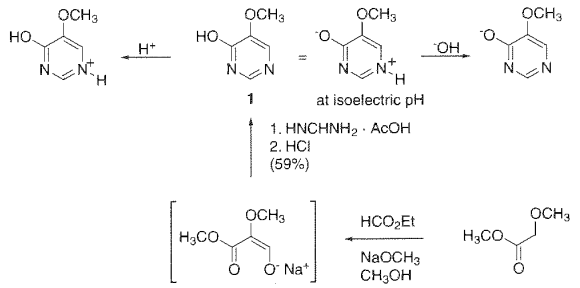


FIGURE 2.1. Ionization of 3-hydroxy-4-methoxypyrimidine due to pH

specialized equipment is usually approved only after detailed cost analyses. Special equipment will be required to scale up some reactions, such as those requiring photolysis, sonication, electrochemistry, specialized crystallization, intimate mixing of heterogeneous reactions, tight temperature control of highly exothermic reactions, and extremely rapid quenching. Some approaches to such specialized conditions will be discussed in Chapter 13.

III.C. Long-Term Availability of Inexpensive Reagents and Starting Materials

To avoid having to depend on one supplier, companies are wise to identify several sources of key reagents, starting materials, and intermediates. Cost, quality, and reliable delivery are critical parameters.

The cost of a material is determined in part by the market demand. For instance, triphenylphosphine is a widely used reagent and is much less expensive than its by-product triphenylphosphine oxide, which has fewer synthetic applications. The cost of starting materials for captopril (Figure 2.2) dropped as the captopril sales reached $1.5 billion per year. The overall development cost of a drug can decrease markedly if process research and development begins with the most appropriate, inexpensive starting material.

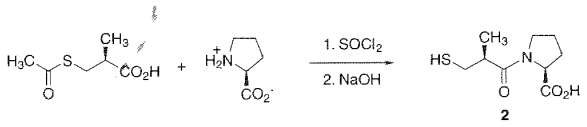


FIGURE 2.2. Preparation of captopril

To ease production schedules, key intermediates may be outsourced from vendors. Reliable delivery of outsourced materials is crucial to making key production goals. By requesting that materials arrive some weeks before they are needed, the company can build a hedge into a campaign schedule. As the success of and demand for the product rises, a company may qualify several suppliers to ensure continued supply of key intermediates.

III.D. Convergent Synthesis

When a synthetic route incorporates convergent subroutes, the total amount of intermediates required for the preparation of a product can decrease dramatically. This is illustrated in Figure 2.3 by four theoretical assemblies of the octapeptide **3**,

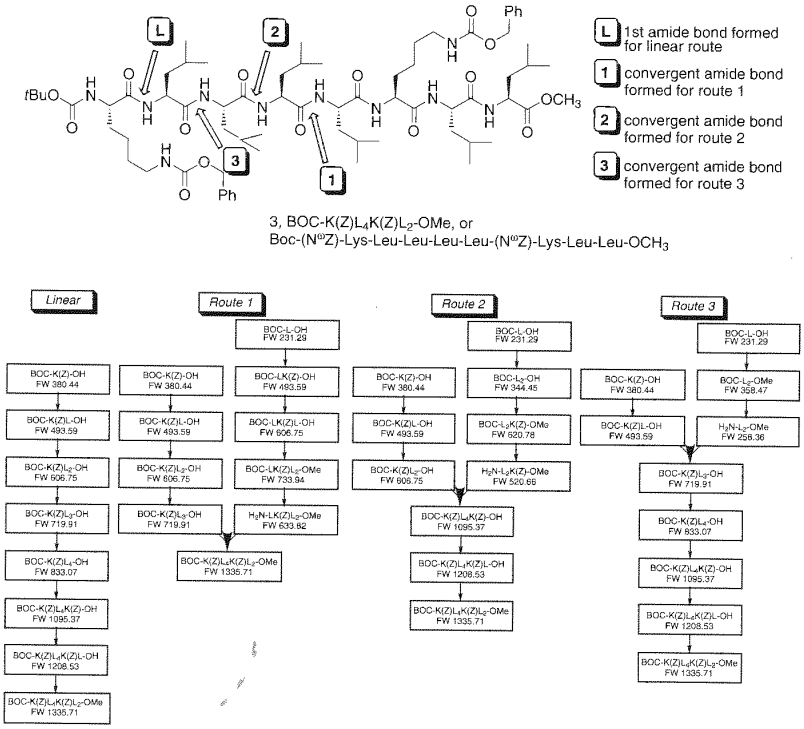
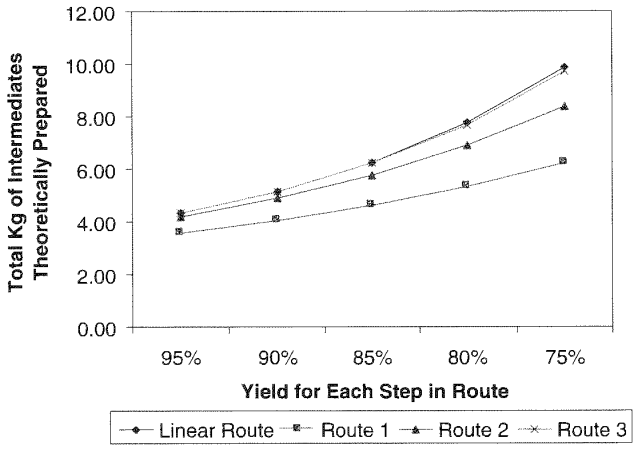


FIGURE 2.3. Model routes for preparing octapeptide **3**

which was prepared by workers at R. W. Johnson [4]. (Compound **3** was prepared by extending the chain from the carbonyl terminus of the amino acid units, an unconventional approach [4].) Figure 2.4 shows that when subroutes converge closer to the end of the synthesis, the total amount of intermediates that need to be prepared decreases significantly. For example, if the yields per step were 75–80%, a linear synthesis would necessitate preparation of about 50 wt% more intermediates than would a synthesis that converged at the end of the route.

Closer examination of Figure 2.4 shows that the total amount of intermediates to be prepared for Route 3 is essentially the same as that for the linear route. To execute the synthesis of the octapeptide in a nonlinear manner, one additional step is required for each convergent route, which increases the amount of intermediates prepared. The additional step is necessary because of the multiple functional groups of amino acids. There are greater savings in the overall amount of intermediates required in routes where the individual subunits do not have multiple reactivity and hence do not require additional steps for selective reactions.

Drawbacks with convergent routes may include the need to prepare and assay an additional intermediate.



Assumptions to model:

1. All derivatized amino acids (e.g., Boc-K[z]-OH and H_2N—L—OMe • HCl) were purchased.
2. After each coupling the intermediate ester was hydrolyzed to the carboxylic acid.
3. All intermediates were stable and no salts were prepared.
4. Yields for each step within a route were identical.

FIGURE 2.4. Effects of convergent synthesis: Total kg of intermediates theoretically required to produce 1 kg of octapeptide **3**

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There are several advantages to incorporating convergency into a synthetic route. First, as the total amount of intermediates decreases, smaller amounts of reagents and starting materials are needed, decreasing cost. Second, smaller batches are needed, which increases flexibility by permitting the use of smaller vessels. If larger equipment is used, fewer batches are needed, which permits equipment and personnel to be used for other purposes. Third, with extended linear syntheses the middle and late intermediates become "increasingly precious," and introducing convergency lessens the value of intermediates and liability from scale-up errors [5].

III.E. Using Telescopic Work-ups

Isolating intermediates has many potential disadvantages. Isolation is usually costly and invariably leads to some loss of valuable material. On a manufacturing scale, isolating intermediates and API requires about 50% of personnel time and about 75% of equipment financial outlay [6]. The additional handling required increases both exposure of operators to pharmacologically potent materials and opportunities for contamination of batches and loss of valuable product. Intermediates may be isolated to ensure key purifications or to comply with protocols filed with the FDA or other regulatory agencies.

Isolations are avoided by telescoping. Telescoping, also known as concatenation or through-processes, is the process of carrying the product of a reaction without isolation into the next step. Inappropriate telescoping can compound the difficulties in isolating a reaction product that is sufficiently pure from the subsequent step, but appropriate telescoping can greatly increase overall yields. For example, three steps were telescoped in the preparation of pergolide mesylate (**4**, Figure 2.5), raising the overall yield from 15–23% to 71% and decreasing the campaign time from 4 - 6 months to less than 2 days [7]. Telescoping enhanced operator safety by reducing possible exposure to these potent compounds: dried solids were handled only twice with the telescoped process, as compared to 18 times with the original route. Route redesign and telescoping for the preparation of ifetroban sodium (**5**, Figure 2.6) reduced the number of steps from 23 to 12 and raised the overall yield from 3 to 28% [8]. In the optimized synthesis, telescoping also eliminated the isolation and handling of the anhydrides, which are potent irritants. Unless significant purification or other benefits are realized by isolating intermediates, telescoping is incorporated as part of cost-effective routes.

III.F. Minimizing Impact from Protecting Groups

Product costs rise due to the cost of reagents and to the additional steps resulting from applying and removing protecting groups. Maximizing atom economy, i.e., "maximizing the number of atoms of all raw materials that end up in the

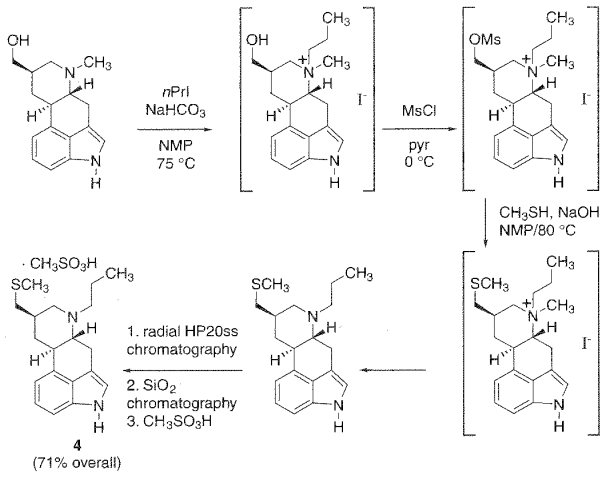


FIGURE 2.5. Preparation of pergolide mesylate by telescoping

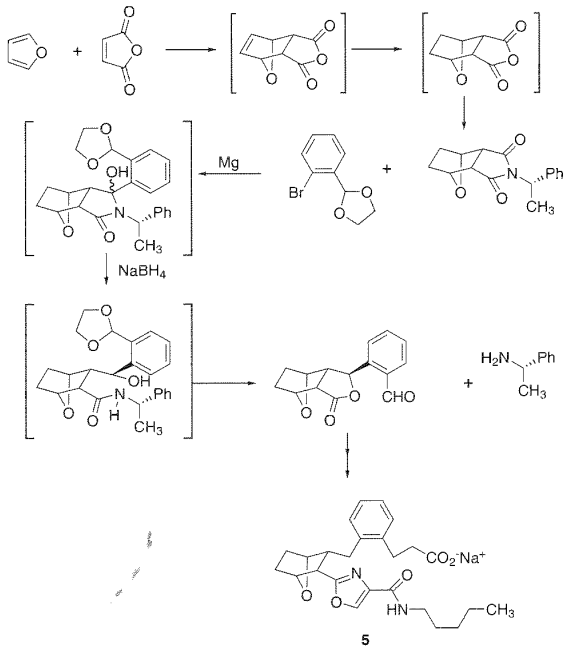


FIGURE 2.6. Preparation of ifetroban sodium by telescoping

product" is an important consideration in minimizing raw material costs, emissions, and waste disposal [9]. For cost-effective routes, it is justifiable to expend considerable effort to minimize the number of protecting groups. Additional considerations are mentioned in Section III.O.

When protecting groups must be used, manufacturers should take care to select the least expensive group on a per mole basis, along with costs associated with protection and deprotection. One consideration often overlooked is minimizing the size of protecting groups: larger groups consume more volume in reactors, thereby decreasing the amount of product skeleton that can be charged. For instance, one should consider using an acetyl protecting group instead of a 9-fluorenylmethoxycarbonyl (Fmoc) group (Figure 2.7), as long as other considerations (e.g., crystallinity of intermediates, ease of deprotection, and elimination of subsequent side reactions) are favorable.

With traditional organic chemistry, it usually has not been possible to avoid protecting groups altogether. Enzymatic transformations often supply the selectivity needed without protecting groups and shorten the length of a synthesis. For example, over 2000 tons per year of aspartame **6** was prepared by the Holland Sweetener Company using thermolysin catalysis (Figure 2.8) [10]. The coupling reaction is remarkable in that it is specific for one enantiomer of racemic phenylalanine methyl ester, and condensation occurs at one of the two carboxylic acid groups in aspartic acid. Selective acylation [11] of a minimally protected sugar derivative is also shown in Figure 2.8.

III.G. Minimized Number of Steps

To decrease the number of operations, an obvious remedy is to redefine the route by using different starting materials that require fewer steps to produce the product. Another similar time-saving approach is to carry out more than one synthetic transformation in one step. For example, three "double reactions" were developed for the benzazepine **7** (Figure 2.9): hydrolysis of a nitrile and an oxazoline, reduction of an amide and an ester/lactone, and cyclization-demethylation [12]. Such "double reactions" save considerable operating time and expenses on scale.

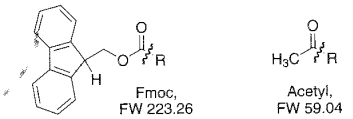


FIGURE 2.7. Relative sizes of fmoc and acetyl protecting groups

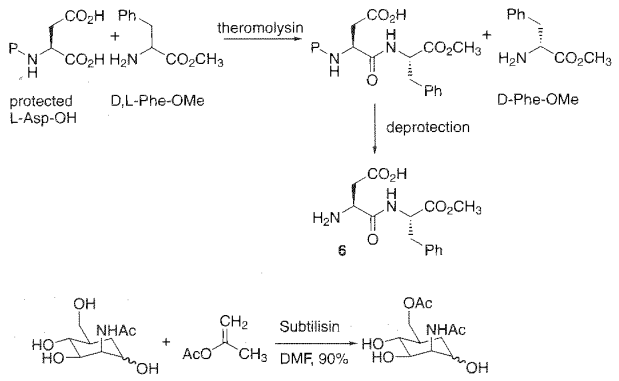


FIGURE 2.8. Selective enzymatic reactions

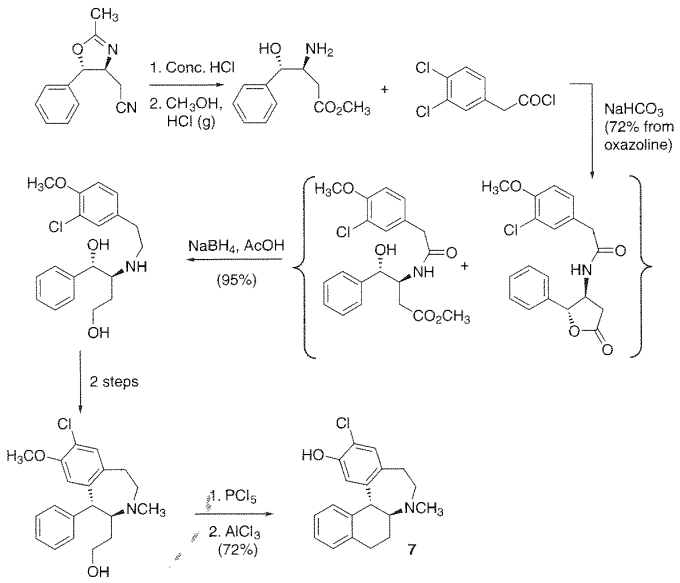


FIGURE 2.9. Three "double reactions" in the preparation of a benzazepine

Some reaction sequences can also be orchestrated so that the first step provides an intermediate that triggers a subsequent conversion. Examples include tandem reactions [13], domino reactions [14], and cascade reactions [15]. A comprehensive review of sequential transformations has been compiled by Tietze and Beifuss [16]. An example of the complexity produced by cascading palladium-catalyzed cyclizations [17] is shown in Figure 2.10.

III.H. Avoiding Adjusting Oxidation States

Adjusting oxidation levels causes unnecessary expenses of time and money if instead intermediates at the suitable oxidation level can be used in the synthetic sequence. The processing burdens of redox steps are greater than those of other steps. Reductions, including reactions with $NaBH_4$ and other hydrides, use or generate hydrogen, either during the reaction or upon work-up. Whenever hydrogen is present, the potential exists for fires and explosions. High-pressure reactors and specially designed reactor suites with blow-out walls may be needed. The expense of preparing specialized facilities to accommodate the presence of hydrogen can limit the number of sites available for processing and hence limit product throughput. Oxidants are often highly reactive and corrosive, requiring specialized handling. In the case of metal-derived oxidants, waste disposal costs can significantly drive up product costs.

For optimal throughput, however, it may be necessary to adjust the oxidation level. In the case of process research leading to losartan (**8**, Figure 2.11), alkylation of the hydroxymethyl imidazole **9** led to a 17:83 ratio of **10**:**11**, favoring the regioisomer that does not produce losartan. Alkylation of the formyl imidazole **12**

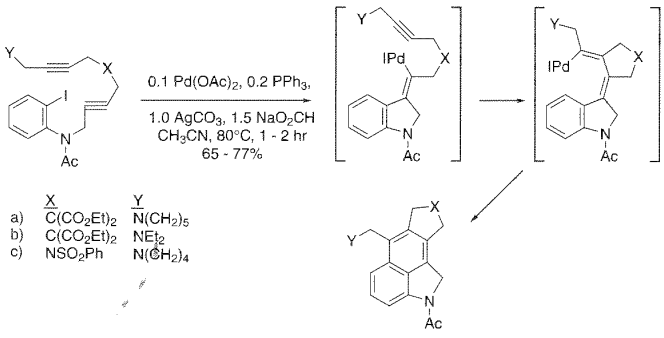


FIGURE 2.10. Palladium-catalyzed cascade reactions

led to an excellent 97:3 ratio in favor of the regioisomer leading to losartan [18]. The dramatically improved yields far outweighed the disadvantage of processing two additional steps.

III.I. Enantiospecific and Stereospecific Reactions

Resolution of enantiomeric materials returns at best only 50% of the mass input, and the remaining material must be converted to product or sent for disposal. If only one chiral center is present, the "wrong" enantiomer can often be racemized, and the desired enantiomer can be isolated by resolution. However, if more than one chiral center is present, racemization of the wrong enantiomer and recovery of the desired enantiomer are often not feasible. A further discussion on asymmetric synthesis may be found in Chapter 16.

> **TIP:** Any reaction that is not enantiospecific or stereospecific should be positioned at the beginning of a synthetic sequence in order to minimize wasted processing downstream.

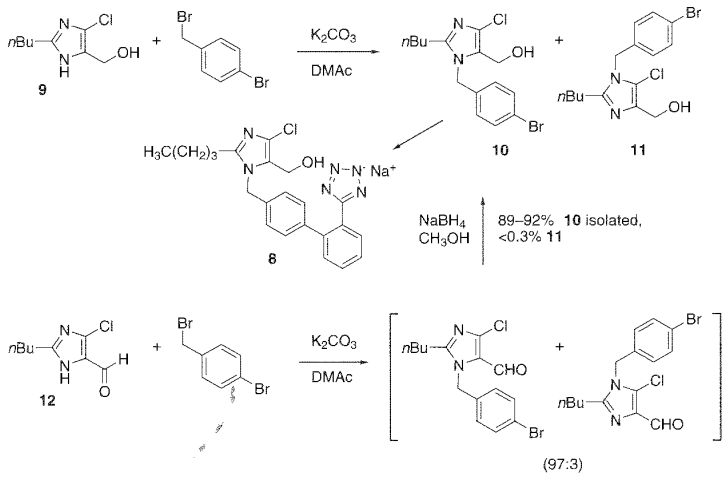


FIGURE 2.11. Alkylation of losartan intermediates

III.J. Incorporating Unexpected Processing

The cost-efficient process will take advantage of unusual occurrences encountered during research and development (Chapter 1, Section VI). For instance, a slow reaction at a sterically congested site may eliminate the need for a protecting group. The by-product of a reaction may oil out of solution, allowing it to be separated as a liquid. By-products may crystallize and be removed by filtration, affording a ready clean-up of the reaction and isolation of the product in good yield.

> **TIP:** When Nature offers a separation, see if it can be exploited to advantage!

III.K. Incorporating Rearrangements

Rearrangements can also be used to incorporate key elements of stereochemistry and regiochemistry from simpler molecules. Silyl-Claisen rearrangement of **13** was reported to lead to a key, chiral vitamin E intermediate (Figure 2.12) [19]. Thermal rearrangement of the salt **14** leads cleanly to the *o*-substituted sulfonic acid **15**, which is a key intermediate in the preparation of dyestuffs (Figure 2.13) [20]. Migration of the acetyl group from the 4-position of **16** to the 6-position affords **17**, a key intermediate in the preparation of sucralose (Figure 2.14) [21]. The acetyl migration affords an equilibrium mixture of **17**:**16** in the ratio of 4:1, and the reaction was driven to completion by crystallization of the product from the reaction mixture. Chlorination of **17** with $SOCl_2$ / Ph_3PO and deprotection provided sucralose.

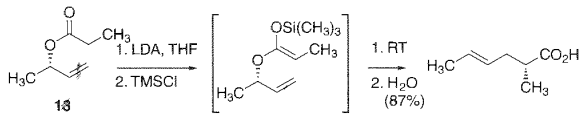


FIGURE 2.12. Silyl-Claisen rearrangement leading to a vitamin E precursor

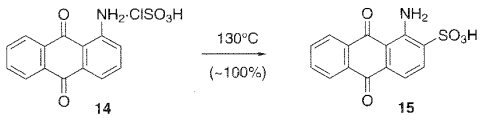


FIGURE 2.13. Preparation of an *o*-sulfonic acid by rearrangement

III.L. Focusing on a Common Penultimate or Key Intermediate

Considerable process research and development may occur on several different routes over time. Usually these routes converge at the penultimate intermediate or key late intermediates. If a drug candidate has been filed with the FDA or other regulatory agency, the characterization of the drug candidate and its penultimate intermediates is of primary importance. Such characterization includes months-long bulk stability studies and detailed analyses [22]. If reaction conditions to prepare a drug substance are different from those previously disclosed to the FDA, bulk stability studies must be repeated to confirm that the quality is the same as or better than that of the drug substance prepared by the filed route. Filing a new route is simplified if the new reaction(s) leads to intermediates that are part of a

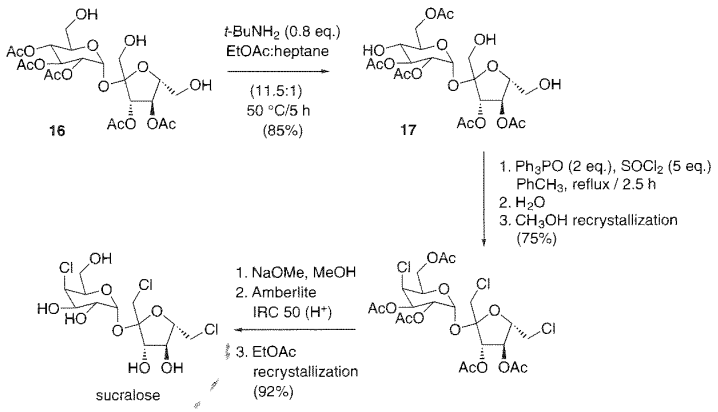


FIGURE 2.14. Preparation of sucralose by migration of an acetyl group and chlorination of an intermediate

filed process. Then it is necessary to demonstrate that high-quality intermediates are produced and that any new impurities generated in preparing the penultimate do not have an adverse impact on the quality of the drug substance.

III.M. Facile Rework for Final Product and Intermediates

The expected quality of final product and intermediates is not always achieved. Cost-effective routes include rework procedures to upgrade batches. Often the products are again subjected to the final crystallization and isolation conditions. In other cases, the chemist develops a purification procedure to upgrade batches contaminated with specific impurities.

To ease purification of the final product, cost-effective routes are designed to incorporate key intermediates that can be readily upgraded without chromatography. Usually a sequence of dissolution followed by hot filtration and recrystallization is employed, but on-scale compounds may also be purified by reslurrying, extraction and reisolation, and other means.

III.N. Patent Protection for Manufacturing Route

Patents allow the assigned company to reap the benefits of selling their researched product without competition for a finite period; the period varies according to the country of origin. For patents issued by the United States Patent and Trademark Office after June 8, 1995, the term begins "on the date of issue and ends 20 years from the effective filing date" [23]. This exclusivity is intended to reward those who have undertaken the risk and cost of developing a new compound. Those who wish to use the material or process described in another's patent are legally required to request permission to do so (usually with the cost of licensing). Failure to do so carries a high risk of legal action.

> **TIP:** Patent laws in the United States require applicants to describe the best conditions embodying their invention that were known at the time of application. Considerable details are published in patents, which supplement the classical chemical literature.

Chemical patents are granted for either composition of matter or processes. Composition of matter patents are filed early in the development of a compound. If the route to prepare large amounts of drug substance is significantly different

from the route described in the composition of matter patent, or if new intermediates or salts are part of the optimized route, filing a process patent may be considered. Years of development time is required to develop optimal processes. In order to avoid helping competitors, some firms never disclose the optimal processes for making valuable API, and few disclose key details. Even so, the details provided in patents may be very useful in developing processes for similar compounds.

TIP: The risk in not applying for a patent on new compounds or processes is that competitors may receive a patent covering the work done in your company. In that case it would be necessary to establish when your work had been done. This underscores the importance of updating, signing, and witnessing notebooks!

When patented intermediates are part of the route to the API, companies may be driven to create patent-unencumbered routes to new drugs to avoid licensing and to contain production costs. An uncommon Mn(III)/air oxidation was developed to circumvent the need to use a patented intermediate **18** in the production of aztreonam [24] (Figure 2.15).

III.O. Minimized Environmental Impact

Environmentally conscientious chemistry is becoming profitable (or at least the alternatives are becoming costly) [25–28]. The driving force for many initiatives is

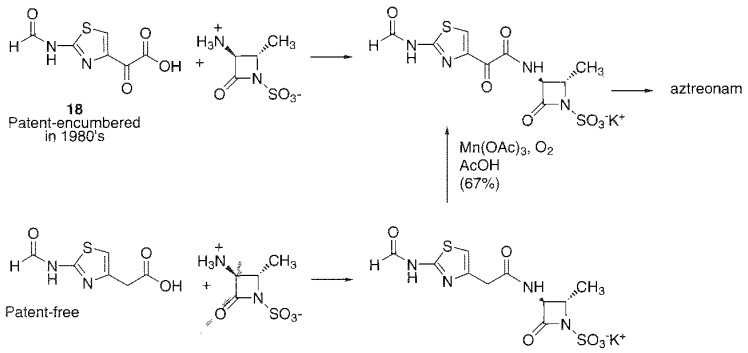


FIGURE 2.15. Preparation of an aztreonam precusor by Mn(III)/air oxidation

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laws implemented by the Environmental Protection Agency (Table 2.2) [29]. The type and volume of waste streams are minimized with a cost-effective route incorporating "green chemistry." For example, reactions generating waste from stoichiometric toxic metal reagents (e.g., the oxidation of a secondary alcohol with pyridinium chlorochromate) are replaced by using catalytic amounts of reagents or reagents that are more environmentally benign (see Figure 2.16) [30]. In a dedicated manufacturing facility, considerable attention is paid to recovering and recycling chemicals, particularly solvents. Some aqueous wastes may be biologically remediated on site [31]. At many scale-up facilities, waste is sent off-site for conscientious disposal by licensed professional firms. With "cradle-to-grave" responsibilities, companies that generate waste can be liable for years. The political importance of minimizing environmental impact is rising with enhanced appreciation of our finite environmental resources.

TIP: Today the cost of conscientiously disposing of a drum of waste streams can be greater than the cost of a drum of reagents.

There are at least three measures of "greenness." Atom efficiency, as defined by Trost, was discussed in Section III.F. "Eco-efficiency" has been defined as the

TABLE 2.2. Selected Environmental Laws Relevant to the Chemical Industry

- Clean Air Act: Air emissions
- Clean Water Act: Discharges of pollutants to waters of the United States
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA): Federal "Superfund" to clean up uncontrolled or abandoned hazardous-waste sites
- Emergency Planning and Community Right-to-Know Act (EPCRA): Community safety (RTK)
  —Every state must do RTK
  —Reporting threshold varies per chemical
- Federal Insecticide, Fungicide, and Rodenticide (FIFRA): Pesticide distribution, sale, and use
- Pollution Prevention Act: Reducing pollution through cost-effective changes in production, operation, and raw materials use
- Resource Conservation and Recovery Act (RCRA): Control hazardous waste from "cradle to grave"
- Toxic Substances Control Act: Authorization to test, regulate, and screen all chemicals produced or imported into the United States
- The Toxics Release Inventory (TRI): Contains information about releases and transfers of more than 650 toxic chemicals and compounds to the environment

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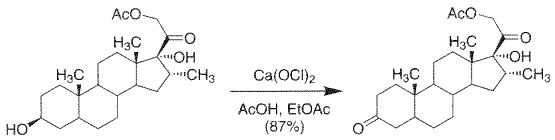


FIGURE 2.16. Oxidation of a secondary alcohol with $Ca(OCl)_2$

"optimal use of material, energy, human resources, and capital to bring innovative products to market" [32]. Sheldon has also introduced the term "E factor," which assesses environmental acceptability as the weight ratio of waste/product. The amount of waste is driven up by the formation of inorganic salts [33]. The E factor is highest by far for the pharmaceutical and fine chemicals industries (Table 2.3) [34]. One can argue that the amount of waste generated by these industries is smaller than that generated by the others, particularly since multiple steps are characteristically involved in preparing pharmaceutical and fine chemicals. Nonetheless, the data indicate that there is room for improvement, and green chemistry considerations will become increasingly important as international attention to the environment builds.

There are two approaches to minimizing waste. The traditional approach is to reduce waste "at the end of the pipeline." Decreased solvent usage, decreased solvent emissions, and better solvent recovery and recycling are included in this approach. With higher-boiling solvents, a smaller emission burden may be expected, but recovery by distillation becomes more costly.

The second green approach is to minimize waste at the source. Catalysts are very important in this approach. Synthetic organic chemists have devised some elegant chemistry involving transition metals with scaffolds. Enzymes have assumed a great importance on manufacturing scales and in the laboratory [35]. Supported, regenerable reagents are being used not only to avoid the burden of one-time use but also to increase the ease of working up reactions. Polymeric

TABLE 2.3. By-Product Waste Generated by Factors within the Chemical Industry

Industry	E factor
Petroleum	<1
Bulk chemicals	1–5
Fine chemicals	5–50
Pharmaceuticals	25–100

reagents and zeolites fall into this category of reagents [36]. "Neat" (solvent-free) reactions are used when appropriate to increase productivity and to avoid the difficulties associated with solvent emissions and recovery. A three-step procedure for making ibuprofen was developed by Boots, BASF, and Hoechst-Celanese to replace a six-step route that generated a large amount of waste by-products (Figure 2.17) [33, 37]. Alternative reagents are being used, such as the oxidation with $Ca(OCl)_2$ in Figure 2.16, and the use of PTC (phase-transfer catalysis) to avoid the use of strong bases and high-boiling water-soluble solvents [38]. An interesting example is the preparation of ibuprofen by methylation alpha to a carboxylic acid group using NaOH instead of strong bases (Figure 2.18) [39]; under other conditions it would be necessary to generate the dianion of **19** with bases such as LDA in order to affect the methylation. New reagents were used as alternatives to DMSO in the Moffat-Pfitzner oxidation of secondary alcohols (Figure 2.19) [40]; the by-products **20** and **21** are odorless, in contrast to the volatile, malodorous dimethyl sulfide generated from DMSO. Minimizing waste at the source will become increasingly important in the future.

IV. USING COST ESTIMATES TO ASSESS THE ULTIMATE ROUTE

The selection of the optimal route is driven by financial considerations. Generating cost estimates for different routes in spreadsheet format allows easy comparison. The key in preparing and using such cost estimates is to use the same assumptions consistently and to be aware of factors not included in the calculations.

Usually cost estimates include the cost and equivalents of starting materials and reagents, yields of products of acceptable quality, and total kilos of intermediates required per kilo of product. Other factors that may be considered include

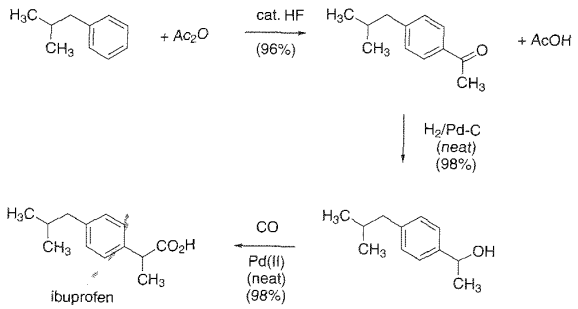


FIGURE 2.17. An efficient three-step process for making ibuprofen

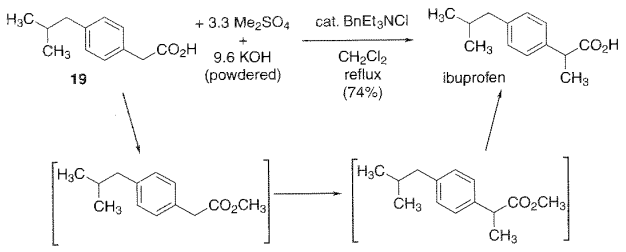
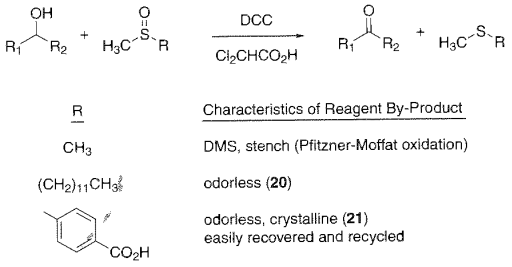


FIGURE 2.18. Methylation of an arylacetic acid by PTC

process throughput (product produced per unit time), disposal costs, the amounts of solvents, reagents, and starting materials that can be recovered and recycled, and the amounts of intermediates and product that can be recovered as second crops. The costs of labor and fixed and variable overhead may not be part of an estimate for material produced in-house: it is simpler to choose processes that maximize product throughput and minimize wastes. Companies that contract a custom manufacturer to provide intermediates or API (outsourcing) can expect to pay the costs of labor and of fixed and variable overheads.

A typical spreadsheet is shown in Figure 2.21. This example estimates the cost of preparing 1 kg of amine **26** using the Curtius rearrangement shown in Figure 2.20 [2]. For this spreadsheet the price of intermediate **22** was estimated to be $200/kg, and for convenience other prices were taken from the 1998–1999 catalog of the Aldrich Chemical Company. For this four-step preparation, only 3.11 kg of intermediates per kilogram of product would need to be prepared and isolated. This low ratio of isolated intermediates to product is due to the few steps involved, the telescoping of one of the steps, the average yield of 92% per step,



R	Characteristics of Reagent By-Product
CH_3	DMS, stench (Pfitzner-Moffat oxidation)
$(CH_2)_{11}CH_3$	odorless (**20**)
	odorless, crystalline (**21**) easily recovered and recycled

FIGURE 2.19. Alternatives to DMSO in the Moffat-Pfitzner oxidation

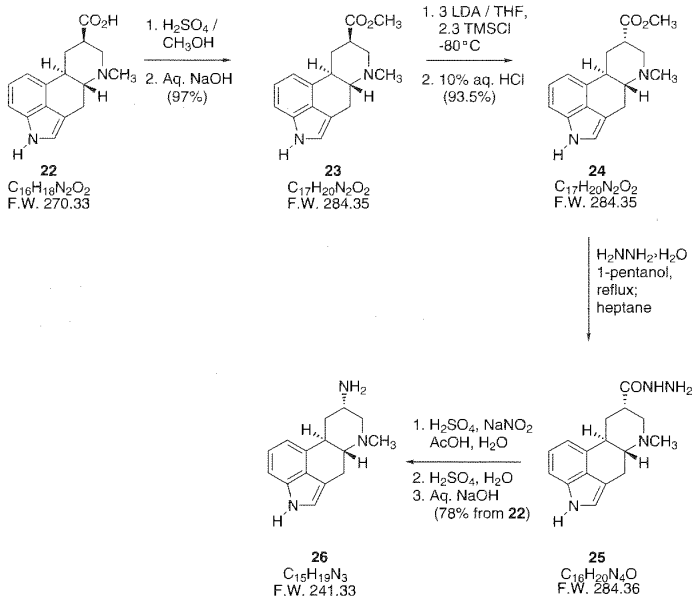


FIGURE 2.20. Preparation of amine **26** by Curtius rearrangement

and the similar molecular weights for intermediates and product. For sequences of 10–15 steps, a total isolated intermediates/product ratio of 10:1 is often set as a goal, and ratios of about 15:1 are common.

Cost estimates can quickly show which components contribute heavily to the cost of the product and indicate where further optimization would be profitable. In the case of the estimate in Figure 2.21, *n*-hexyl lithium, the starting material **22,** and THF are the two most expensive components for preparing 1 kg of **26**. Bulk amounts of these materials could be purchased more cheaply than catalog amounts. A cheaper base to generate lithium diisopropylamide could be substituted for *n*-hexyl lithium, but reagent cost is not always the primary consideration. The authors chose *n*-hexyl lithium over *n*-butyl lithium because the by-product hexane is more recoverable, affording a more eco-efficient process. Using less THF or reusing this solvent could decrease the overall cost considerably.

Assigning monetary values to other considerations may be difficult or impossible. Process flexibility and equipment availability may be critical. For instance, to accommodate beneficial trade considerations it may be desirable to manufacture a product in another country, whereas a route that uses locally available equipment may be selected. Financial projections may be necessary to decide whether

Step	Reaction Yield	Raw Material	F.W.	Cost	density kg / L	Cost	Published Charges	Equiv. per rxn.	Amt. per kg of 1	Cost per kg of 5	Contribution to Total Cost
1	97.0%	Acid 22	270.33	$200 / kg (estimate)		$54.07 / mol	175 g	1.00 mol	1.57 kg	$314.67	18.8%
(esterification)		Sulfuric acid, 95-98%	98.08	$82.60 / 10 L	1.840	$0.44 / mol	1.78 mol	2.75 mol	16.00 mol	$7.05	0.4%
		MeOH	32.04	$82.35 / 18 L	0.791	$4.58 / L	1100 mL	6.29 L / kg of 1	9.89 L	$45.25	2.7%
		NaOH (in 2% aq.)	40.00	$111.80 / 12 kg		$0.37 / mol	3345 mL	2.58 mol	15.04 mol	$5.60	0.3%
2	93.5%	Ester 23	284.35				52.6 g	1.00 mol	1.61 kg	NA	
(epimerization)		Diisopropylamine	101.19	$170.00 / 18 L	0.722	$1.32 / mol	74.7 mL	2.88 mol	16.27 mol	$21.53	1.3%
		n-HexLi, 2.5 M in hexane	92.11	$93.90 / 1L	0.699	$37.56 / mol	0.53 mol	2.84 mol	16.05 mol	$602.96	36.0%
		TMSCl	108.64	$25.15 / 500 mL	0.856	$6.38 / mol	51 mL	2.17 mol	12.26 mol	$78.29	4.7%
		THF	72.11	$145.15 / 18 L	0.889	$8.06 / L	675 mL	12.83 L / kg of 2	20.60 L	$166.12	9.9%
		HCl, 37% in water	36.46	$66.00 / 10 L	1.200	$6.60 / L	146 mL	2.78 L / kg of 2	4.46 L	$29.41	1.8%
		Potassium carbonate	138.21	$60.25 / 5 kg		$12.05 / kg	100 g	1.90 kg / kg of 2	3.05 kg	$36.78	2.2%
		Activated carbon		$84.75 / 5 kg		$16.95 / kg	2.5 g	0.05 kg / kg of 2	0.08 kg	$1.29	0.1%
		Filter agent, approx.		$29.00 / 2.5 kg		$11.60 / kg	10 g	0.19 kg / kg of 2	0.31 kg	$3.54	0.2%
		iPrOH	60.10	$98.15 / 18 L	0.785	$5.45 / L	430 mL	8.17 L / kg of 2	13.12 L	$71.56	4.3%
3	100.0%	Ester 24	284.35				100 g	1.00 mol	1.50 kg	NA	
(hydrazide	(assumed;	Hydrazine monohydrate	50.06	$138.05 / 2.5 kg	1.032	$2.76 / mol	44 mL	2.58 mol	13.61 mol	$37.64	2.2%
formation)	telescoped)	1-Pentanol	88.15	$105.70 / 18 L	0.811	$5.87 / L	800 mL	8.00 L / kg of 3	12.01 L	$70.51	4.2%
		Heptane	100.21	$70.60 / 16 L	0.684	$4.41 / L	700 mL	7.00 L / kg of 3	10.51 L	$46.36	2.8%
4	78.5%	Hydrazide 25	284.36				from above	1.00 mol	NA kg	NA	
(rearrangement)	from ester 3	Sodium nitrite	69.00	$20.00 / 3 kg		$0.46 / mol	29.8 g	1.23 mol	6.48 mol	$2.98	0.2%
		98% Sulfuric acid	98.08	$82.60 / 10 L	1.840	$0.44 / mol	66.4 g	0.66 kg / kg of 3	1.00 kg	$0.44	0.0%
		Acetic acid	60.05	$142.70 / 19 L	1.049	$7.51 / L	171 mL	1.71 kg / kg of 3	2.57 kg	$19.28	1.1%
		Aminosulfonic acid (Alfa)	97.09	$56.60 / 0.5 kg		$10.87 / mol	7.2 g	0.21 mol	1.11 mol	$12.10	0.7%
		NaOH, in 30% aq.	40.00	$111.80 / 12 kg	1.300	$0.37 / mol	553 g	39.31 mol	207.51 mol	$77.33	4.6%
		Filter agent, approx.		$29.00 / 2.5 kg		$11.60 / kg	16 g	0.16 kg / kg of 3	0.24 kg	$2.79	0.2%
		MeOH	32.04	$88.20 / 18 L	0.791	$4.90 / L	321 mL	3.21 L / kg of 3	4.82 L	$23.61	1.4%
		Amine 26	241.33						1.00 kg		
		Total isolated intermediates to prepare 1 kg of 26							3.11 kg		
Total cost to prepare 1 kg of 26										$1,677.08	

Using best prices from Aldrich 1998 - 1999 catalog, except where indicated.

FIGURE 2.21. Cost estimate worksheet for preparing 1 kg of amine **26**

long-term profits can justify the purchase of specialized equipment. Highly reliable processes are preferred in manufacturing sites, so that the need to rework batches is minimized. Chemical engineers should be involved to help in assessing processing reliability. Routes that prepare stable intermediates are preferred, because poor shelf life limits the overall flexibility in processing. The ideal route will not generate irritating and toxic intermediates. To define the ultimate route, it is best to consider route characteristics for each product to be manufactured.

V. SUMMARY

Many factors are important in route selection. The range of criteria can be covered by considering the characteristics of the two extremes, expedient routes and optimal routes. The priorities of factors for route selection depend greatly on the amount of time available and other factors, as discussed in Chapter 1.

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CHAPTER 3

Reagent Selection

I. INTRODUCTION

After choosing the synthetic route to a target compound, the chemist can readily focus on selecting the appropriate reagents. The primary goal for selecting reagents is to obtain the desired product in high yield with minimal effort during work-up. The suitability of reagents for scale-up work is determined by reactivity/selectivity, cost, availability, ease of scale-up operations, and many other practical considerations. This chapter will discuss characteristics of the ideal reagent, safety and toxicity considerations, the importance of examining the cost of reagents and atom efficiency and will give examples from families of reagents useful for scale-up. Fundamental trends in reagents, e.g., the decreasing basicity of the series *n*BuLi>LDA>NaH>KO*t*Bu>NaOMe~NaOH>Na_2CO_3>$NaHCO_3$, are not discussed here.

II. THE IDEAL REAGENT FOR SCALE-UP

The ideal reagent produces the desired product in high yield in the expected time frame with minimal effort needed for work-up and isolation of the product.

Sun Ex. 1022

When reactions are run repeatedly in order to accumulate material (campaigns), using the best reagent may be critical to minimize problem-solving needed for any run. Cost, availability, ease of handling, waste disposal considerations, and other factors become increasingly important as more material is required. Some of the characteristics of the ideal reagent are shown in Table 3.1; no reagent satisfies all of these characteristics.

II.A. Importance of Writing a Balanced Equation

One of the first steps in selecting reagents is to write a balanced equation for the reaction being developed. This exercise often reveals many aspects of process

TABLE 3.1. Characteristics of the Ideal Reagent

Characteristics	Comments
Specific for the desired synthetic transformation	With increased reactivity, shortened reaction times result, often at the expense of reaction selectivity.
Nontoxic to operators and analysts	Increased time required for handling more toxic reagents.
Poses no chemical reaction hazard to personnel	Consider the safety of operators, equipment, and the community.
Inexpensive	Minimize overall cost of product.
Readily available	Consider outsourcing specialized compounds, perhaps from multiple vendors. Note that shipping regulations may vary for different states and countries.
Consistent quality from batch to batch	May eliminate the need for running use-tests.
Stable, with good shelf-life	Good stability at room temperature preferred.
Readily generated and used if not stable	Reproducible generation minimizes or eliminates analysis time.
Handled without attention to special conditions, e.g., stable to the moisture and oxygen in air	Inert gases routinely used on scale for safety.
Readily transferred into reactors	Liquids and solutions are preferred. Solids, particularly dusts, may pose difficulties.
Chosen to facilitate work-up and efficient isolation of pure product	Should have no adverse effect on the work-up of the product.
Produces non-toxic by-products	Minimize disposal costs.
Catalytic, and readily recovered and reused	Recovery and reuse are important for costly catalysts used on large scale.
Requires no specialized equipment or facilities	Selectivity and high-yielding reactions may justify purchase of specialized equipment, e.g., hydrogenation facilities.
Has desired solubility for reaction and work-up	High solubility under reaction conditions permits fast reactions and high productivity; insoluble reagents may be preferred for ease of work-up.

development that are important for running the reaction and for optimizing work-up. Feedback from these considerations may determine reagent selection.

The hydrogenolysis of the chlorinated oxindole **1** provides an interesting example (Figure 3.1). Transfer hydrogenation was used, with $H_2NNH_2 \cdot H_2O$ (**2**) as the reductant [1]. The authors did not discuss why this reagent was chosen over H_2 or other reagents (e.g., ammonium formate) that generate H_2 under transfer hydrogenation conditions. Hydrazine (rocket fuel) was routinely used for reductions at this site, and **2** is safer than anhydrous hydrazine. A benefit of using **2** is that the by-product (N_2) is readily removed from the reaction. Cyclohexadiene, sometimes used for transfer hydrogenations, is not a desirable substitute for **2** because the by-product is benzene, which requires additional considerations to comply with regulatory agencies. When $NaH_2PO_2 \cdot H_2O$ was used in place of **2**, the by-product inorganic salts complicated work-up, as extractions at 70°C were needed to recover the catalyst. Based on the by-products generated from reduction, **2** is preferred over hydrazine, cyclohexadiene, and $NaH_2PO_2 \cdot H_2O$. The use of hydrogen seems to be a reasonable alternative to **2**, but at least for scale-up this facility was familiar with and preferred to use $H_2NNH_2 \cdot H_2O$.

II.B. Safety and Toxicity Considerations

The wise chemist consults the material safety data sheet (MSDS) before handling any new chemical in the laboratory. The reaction hazards posed by chemicals must be thoroughly assessed before any reaction is run on scale. The MSDS also includes information that has been compiled about the toxicological hazards of specific chemicals. An MSDS may be found with the shipment of a chemical, in databases within a company, or in databases accessible through the Internet [2].

All chemists should be aware of basic toxicological considerations for chemicals they use. Many companies arrange for intermediates and target compounds to be subjected to toxicology screens in order to gather information for the safety of those preparing or handling these compounds and ultimately for filing with regulatory agencies. Unfortunately, the MSDS or in-house databases may not be up to date, or testing may not have been completed on compounds that have recently come into development. In spite of these efforts and the information in MSDSs,

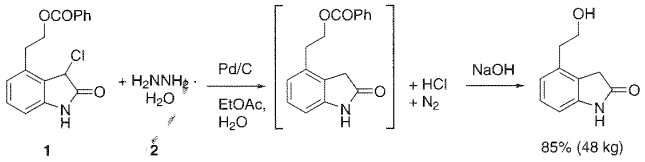


FIGURE 3.1. Hydrogenolysis of a chlorinated oxindole

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the chemist is ultimately responsible for his or her safety and the safety of coworkers.

Toxicological considerations can be broken down primarily into four areas: corrosivity, selective metabolic poisons, electrophilicity, and bioactivation [3–5]. Corrosivity is familiar to the chemist: examples include mineral acids, HCO_2H, NaOH, and phenol. Other compounds generate corrosive by-products, as in the reaction of an acid chloride with nucleophiles, including atmospheric water, to generate HCl. Selective metabolic poisons include cyanide and H_2S. Some pharmaceutical agents and intermediates may also be considered selective metabolic poisons. Included in this group are anticancer agents and compounds with low margins of safety.

Electrophilic reagents can react with the nucleophilic groups of proteins and genetic material to produce covalently modified products, damaging tissue and perhaps leading to cancer. Reactions of some functional groups are shown in Figure 3.2. Especially toxic are compounds containing two or more electrophilic centers, as reactions can lead to cross-linking and significant damage to tissue and cellular material. Drugs and foreign compounds are metabolized by oxidation, reduction, and hydrolysis, and metabolism usually aids in removing such compounds from the body [6]. Metabolism can also generate electrophiles by bioactivation [7], and some examples are shown in Figure 3.2.

Guidelines for repeated exposure to chemicals have been established by the American Council of Governmental and Industrial Hygienists (ACGIH) [8], and these may be used to assist in controlling health hazards. Threshold Limit Values (TLVs) are the concentrations of airborne substances to which it is believed that people can be exposed daily without adverse health effects. TLVs are measured in units of ppm (parts per million) or mg/m^3. There are three categories of TLVs: the TLV-Time-Weighted Average (TLV-TWA), the TLV-Short-Term Exposure Limit (TLV-STEL), and the TLV-Ceiling (TLV-C). The TLV-TWA is the amount of a substance that most people can be exposed to for an average of 8 hours a day over a 40-hour week without adverse effects. The TLV-STEL is the concentration that should not be exceeded over a 15-minute period, and the TLV-C is the concentration that should never be exceeded. It must be stressed that TLVs are guidelines.

II.C. Cost of Reagents

Often a family of reagents has been developed to carry out a synthetic transformation. For example, many reagents have been employed to form a peptide bond, which is essentially a dehydration (Figure 3.3). Table 3.2 lists several reagents ranked by decreasing cost, along with some advantages and disadvantages of these reagents. In this case **the costs per mole differ by as much as two orders of magnitude**. Specific costs are not included in this table, as the costs of such

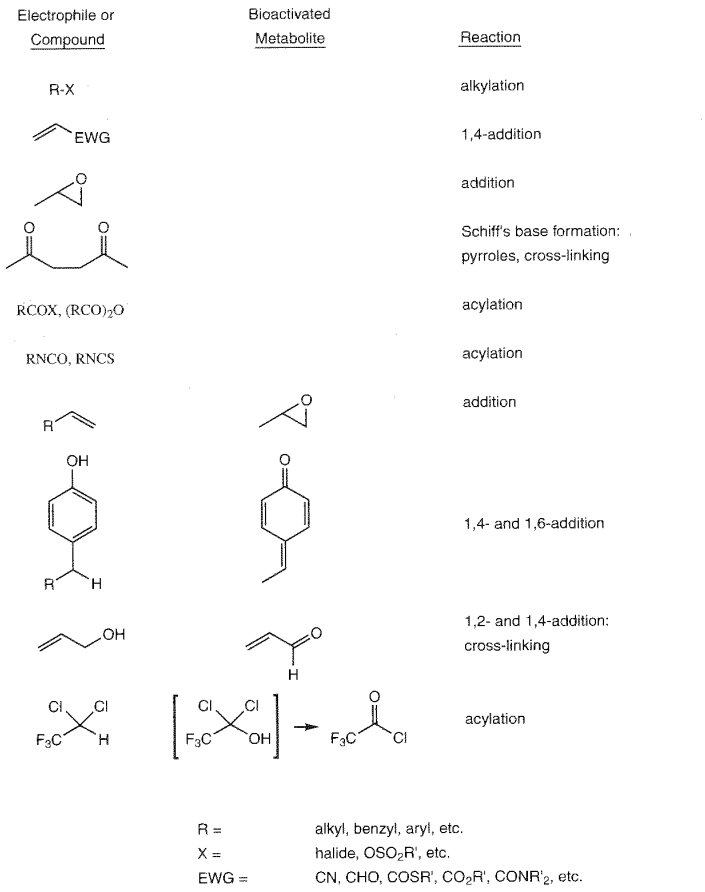


FIGURE 3.2. Toxicological considerations: Reaction of electrophiles

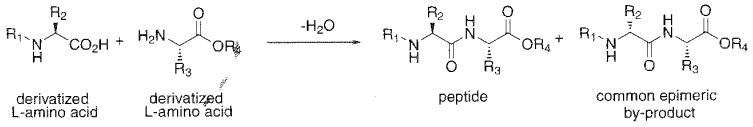


FIGURE 3.3. Generalized peptide bond formation

TABLE 3.2. Selected Peptide-Bond Forming Reagents Arranged in Order of Decreasing Cost[a]

Reagent	Relative cost[b]	Mechanism to activate RCO_2H	Comments
Woodward's Reagent K	830	Active ester	Water-soluble by-products ease work-up.
1-(3-Diethylaminopropyl)-3-ethylcarbodiimide ("water–soluble carbodiimide," or WSC, or EDC)	240	Active ester	Water-soluble by-products ease work-up.
Vilsmeier reagent (chloromethylene-dimethylammonium chloride); amine and base	100	Acid chloride[c,d]	Epimerization α- to carbonyl may prove problematic[e].
Propane phosphonic acid Anhydride[f]	35	Mixed anhydride	Water-soluble by-products ease work-up.
Diethyl chlorophosphate and base; amine and base[g]	20	Mixed anhydride	Water-soluble by-products ease work-up.
Dicyclohexylcarbodiimide (DCC)	6	Active ester	Complete removal of by-product DCU may be difficult[h]; N-acyl urea by-products may form[i].
Isobutyl chloroformate and base; amine and base[j]	3	Mixed anhydride	Typically run at −15 to 5°C; water-soluble by-products
Pivaloyl chloride and base; amine and base	2	Mixed anhydride	Some pivalamide may form; water-soluble by-products
Thionyl chloride; amine and base	1	Acid chloride[c,d]	Epimerization α- to carbonyl may prove problematic[e].

[a]Relative cost per mole of coupling reagent for research quantities.

[b]Cost of base ignored for purpose of spreadsheet.

[c]Bechtolsheimer, H.-H.; Kunz, H., "Coupling of Sterically Hindered Peptide Bonds - A Renaissance of the Acid Chloride Method." *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 630.

[d]Stoner, E. J.; Stengel, P. J.; Cooper, A. J., "Synthesis of ABT-378, an HIV Protease Inhibitor Candidate: Avoiding the Use of Carbodiimides in a Difficult Peptide Coupling." *Org. Process Res. Dev.* **1999**, *3*, 145.

[e]Racemization through oxazolone formation: Kemp, D. S.; Wang, S.-W.; Rebek, Jr., J.; Mollan, R. C.; Banquer, C.; Subramanyam, G., "Peptide Synthesis with Benzisoxazolium Salts - II." *Tetrahedron* **1974**, *30*, 3955.

[f]Bernhagen, W., "PPA: a new reagent for peptide synthesis." *Pharmaceutical Biotechnology International*, **1996**, p. 31. See also Millbanks, C., "*n*-Propylphosphonic Anhydride," in *Encyclopedia of Reagents for Organic Synthesis*; Vol. 6; Paquette, L. A., Ed.; Wiley: New York; 1995; p. 4336.

[g]Gaede, B., "Preparation of Carboxamides via Carboxylic-Phosphoric Anhydrides." *Org. Process Res. Dev.* **1999**, *3*, 92.

[h]DCU is relatively insoluble in DMF, *i*PrOAc, and THF-H_2O.

[i]Bernasconi, S.; Comini, A.; Corbella, A.; Gariboldi, M. S., "Activation of 2-Alkenoic Acids as Mixed Anhydrides with Diphenylphosphinic Acid for the Formation of Carboxamides." *Synthesis* **1980**, 385.

[j]Chen, F. M. F.; Steinauer, R.; Benoiton, N. L., "Mixed Anhydrides in Peptide Synthesis. Reduction of Urethane Formation and Racemization Using N-Methylpiperidine as the Tertiary Amine Base." *J. Org. Chem.* **1983**, *48*, 2939; Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M., "An Expedient Synthesis of 3-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one." *Tetrahedron Lett.* **1987**, *28*, 939.

TABLE 3.3. Relative Costs of Some Alkali Metal Hydroxides

Hydroxide	Relative cost per mol of nonhydrated MOH
$LiOH \cdot H_2O$	3.8
NaOH (pellets)	1.0
NaOH (50%)	1.1
KOH (85%)	2.0

materials are subject to market pressure and generally decrease as the amount purchased increases. Substituting one member of a family for another may lead to greatly reduced costs and should be considered whenever possible.

All families of reagents can be examined for relative costs, including even reagents that might be overlooked due to familiarity. Table 3.3 shows the relative costs for LiOH, NaOH, and KOH. While NaOH as a 50% aqueous solution is (marginally) more expensive than NaOH pellets, the convenience of transferring a liquid may make 50% NaOH the preferred reagent.

The cost savings from using NaOH instead of LiOH would be significant only on large scale: For instance, in the four-step synthesis shown in Chapter 2 (Figures 2.20 and 2.21), the cost of NaOH contributes only 5% to the overall cost estimate. Despite the similarity of LiOH, NaOH, and KOH, the by-products formed during work-up have significantly different solubilities. KOH may generate carboxylate salts, which are more water-soluble, and improve process productivity. In the condensation of proline with N-carbonic anhydride derivatives of amino acids, the use of KOH with K_2CO_3 produced 0.5 M solutions, while with solutions prepared from $NaOH/Na_2CO_3$ crystallization occurred at concentrations of only 0.1 M [9]. Unexpected chemistry can occur when substituting one alkali hydroxide for another; for example, KOH treatment led to epimerization of the carboxylic acid in Figure 3.4, but epimerization did not occur with NaOH treatment [10]. Thus, initially developing a process using the cheapest reagent (NaOH in this case) could avoid scale-up difficulties later in the development of a compound.

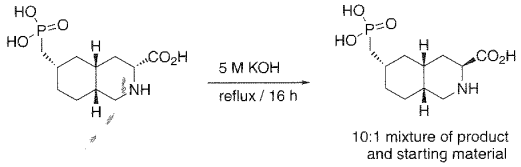


FIGURE 3.4. KOH-mediated epimerization

TIPS:
- To minimize development efforts overall, try to develop the preliminary processes using the least expensive materials.
- In future optimizations, all reagents considered as substitutes for established reagents should be examined by use-tests.

II.D. Atom Efficiency

There is a growing movement to select reagents based on atom efficiency in order to minimize both environmental impact and disposal costs. These costs must be considered in conjunction with overall costs of reagents and productivity. Table 3.4 compares characteristics for some methylating reagents.

Sometimes the greenest reagent has undesirable physicochemical or toxicological characteristics or does not exhibit the desired selectivity or reactivity. For instance, CH_3Cl is more atom-efficient as a methylating agent than CH_3I, but CH_3Cl is less reactive, and pressurizable equipment may be required to run reactions with this low-boiling material. Any considerations that extend processing times may lead to a more costly product. When selecting reagents, all ramifications must be considered.

TABLE 3.4. Characteristics of Some Methylating Agents[a]

Reagent	FW	Atom efficiency	Comments / Some Uses
$CH_3OSO_2OCH_3$	126.13	12%, 24%	bp 188 °C
CH_3OTs	186.23	8%	mp 27.5 °C
CH_3I	141.94	11%	bp 41 °C. Simvastatin example, Figure 1.4.
CH_3Br	94.94	16%	bp 4 °C
CH_3Cl	50.49	30%	bp −24 °C
$CH_3OCOOCH_3$	90.08	17%	bp 90 °C. Monomethylation[b] of active -CH_2-
$HCHO / H_2$	32.04	47%	Methylation of amines. Toxicity of HCHO.
CH_3OH / cat. H^+	32.04	47%	bp 65 °C. Fischer esterification.
CH_2N_2	44.04	34%	bp −23 °C. May be explosive in presence of some impurities. Must be generated prior to use. Reactions performed on scale by specializing contractors.

[a]All methylating reagents should be considered cancer-suspect agents, and handled with due caution and appropriate safeguards.

[b]Tundo, P.; Selva, M.; Bomben, A., "Mono-C-methylation of Aryacetonitriles and Methyl Arylacetates by Dimethyl Carbonate: A General Method for the Synthesis of Pure 2-Arylpropionic Acids. 2-Phenylpropionic Acid." *Org. Syn.* **1998**, *76*, 169.

III. FAMILIES OF REAGENTS USEFUL FOR SCALE-UP

Some examples of families of reagents commonly used on scale are discussed in the following pages. These reagents and examples illustrate some of the principles discussed earlier. The reader may find these examples useful either for direct application or for generating ideas for other applications.

III.A. Reagents for Deprotonation

In academia, *n*-BuLi and NaH are commonly used to deprotonate weakly acidic molecules and allow further reactions. On scale, these reagents are rarely selected, because they are pyrophoric. The by-products, butane and hydrogen, are volatile, flammable compounds that must be considered as emissions. Many alternatives to *n*-BuLi and NaH are shown in Table 3.5, which includes *n*-BuLi for comparison.

The reagents in Table 3.5 are preferred over *n*-BuLi and NaH, usually for safety reasons. For instance, *n*-hexyl lithium and *n*-octyl lithium are not pyrophoric and can be stored at room temperature. The by-products from these reagents are more recoverable, hence more eco-efficient [11] (Figure 3.5). The alkali metal salts of hexamethyldisilazane are moderately strong bases, do not generate H_2 as a by-product, and after aqueous work-up afford $Me_3SiOSiMe_3$ (bp 101°C) as a readily recoverable by-product. Figure 3.6 shows reaction with $NaN(SiMe_3)_2$ to form intermediate **3** in the preparation of a PDE IV inhibitor [12], and reaction with

TABLE 3.5. Reagents for Deprotonation[a]

Reagent	Typical concentration	Comments
*n*BuLi	10–30 in $PhCH_3$	Pyrophoric, store at 0 °C.
*n*HexLi	25–40% in hexane	Not pyrophoric, store at RT or below.
*n*OctLi	15–40% in hexane	Not pyrophoric, store at RT or below.
LDA[b]	1.8 M in THF / heptane	Contains "Mg stabilizer."
$LiN[SiMe_3]_2$	1.0 M in THF or hexanes	Also available as a solid.
$NaN[SiMe_3]_2$	1.0 M in THF; 0.6 M in $PhCH_3$	Also available as a solid.
$KN[SiMe_3]_2$	0.9 M in THF 0.7 M in $PhCH_3$	Also available as a solid.
NaOH	30–50% aqueous	Phase-Transfer Catalysis (PTC)

[a]Data from FMC Corporation, New Product Safety and Data Sheets, 3/94 and 6/94; Callery Chemical Company: www.callery.com; and Aldrich Chemical Company

[b]Lithium diisopropylamide

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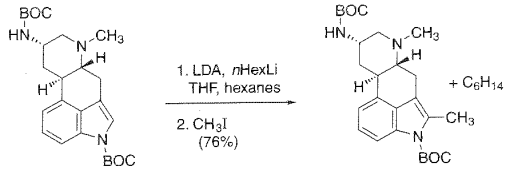


FIGURE 3.5. Deprotonation with *n*Hex-Li

$LiN(SiMe_3)_2$ to form crixivan intermediate **4** [13]. The reactivity of bases may be dependent on the nature of the alkali metal portion of the base, as seen in the hetero-Michael additions shown in Figure 3.7 [14]. Phase-transfer catalyzed reactions (PTC) are often overlooked [15], and can provide safe, economic, and very productive alternatives to reactions using strong bases (see Figure 2.18).

III.B. Alkoxide Bases

KO*t*-Bu is often used in academia as a moderately strong base. The use of KO*t*-Bu on scale may be hampered by its relatively low solubility in organic solvents. The salts of *t*-AmOH have much greater solubility (Table 3.6) and should be considered for use on scale in place of KO*t*-Bu. NaO*t*-Am and KO*t*-Am are readily available.

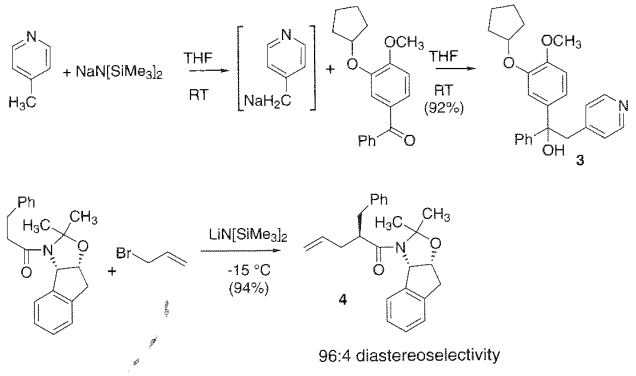


FIGURE 3.6. Deprotonation with $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$

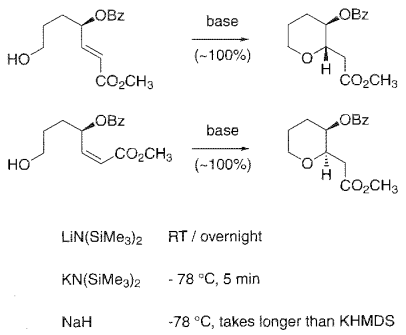


FIGURE 3.7. Hetero-Michael additions using moderately strong bases

III.C. Amine Bases

In academia, triethylamine is probably the amine most commonly used to scavenge acids generated during reactions. Triethylamine is readily used on scale; however, in some cases, there are many other amines that can provide distinct advantages. Table 3.7 shows some inexpensive amines useful for scale-up, grouped as primary, secondary, and tertiary amines. It is significant to note that secondary amines are more basic in water than the analogous tertiary amines. This is probably due to the increased stabilization from hydrogen bonding with water that is possible for protonated secondary amines (Figure 3.8) [16]. In solvents in which hydrogen bonding cannot occur, basicities are expected to be consistent with the inductive effect for substituted amines: the order of basicity in chlorobenzene is $BuNH_2 < Bu_2NH < Bu_3N$ [17].

TABLE 3.6. Solubilities of Selected Alkoxides in Organic Solvents at 25 °C[a]

Solvent	NaO*t*Bu	KO*t*Bu	NaO*t*Am	KO*t*Am
Toluene	6 wt%	2.3 wt%	46 wt%	36 wt%
Cyclohexane	14 wt%	NA	>50 wt%	27.6 wt%
Hexanes	11 wt%	0.3 wt%	>50 wt%	30.0 wt%
t-Butanol	NA	17.8 wt%	NA	NA
Pyridine	NA	19.0 wt%	NA	NA
Diglyme	22 wt%	42.0 wt%	47 wt%	47.0 wt%
Tetrahydrofuran	38 wt%	>25 wt%	>30 wt%	>50 wt%

[a]Data from Callery Chemical technical bulletins, 8/97.

TABLE 3.7. Characteristics of Some Amines Useful for Scale-Up

Compound	Boiling point	pKa	Comments
NH_3	−33 °C	9.25	
Methylamine	−6 °C	10.63	
Ethylamine	17 °C	10.70	
3-Dimethylaminopropylamine	133 °C	~10.6-11	Used to remove excess RCOCl[b]
Diethylamine	56 °C	11.02	
Diisopropylamine	84 °C	11.05	
Piperidine	106 °C	11.12	
Morpholine	129°C	8.33	
Dimethylisopropylamine	66 °C	10.36	
1-Methylpyrrolidine	81 °C	10.32	
Triethylamine	89 °C	10.75	HCl salt insoluble in CH_3CN[c]
1-Methylpiperidine	106-7°C	10.08	
Diisopropylethylamine	127 °C	10.4	HCl salt soluble in CH_3CN[c]
4-Methylmorpholine	115 °C / 750 mm	7.13	Used in peptide coupling[d]
Imidazole	89–91 °C (mp)		Used in peptide coupling[e], silylation[f]
Pyridine	115 °C	5.25	
2-Methylpyridine (2-Picoline)	128 °C	5.97	
2,6-Dimethylpyridine (2,6-Lutidine)	143 °C	6.65	Useful for sulfation[g]
4-Dimethylaminopyridine (DMAP)	mp 112−4 °C	9.7	Acylation catalyst[h,i]
1,4-Diazabicyclo[2.2.2]octane (DABCO)	158 °C	8.6	
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	80°C / 0.6 mm	13.2	
1,5-Diazabicyclo[4.3.0]undec-7-ene (DBN)	95°C / 7.5 mm	~13.2	

[a]Sources:

The Merck Index 12th edition, Budavari, S., Ed., Merck & Co., Inc.: White House Station, NJ; 1996. Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pKa Prediction for Organic Acids and Bases;* Chapman and Hall: New York; 1981. Serjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Aqueous Solution;* Pergamon: New York; 1979. *CRC Handbook of Chemistry and Physics;* 76th ed.; CRC Press: New York; 1995–1996. *Lange's Handbook of Chemistry,* Dean, J. A., Ed, 14th edition; McGraw-Hill: New York, 1992.

[b]Evans, D. D.; Evans, D. E.; Lewis, G. S.; Palmer, P. J.; Weyell, D. J., "A Novel Method for the Preparation of Steroid Esters." *J. Chem. Soc.,* **1963**, 3578.

[c]Reference 22.

[d]Anderson, G. W.; Zimmermann, J. G.; Callahan, F. M., "Racemization Control in the Synthesis of Peptides by the Mixed Carbonic-Carboxylic Anhydride Method." *J. Am. Chem. Soc.* **1966**, *88*, 1338.

[e]Stoner, E. J.; Stengel, P. J.; Cooper, A. J., "Synthesis of ABT-387, an HIV Protease Inhibitor Candidate: Avoiding the Use of Carbodiimides in a Difficult Peptide Coupling." *Org. Process Res. Dev.* **1999**, *3*, 145.

[f]Yasuda, N.; Huffman, M. A.; Ho, G.-J.; Xavier, L. C.; Yang, C.; Emerson, K. M.; Tsay, F.-R.; Li, Y.; Kress, M. H.; Rieger, D. L.; Karady, S.; Sohar, P.; Abramson, N. L.; DeCamp, A. E.; Mathre, D. J.; Douglas, A. W.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J., "Practical Synthesis of Anti-Methicillin-Resistant *Staphylococcus Aureus* (MRSA) Carbapenem L-742,728." *J. Org. Chem.* **1998**, *63*, 5438.

[g]Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M., "Monobactams. Preparation of (*S*)-3-amino-2-oxoazetidine-1-sulfonic acids from L-α-amino-β-hydroxyacids via their hydroxamic esters. *J. Org. Chem.* **1982**, *47*, 5160.



FIGURE 3.8. Hydrogen bonding of secondary and tertiary ammonium cations

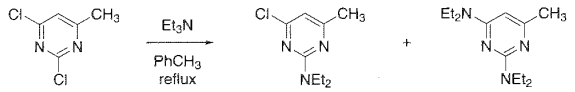


FIGURE 3.9. Reaction of triethylamine with a dichloropyrimidine

The nucleophilicity of tertiary amines and pyridines can be used to advantage but can also cause problems for the unaware. 4-Dimethylaminopyridine (DMAP) is used as an acylation catalyst [18]. On scale, catalytic amounts of pyridine can sometimes be substituted for the more expensive DMAP. Moderately more basic than either 2-picoline or pyridine is 2, 6-lutidine, and the steric congestion of the two methyl groups moderates its reactivity [19]. The nitrogen atoms in diazabicyclooctane (DABCO) are especially reactive, as tying back the alkyl substitutents in the bicyclic ring exposes the free electron pairs. DABCO is a component of the Bayliss-Hillman reaction (see Figure 4.15d). Triethylamine can react as a nucleophile, as shown in Figure 3.9 [20], and such reactivity can pose unexpected problems. In a preparation of imipenem (**6**, Figure 3.10), the more hindered base

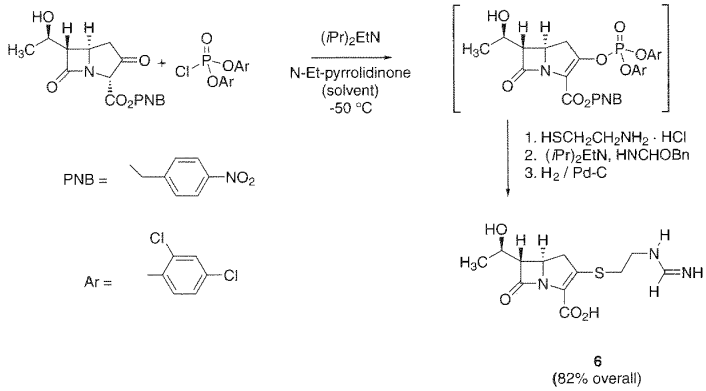


FIGURE 3.10. Preferred phosophorylation in the presence of diisopropylethylamine

[h]Hofle, G.; Steglich, W.; Vőrbruggen, H. "4-dialkylaminopyridines as highly active acylation catalysts." In *Angew. Chem. Int. Ed. Eng.* **1978**, *17*, 569.

[i]Hassner, A., "4-dimethylaminopyridine." In *Encyclopedia of Reagents for Organic Synthesis,* Vol. 3; Paquette, L. A. ed.; John Wiley & Sons: New York, 1995, p. 2022.

diisopropylethylamine (one of Hünig's bases) was similarly preferred over Et_3N because diisopropylethylamine reacted with phosphorylating reagents less than Et_3N [21].

The solubility of acid salts of the amines (Table 3.7) can provide some operating advantages on scale. Diisopropylethylamine afforded a very convenient work-up for the condensation of the substituted piperidine **7** with the dichloropyrimidine **8** in acetonitrile (Figure 3.11): After coupling, the $(iPr)_2EtN{\cdot}HCl$ by-product stayed dissolved in the reaction, allowing the product to be isolated by crystallization [22]. Substituting Et_3N for $(iPr)_2EtN$ was not convenient, as $Et_3N{\cdot}HCl$ is insoluble in acetonitrile and contaminated the product. Diisopropylethylamine was also preferred over Et_3N for chlorination of the hydroxypyrimidine **9** (Figure 3.11), because chlorination in the presence of Et_3N produced

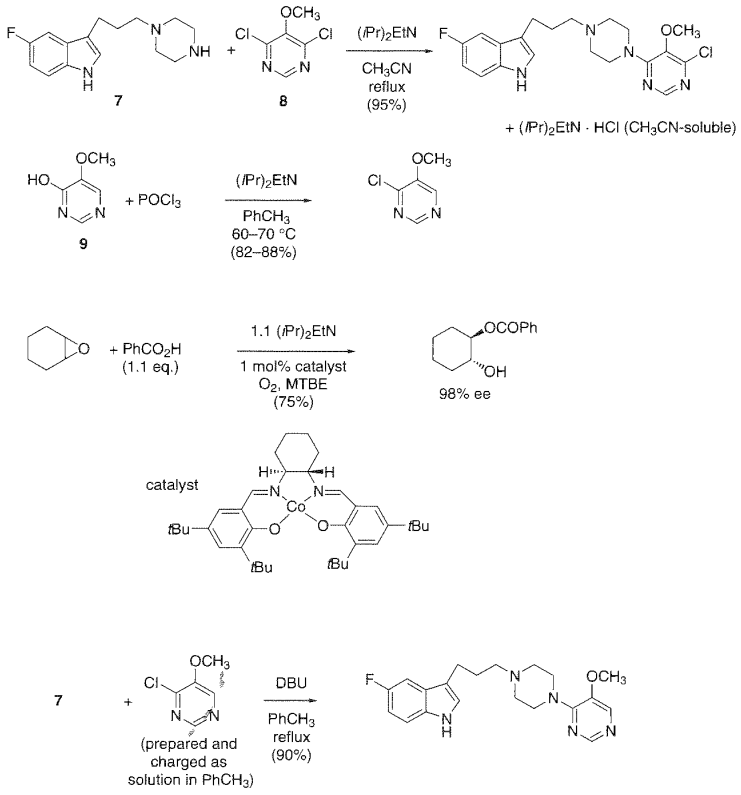


FIGURE 3.11. Preferred reactions using selected amines

incomplete reactions [22]. The use of $(i\text{Pr})_2\text{EtN}$ also increased the yield, reaction rate, and enantioselectivity for the ring-opening of cyclohexene oxide by benzoic acid; the amine confers good solubility of benzoic acid in MTBE without ionization [23]. Treatment with DBU dissolved **7** in toluene at 60–70°C (Figure 3.11), leading to a rapid reaction that was not seen under heterogeneous conditions using other bases [22]. Dissolution may have been effected by salt formation between the 5-fluoroindole **7** (ca. pK_a 16.3) and DBU (pK_b 13.2); in this case, more than lipophilicity was involved, as $(n\text{Bu})_3\text{N}$ was ineffective at producing a solution. These examples illustrate the importance of examining alternative amines.

III.D. Oxidations

Oxidations are among the most troublesome reactions to scale up, due to the toxicity and hazardous nature of the reagents, disposal costs from use of reagents containing heavy metals such as chromium, and often laborious work-ups. Many improvements have been made recently, particularly in using catalytic amounts of reagents with primary oxidants. One example of this is the ruthenium-catalyzed oxidation of the primary alcohol **10** in Figure 3.12; N-methylmorpholine N-oxide (NMO) is the primary oxidant [24]. Marko's group showed that O_2 and copper catalysts can be used to oxidize benzylic alcohols to aldehydes, even in the presence of aryl thioethers (Figure 3.12) [25]. Excellent yields were obtained for each of these reactions.

An attractive alternative to CrO_3-mediated oxidations may be found in the use of Magtrieve, which is a form of ferromagnetic CrO_2 produced for magnetic

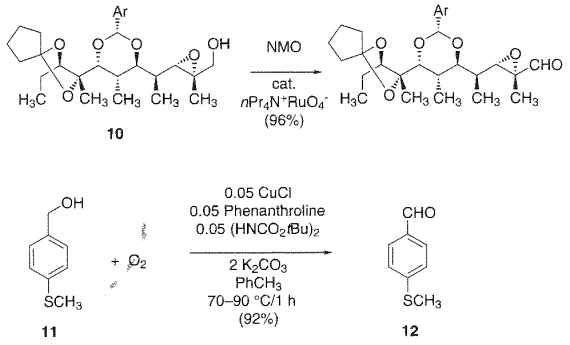


FIGURE 3.12. Metal-catalyzed oxidations of alcohols to aldehydes and ketones

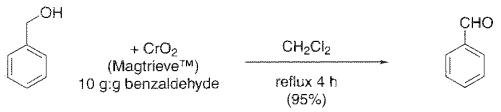


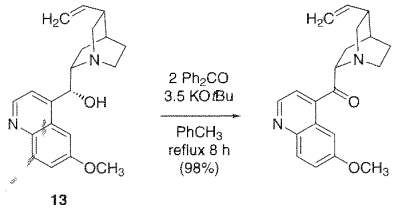
FIGURE 3.13. Oxidation of benzyl alcohol using Magtrieve

tape [26]. An excess of this reagent was used, and the reduced Cr(III) species remained bound to the surface of the crystals. The reagent was separated by holding a magnet to the flask as the reaction solution was decanted. Yields for the oxidation of benzylic alcohols were excellent (Figure 3.13), and chromium in the product was measured at <12 ppm. On scale, perhaps the metal salts could be separated from the product solution by passing the reaction through a magnetized filter. The anticipated low cost of this reagent and low levels of contaminating metal salts in the product make this chemical a promising oxidant.

The Oppenhauer oxidation can also afford a convenient alternative to more traditionally used oxidants. Oxidation of quinine **(13)** using benzophenone and KO*t*Bu gave the ketone in excellent yield (Figure 3.14); other oxidants were less effective [27]. This reaction can be viewed as an Oppenauer oxidation or a Meerwein-Pondorf-Verley reduction, depending on whether one considers the oxidation or the reduction to be the primary reaction. A magnesium-catalyzed Meerwein-Pondorf-Verley reduction was determined to form significant amounts of impurities in a Grignard reaction [28].

In some cases, primary alcohols can be oxidized to aldehydes and lactones by treatment with platimum and oxygen. The tetraol **14** was selectively dehydrogenated to the lactone **15.** Under these conditions (Figure 3.15), a trace of sodium dodecyl sulfate (SDS) was necessary for good conversion rates [29]. A similar oxidation is used to prepare the losartan precursor **16** (Figure 3.15) [30].

Primary alcohols have been efficiently oxidized to carboxylic acids without using metal catalysts, as shown in Figure 3.16 [31]. Treatment of the primary alco-



13

FIGURE 3.14. Oxidation of quinine under Oppenauer conditions

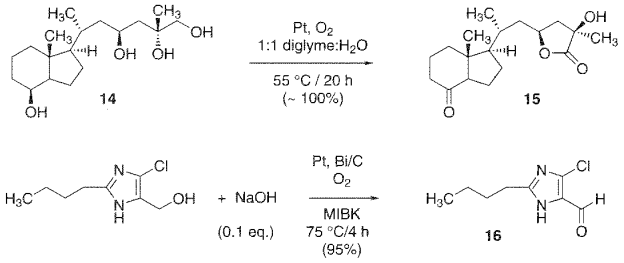


FIGURE 3.15. Oxidation of alcohols using platinum and oxygen

hol **17** with catalytic 2,2,6,6,-tetramethyl-1-piperidinlyoxy radical (TEMPO), catalytic bleach, and sodium chlorite as the bulk oxidant produces **19** in excellent yield. The reaction proceeds through the aldehyde **18** (see also Figure 9.10).

Noyori's group has developed tungsten-catalyzed oxidations using 30% H_2O_2 under solvent-free conditions (Figure 3.17). The key to this work is the use of PTC under chloride-free conditions: NaCl retarded the epoxidations performed in the presence of (aminomethyl) phosphonic acid (**20**) [32]. When **20** was absent, secondary alcohols were selectively oxidized to ketones, even in the presence of olefins [33]. Cyclohexene was oxidized to adipic acid using only a slight excess of the four equivalents of H_2O_2 needed [34]. Yields from this tungsten-catalyzed work are excellent, and industrial applications are very likely.

The urea-H_2O_2 addition compound ("percarbamate," **21**) has been used as an anhydrous source of H_2O_2 (Figure 3.18). Treatment of **21** and trifluoroacetic anhydride generated trifluoroperacetic acid **22**, and addition of the β,γ-unsaturated ketone **23** led to the epoxide **24** in 60% yield after distillation [35]. Treatment

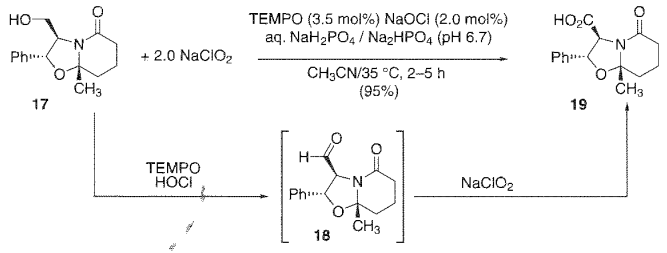


FIGURE 3.16. Oxidation of a primary alcohol to the carboxylic acid using TEMPO, NaOCl, and $NaClO_2$

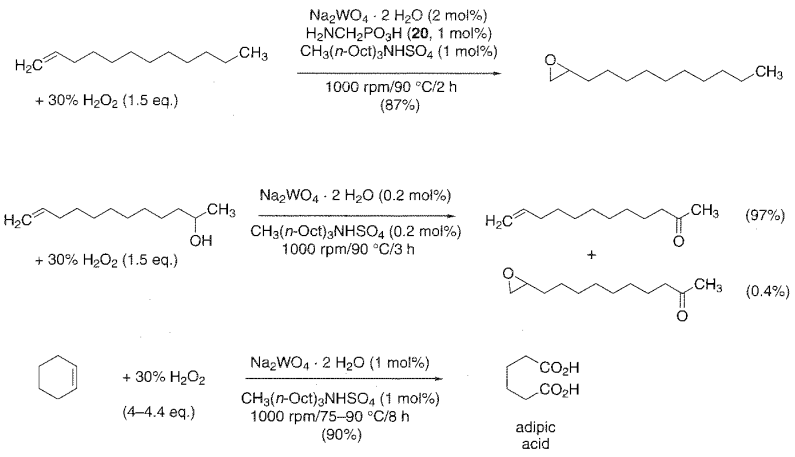


FIGURE 3.17. Tungsten-mediated PTC oxidations of olefins and secondary alcohols

of **18** with phthalic anhydride generated monoperoxyphthalic acid (MPPA, **25**), which was used to oxidize the quinoline **26** [36]. These conditions are practical alternatives to using *m*-chloroperoxybenzoic acid (MCPBA), which is no longer commercially available in high purity and has restricted options for site delivery.

Some water-soluble reagents provide good alternatives to MCPBA for epoxidizing olefins (Figure 3.19). Reaction of trifluoromethyl acetone and Oxone® (potassium monopersulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in aqueous acetonitrile generated the dioxirane **28**, which led to the epoxidation of the glucal **27** in 84% yield [37]. The diastereoselectivity of epoxidations can be tuned by employing ketones other than trifluoromethyl acetone [38]. Treatment of 2-cyclohexenol with **25** afforded primarily the *cis*-epoxide **31** [39]. Magnesium monoperoxyphthalate (MPPA) has been used to epoxidize olefins in *n*-BuOH - H_2O mixtures,

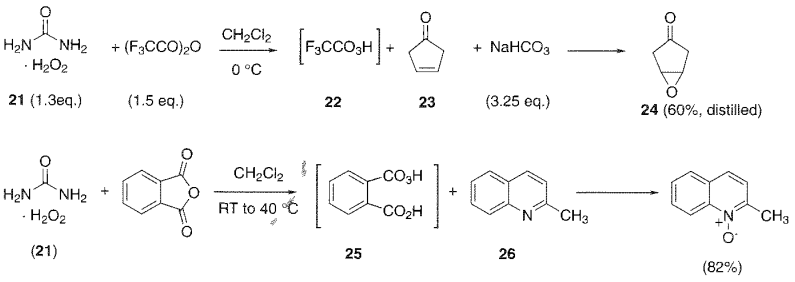


FIGURE 3.18. Oxidations under anhydrous conditions

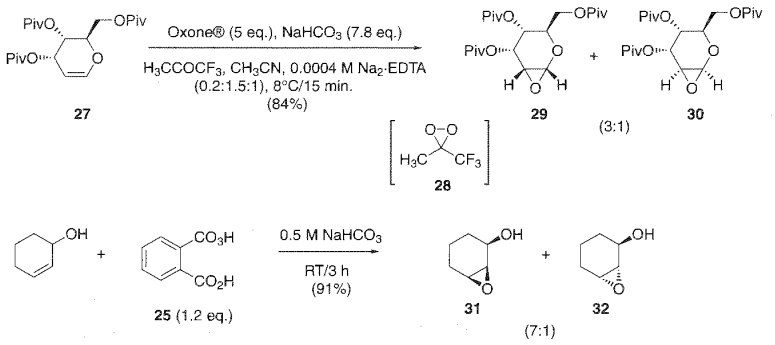


FIGURE 3.19. Epoxidizing olefins in aqueous solvents

with work-up facilitated by removing the aqueous phase containing the spent reagent [40].

III.E. Reductants

Reductions often pose scale-up concerns. The primary difficulty is that hydrogen is used or generated, which requires additional considerations and equipment for safe handling. At the end of a reaction, safely quenching any residual reducing capability is a concern on scale. Work-up can be tedious, especially if colloidal salts are formed. Disposing of metal salt by-products can be costly, and environmental concerns arise. Considerable attention to details is necessary to develop a reliable reduction for scale-up. In spite of these potential drawbacks, once the process has been developed and the appropriate equipment has been commissioned, reductions can be extremely reliable.

Table 3.8 lists some reliable, inexpensive reductants that have been used on scale. The table shows some of the advantages and disadvantages of these selected reagents.

III.F. Hydroboration

A recent development in hydroborating reagents is complexes of BH_3 with silylated amines [41]. These stable, crystalline reagents provide a form of BH_3 that may be convenient for some small-scale operations (Figure 3.20).

TABLE 3.8. Characteristics of Some Inexpensive Reductants Used on Scale

Reductant	Characteristic / Typical Reaction	Disadvantages[a]
H_2 / catalyst	Broad range of reducing capability extremely reliable reductive amination[c]	Pressurizable reactors and specialized facility may be needed; transfer hydrogenations may decrease equipment cost.
$NaBH_4$	Extremely reliable: additives may increase range of reducing capability.	May generate borate salts with amines.
$LiAlH_4$	Broad range of reducing power: available in pellets and packets[b]	Work-up of Al salts can be tedious; disposal costs may be high.
$Na(MeOCH_2CH_2O)_2AlH_2$ Red-Al® (available as a 65 wt% solution in $PhCH_3$)	Broad range of reducing power; convenient for charging on scale	Work-up of Al salts can be tedious; a by-product is the relatively toxic methoxyethanol; disposal costs may be high.
Raney Nickel	Broad range of reducing capability	Disposal of Ni and Al salts
BH_3	Hydroboration Reduction of imides, acids	$BH_3 \cdot Me_2S$ has been preferred over BH_3·THF because of cost and stability[d,e]
Li(0), Na(0) / NH_3(l)	Birch reductions	Specialized equipment needed for use of NH_3(l) or volatile amines at low temperature, and recovery; amines can be malodorous
Fe(0) / H^+	Reduction of $ArNO_2$	Disposal of iron salts may be costly; recovery and recycle may be costly.
Zn(0) / H^+	Reduction of S-S	Disposal of zinc salts may be costly; recovery and recycle may be costly.
$Na_2S_2O_4$ (Sodium dithionite)	Reduction of $ArNO_2$	Penetrating odor of reagent and by-products

[a]With the exception of $Na_2S_2O_4$, all reagents use or generate hydrogen, which must be considered for safe operations.

[b]Containment in packets minimizes handling concerns. A commercially available form is SecuBag®, from Chemetall Chemical Products, Inc., Berkeley Heights, NJ.

[c]Blacklock, T. J.; Shuman, R. F.; Butcher, J. W.; Shearin, W. E., Jr.; Budavari, J.; Grenda, V. J., "Synthesis of Semisynthetic Dipeptides Using *N*-Carboxyanhydrides and Chiral Induction on Raney Nickel. A Method Practical for Large Scale." *J. Org. Chem.* **1988**, *53*, 836.

[d]Deshpande, M. N.; Cain, M. H.; Patel, S. R.; Singam, P. R.; Brown, D.; Gupta, A.; Barkalow, J.; Callen, G.; Patel, K.; Koops, R.; Chorghade, M.; Foote, H.; Pariza, R., "A Scalable Process for the Novel Antidepressant ABT-200." *Org. Process Res. Dev.* **1998**, *2*, 351.

[e]In the 1990's there were two explosions of bottles of BH_3·THF in separate BMS laboratories. The causes of these incidents were never satisfactorily identified.

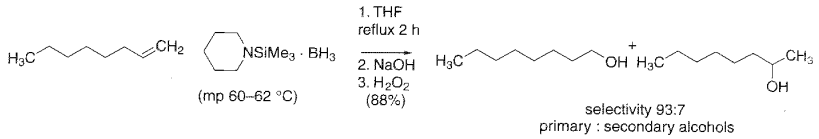


FIGURE 3.20. Hydroboration using a BH_3 · silylated amine complex

III.G. Catalytic Reagents

Catalytic reagents can sharply decrease costs of both reagents and waste disposal and can increase overall productivity. Catalytic hydrogenation has been a mainstay of the chemical industries for many years [42]. In the past two decades, the use of catalytic reagents for forming carbon-carbon bonds has been a very popular quest, and some extremely creative chemistry has emerged [43]. Discussion on optimizing catalytic reactions may be found in Chapter 9.

The design of suitable ligands is the key to the recent successes in metal-containing catalytic reagents. Industry has capitalized on the use and reuse of water-soluble catalysts when the products are water-insoluble. One example is the use of TPPTS (**33**), which is prepared by sulfonating triphenylphosphine (Figure 3.21). TPPTS essentially immobilizes the rhodium catalyst in the aqueous phase for hydroformylation ("Oxo") reactions, as practiced by Union Carbide and Hoechst AG [44, 45]. As the gaseous starting materials are combined with the aqueous solution of the Rh-TPPTS catalyst, the hydrophobic products separate. Drawing off the product leaves the catalyst dissolved in the aqueous phase for recycle. A similar aqueous approach is used for Clariant's Pd-TPPTS preparation of a key sartan precursor OTBN by a Suzuki coupling (**34**, Figure 3.21).

BINAP is a ligand that is key for many synthetic transformations, especially chiral reductions. One example is the preparation of chiral lactones using the BINAP-$Ru(OAc)_2$ catalyst **35** (Figure 3.22) [46]. The use of polymer-bound, chiral BINAP-ruthenium catalysts has led to the formation of hydrogenated products with up to 99% ee [47]. The insolubility of the reagent led to good recovery and reuse of the catalyst. Analysis of the products showed that only 1% of the ruthenium was leached from the catalyst, which may simplify purification of the products. The reuse of polymeric reagents such as **36** should decrease the overall cost of the relatively expensive BINAP ligand.

III.H. Polymeric Reagents

By localizing reagents in polymers, recovery of valuable reagents is eased. Often a convenient filtration removes the polymers and facilitates work-up. Frequently

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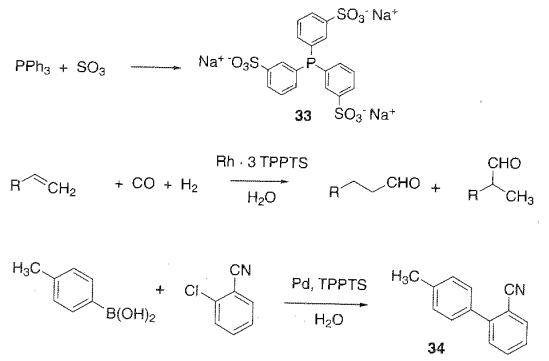


FIGURE 3.21. Use of metal catalysts with TPPTS ligands

the disadvantage of polymeric reagents is a decreased reaction rate relative to the soluble reagents [48], but suitable reaction rates can be obtained with polymeric reagents.

Ion-exchange resins have long been used as insoluble catalysts. The preparation of the bicyclic ketal in Figure 3.23 [49] was facilitated by the use of such a resin. Hot filtration removed the acid catalyst completely, eliminating the need for neutralizing a soluble reagent. (If a soluble acid catalyst had been used, simply adding aqueous base to the reaction would probably have led to some hydrolysis of the ketal.) In this reaction the product crystallized from the filtrate. A further

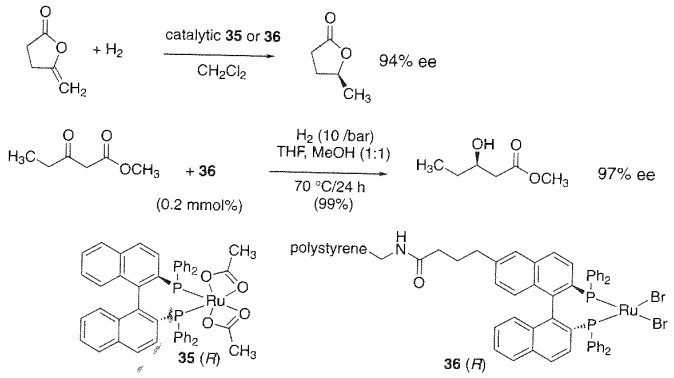


FIGURE 3.22. Chiral reductions mediated by *R*-BINAP-Ru(II)

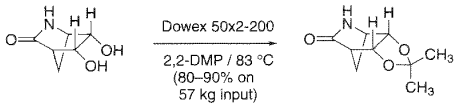


FIGURE 3.23. Preparation of a ketal using ion-exchange resin

advantage of using the resin was that some colored impurities were removed from the product by adsorption to the resin.

Seebach's group demonstrated the utility of polymer-bound, chiral titanium TADDOLates in preparing chiral secondary alcohols (Figure 3.24). The polymeric catalyst **37** was contained inside a mesh "tea bag," and was reused by simply charging fresh reagents and solvent. The ruggedness of the system was shown when the product enantioselectivity dropped from 96% (*S*) to only 92% (*S*) over 20 successive runs, and the average yield was 90% [50].

Microencapsulated $Sc(OTf)_3$ has shown considerable promise for both batch and flow reactions in those procedures in which the reaction was recirculated through columns containing the reagent. This reagent was found to be more reactive than the monomeric Lewis acid. One example is the TMS-mediated Michael reaction shown in Figure 3.25. Microencapsulated $Sc(OTf)_3$ was also found to be useful for Mannich reactions, Michael additions, and Friedel-Crafts–like acylations [51].

In the future, compounds may be recovered on scale by selective adsorption to resins (resin capture). In this way the product could be "fished out" from a mixture of compounds, even if the product were there in relatively dilute conditions. The biochemical analogy is affinity chromatography, e.g., the isolation of biotin and biotin-containing compounds by adsorption to avidin. In a recent example, propranolol (**38**) was fished out from a crude preparation by binding to

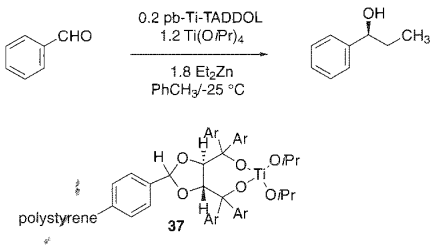


FIGURE 3.24. Use of an immobilized TADDOL reagent to prepare a chiral secondary alcohol

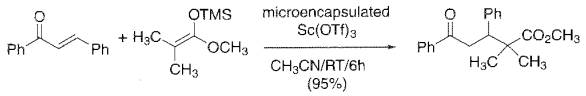


FIGURE 3.25. TMS-mediated Michael reaction using microencapsulated $Sc(OTf)_3$

a polymeric dialkyl borane (Figure 3.26) [52]. If resin capture is used on scale, it probably will be limited to isolation of high value-added compounds.

III.I. Biocatalysts as Preparative Reagents

While enzymes have been used commercially for many years, a resurgence in using enzymes to prepare optically active materials is underway. This is due to the increasing interest in preparing chiral drugs [53] (see also Chapter 16). The greatest growth area for those companies developing enzymes is in the pharmaceutical market [54].

Biocatalysis is often used to prepare molecules with two or more chiral centers or to prepare intermediates from simple precursors when selective chemical transformations would be difficult [55]. Molecules with one chiral center are generally prepared by classical chemical resolution or by transferring chirality into achiral starting materials using chiral reagents. The launch of atorvastatin was initially carried out by classical conversion of **39** to the chiral diol **40** (Figure 3.27), and a biocatalyzed preparation of **40** was also developed [56]. The biocatalyzed route may now be the preferred route for preparing **40** [55].

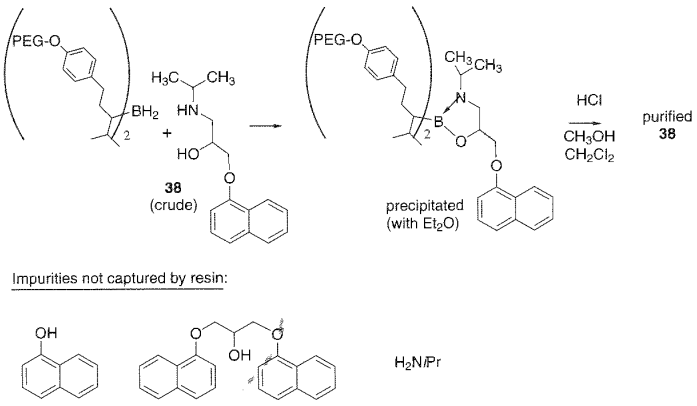


FIGURE 3.26. Resin capture to isolate propranolol

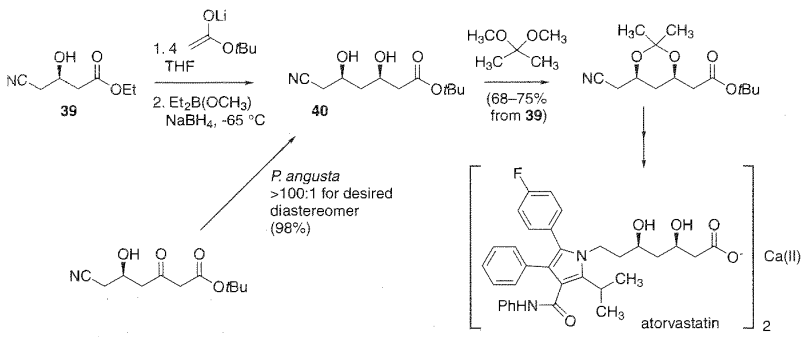


FIGURE 3.27. Routes to atorvastatin

The benefits of using enzymes are that many enzyme-catalyzed reactions can be run in water, at room temperature, and with minimal or no protecting groups. The barriers to increased enzyme use have been low operational stability, high cost, sometimes-poor stereoselectivity [57], and the relatively dilute conditions often required. Reactions with enzymes can also be run in organic solvents [58].

Many of these concerns for using enzymes on scale are being addressed. The stability of enzymes can be enhanced by immobilization on solid supports, such as glass beads, agarose, or silica gel [59, 60]. Optimal conditions for immobilizing the enzyme are critical for maintaining the catalytic activity [61]. Immobilizing the reagent can allow for recovery and recycle, thus decreasing the overall cost of the enzyme. Parameters for conducting the desired reactions need to be thoroughly investigated [62]. The cost of enzymes can also be decreased by screening and subsequent cloning of selected organisms to increase the yield of enzyme.

Cross-linked enzyme crystals (CLEC, [63]) can have greatly improved catalytic activity over native enzyme. Their practical utility has recently been demonstrated for the hydrolytic kinetic resolution of the acetates of 1-phenylethanol (Figure 3.28) [64]. The catalyst was recovered and recycled eight times, on a 100-liter scale. The future will show increased use of enzymes.

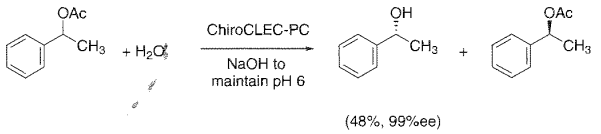


FIGURE 3.28. Hydrolytic kinetic resolution of racemic acetates using ChiroCLEC-PC

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CHAPTER 4

Solvent Selection

I. INTRODUCTION

Solvents are selected to increase reaction rates, to increase the reproducibility and ease of running reactions, and to ensure that the desired quality and yield of product is reached. Other important considerations are to decrease waste and allow for efficient solvent recovery and reuse. Each of these goals has a direct effect on productivity and product cost for a manufactured product. In early stages of development, providing material by any means is crucial, and solvents are selected to ensure that the desired product can be prepared within the timeline with minimal difficulty.

A brief discussion of solvent classifications, solvation, and key physical parameters follows. For more details, the reader is referred to Reichardt's excellent text on solvents [1].

I.A. Solvation and Primary Solvent Characteristics

Many of the characteristics of solvents are determined by functional groups. The categories of solvents include

Sun Ex. 1022

- "protic," or hydrogen bond donating solvents (HBD, Lewis acids), e.g., H_2O, NH_3, CH_3OH, and AcOH;
- hydrogen bond acceptor solvents (HBA, Lewis bases), e.g., H_2O, Et_3N, EtOAc, THF, NMP (N-methyl-pyrrolidinone), and acetone;
- "polar aprotic solvents," better termed "non-hydroxylic solvents," e.g., DMSO and DMF;
- chlorocarbon and fluorocarbon solvents; and
- hydrocarbon solvents, both saturated and unsaturated [1].

When solutes are dissolved, they are said to be solvated. Solvation is defined as the "surrounding of each dissolved molecule or ion by more or less tightly bound solvent molecules" [1]. In water the dissolved molecule or ion is said to be hydrated. Dissolution can be endothermic or exothermic; similarly, crystallization can be exothermic or endothermic. (Exotherms may not be noticed for laboratory crystallizations; on scale, however it is not uncommon for crystallization to raise a batch temperature by 1–2°C.) The degree of solvation increases with increased ion charge and decreased ion size, and the number of solvent molecules associated with a solute (the solvation number) varies with the solvent. For example, the solvation number for Li^+ ranges from 1.4 in sulfolane, to 7 in MeOH, to 9 in CH_3CN, and to 21 in H_2O [1]. The extent of solvation influences reactivity. "Naked" anions, which are generated under PTC conditions, are minimally solvated in organic solvents and are much more reactive than highly solvated ions. Polar non-hydroxylic solvents such as DMSO can solvate cations, but the C-H bonds are not polarized enough to appreciably solvate anions. Hence reactions of NaCN and other nucleophiles are accelerated in DMSO [2].

The simple approach of "like dissolves like" is still a good beginning point for selecting a solvent. Sometimes a mixture of solvents will dissolve a compound much better than any one solvent (see Figure 4.8). Different solvents may solvate different parts of the molecule.

TIP: Use solubility from a multiple solvent system to advantage. Consider a compound which can be dissolved in acetone-H_2O, but not in H_2O alone. Recrystallization could be effected by dissolution in a mixture of acetone-H_2O, and distilling off the acetone to crystallize the solute.

Many efforts have been made to quantitate and predict the ability of solvents to dissolve molecules. A parameter frequently used to assess the polarity of a solvent is the dielectric constant, ε_r, which "measures the ability of a material to reduce electric force between two charges separated in space" [3]. Solvents that are more polarizable conduct electric charges better and have higher dielectric constants. Dielectric constants are measured relative to vaccum (defined as 1.0),

and for typical solvents the dielectric constant appears in the range from about 2 (cyclohexane) to 80 (water). Higher dielectric constants are found for other compounds, e.g., for N-methylformamide and formamide the values are 182.4 and 111, respectively; however, the reactivity of these compounds limits their use as solvents for organic reactions.

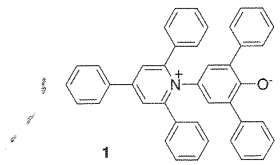
The polarity of solvents has also been measured by a spectroscopic system that Reichardt has refined. Increasing solvation stabilizes the betaine dye **1** (Figure 4.1) more in the ground state than in the excited state. The difference between the ground state and the excited state is quantitated as E_N^T values, which range from 1.00 (water) to about 0.006 (cyclohexane).

I.B. Primary Solvent Physical Characteristics

For the chemist concerned about the safe, reliable scale-up of processes, knowledge of key physical characteristics of solvents are key to selecting and using solvents (Table 4.1). Other texts provide thorough information on the physicochemical data of solvents [4, 5].

II. SELECTING SOLVENTS BASED ON PHYSICAL CHARACTERISTICS

Solvents are usually chosen based on compatibility with the selected reagents. The process chemist quickly discards solvents that are inappropriate for use because the reagent reacts with the solvent. For instance, adding *n*BuLi to a methanolic solution of the substrate leads to the (highly exothermic!) generation of the weaker base LiOMe, and the desired deprotonation of the substrate molecules may not occur. DMF is known to react exothermically with NaH at 50°C [6] and with $NaBH_4$ [7, 8]. The reaction of reagent with solvent may be acceptable if there are no adverse effects: for instance, many $NaBH_4$ reductions have been run in EtOH, even though the reagent reacts with the solvent (generating H_2). In this case, the by-products $NaHB(OEt)_3$, $NaH_2B(OEt)_2$, and NaH_3BOEt are themselves reducing agents.



1

FIGURE 4.1. Dye used to calculate solvation parameter E_N^T

TABLE 4.1. Primary Physical Characteristics of Solvents for Scale-up

Parameter	Consideration
Polarity	Must be compatible with and encourage the desired chemistry.
Freezing point	May limit range of low-temperature reactions.
Boiling point	A higher bp extends the temperature range of a reaction without using a pressurized reactor. A lower-boiling solvent is easier to remove by distillation, but complete condensation of the vapors is more difficult.
Flash point	Temperature at which a liquid produces ignitable vapors. Lower-boiling compounds typically have lower flash points. Any liquid with flash point below 15°C should be considered dangerously flammable and suitable precautions should be put in place.[a]
Peroxide formation	Occurs primarily in etheric solvents; slower in ketones, amides, and secondary alcohols. Solvents with a tendency for peroxide formation should be monitored routinely.[b]
Viscosity	Solvents with increased viscosity, e.g., *i*PrOH, display slower filtration rates.
Water-miscibility	Solvents with low water-miscibility allow for easier extractive work-ups.
Azeotroping ability	Removing water by azeotroping readily dries solvents and reactors for anhydrous reactions on scale; control of water content may be crucial for efficient crystallization. Other compounds may also be removed by azeotroping.
Exposure limits	TLVs (Chapter 3).

[a] *Vogel's Textbook of Practical Organic Chemistry,* 5th ed.; Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., Eds.; Addison Wesley Longman: Essex, England, 1989, p. 40.

[b] Kelly, R. J., "Review of Safety Guidelines for Peroxidizable Organic Chemicals." *Chemical Health & Safety September/October 1996,* 28.

After reactive solvent-reagent combinations have been discarded, a broad range of solvents is available for use on scale.

II.A. Solvents Inappropriate for Scale-up

Many solvents commonly used in academia are rarely used for scale-up in industry. A list of such solvents is shown in Table 4.2, along with the disadvantages of these solvents and alternative solvent choices. While any solvent *can* be used on scale, one must compare the advantages of using an undesirable solvent to the inconvenience, additional costs, and extended process times required to protect operators and equipment. All of these considerations reduce productivity and drive up processing costs on scale.

The extended ramifications for using hazardous solvents and chemicals on scale may be illustrated by the use of benzene, a known carcinogen. Concerns about benzene's toxicity dictate that operators wear protective clothing and be supplied with breathing air. More complete considerations must be paid to capture any fugitive emissions or spills. These requirements necessitate additional planning before any reaction is run on scale. At the start of a campaign, additional personnel may be needed on the floor of the scale-up facility to ensure safe operations.

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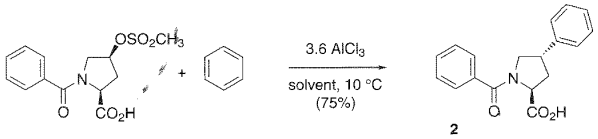
TABLE 4.2. Solvents Rarely Used on Scale

Solvent	Undesirable characteristic	Alternative
Et_2O	Flammable	MTBE
$(iPr)_2O$	Peroxide formation	MTBE
HMPA(hexamethyl phosphortriamide)	Toxicity	N-Methylpyrrolidinone (NMP) N-Ethylpyrrolidinone (NEP)
Pentane	Flammable	Heptane
Hexane	Electrostatic discharge Neurological toxicity	Heptane
Benzene	Toxicity	$PhCH_3$
$CHCl_3$	Mutagenicity, environmental	CH_2Cl_2
CCl_4	Mutagenicity, environmental	CH_2Cl_2
CS_2	Flammability, toxicity	?
$ClCH_2CH_2Cl$	Cancer suspect agent	CH_2Cl_2
Ethylene glycol	Toxicity	1,2-Propanediol
$HOCH_2CH_2OR$ (R = Me or Et, the cellosolves)	Toxicity	1,2-Propanediol
1,2-Dimethoxyethane (glyme)	Teratogenicity	Diethoxymethane
1,4-Dioxane	Cancer suspect agent	Diethoxymethane
Liquid ammonia	bp −33°C, requires specialized equipment to use safely as a liquid	Et_2NH (bp 55°C); $EtNH_2$ (bp 17°C)

Additional instruments may be needed to monitor the levels of benzene vapors during the runs. When the scale-up runs have been completed, operators will pay special attention to removal of clothing that may be contaminated and to showering. Any devices ("badges") that operators wear to monitor benzene exposure levels must be assayed, and the results must be compiled. The Friedel-Crafts reaction in Figure 4.2 was initially run in benzene on a laboratory scale [9]; during manufacturing of **2**, however, several equivalents of benzene are used with a cosolvent to decrease the concerns of handling bulk amounts of benzene [10].

II.B. Solvents Useful for Scale-up

Suitable solvents dissolve the desired materials, are liquid at the desired processing temperatures, and have the desired amount of water miscibility. Solvents should also allow for safe, convenient operations. Table 4.3 lists characteristics of many



2

FIGURE 4.2. A Friedel-Crafts reaction using benzene

TABLE 4.3. Solvents Useful for Scale-up

Solvent	E_N^T	Dielectric constant, ε_r	mp	bp	Flash point	Solubility in H_2O, wt%	H_2O dissolved in, wt%	bp of H_2O —solvent Azeotrope	Wt% of H_2O removed by— Azeotrope
Water	1.000	80.1	0°C	100°C	—	—	—	None	None
MeOH	0.762	33.0	−98°C	65°C	11°C	∞	∞	None	None
1,2-Propanediol	0.722	27.5	−60°C	188°C	99°C	∞	∞	None	None
EtOH	0.654	25.3	−114°C	78°C	13°C	∞	∞	78°C	4.0
AcOH	0.648	6.2	17°C	118°C	39°C	∞	∞	None	None
n-BuOH	0.602	17.8	−90°C	118°C	37°C	7.45	20.5	93°C	43.5
i-PrOH	0.546	20.2	−90°C	82°C	12°C	∞	∞	80°C	12.6
CH_3NO_2	0.481	38.3	−29°C	101°C	35°C	∞	∞	86°C	23.6
CH_3CN	0.460	36.6	−48°C	81°C	6°C	∞	∞	76°C	14.2
DMSO[a]	0.444	47.2	18°C	189°C	95°C	∞	∞	None	None
DMF[a]	0.404	38.3	−61°C	152°C	58°C	∞	∞	None	None
t-BuOH	0.389	12.5	25°C	83°C	11°C	∞	∞	80°C	11.8
NMP[a]	0.355	32.6	−24°C	204°C	96°C	∞	∞	None	None
Acetone	0.355	21.0	−94°C	56°C	−20°C	∞	∞	None	None
t-AmOH	0.318	5.8	−12°C	102°C	21°C	11.0	23.5	87°C	27.5
CH_2Cl_2	0.309	8.9	−97°C	40°C	—	1.3	0.2	38°C	1.5
Pyridine	0.302	13.3	−42°C	115°C	20°C	∞	∞	94°C	43
MeOAc	0.287	7.1	−98°C	56°C	−10°C	24.5	8.2	56°C	5
MIBK[a]	0.269	13.1	−80°C	117°C	18°C	1.7	1.9	88°C	24.3
DME[a]	0.231	7.3	−58°C	85°C	5°C	∞	∞	76°C	10.5
EtOAc	0.228	6.1	−84°C	77°C	−4°C	8.1	3.3	70°C	8.5
THF[a]	0.207	7.5	−108°C	66°C	−14°C	∞	∞	64°C	5.3
i-PrOAc[a]	NA	5.7	−73°C	89°C	2°C	2.9	1.8	77°C	10.6
PhCl	0.188	5.7	−45°C	132°C	28°C	0.05	0.05	90°C	28.4
2-MeTHF[a]	0.179	7.0	−136°C	77°C	−11°C	15.1	5.3	71°C	10.6
i-BuOAc	NA	5.1	−99°C	117°C	18°C	0.6	1.02	87°C	16.5

1,4-Dioxane	0.164	2.2	12°C	101°C	12°C	∞	∞	88°C	17.6
MTBE[a]	0.148	4.5	−109°C	55°C	−28°C	4.8	1.4	53°C	4
$(EtO)_2CH_2$	0.099	2.5	−67°C	88°C	−6°C	4.2	1.3	75°C	10
$PhCH_3$	0.099	2.4	−93°C	111°C	4°C	0.06	0.05	84°C	13.5
Et_3N	0.043	2.4	−115°C	89°C	−7°C	5.5	4.6	75°C	10
Xylenes[b]	NA	~2	[b]	137–144°C	~27°C	~0.02	~0.04	~93°C	~45
Heptane	0.012	1.9	−91°C	98°C	−4°C	0.0004	0.01	79°C	12.9
Cyclohexane	0.006	2.0	6°C	81°C	−20°C	0.006	0.01	69°C	9

[a]Abbreviations: DMSO, dimethylsulfoxide; DMF, dimethyl formamide; NMP, N-methylpyrrolidone; MIBK, methyl isobutyl ketone; DME, 1,2-dimethoxyethane; *i*PrOAc also known as IPAc; THF, tetrahydrofuran; 2-MeTHF, 2-methyltetrahydrofuran; MTBE, methyl *t*-butyl ether; NA, not available.

[b]Includes ethyl benzene and isomers of xylene. Melting point, flash point, and azeotropic characteristics will vary slightly with composition.

Sources:

1. Horsley, L. H. *Azeotropic Data–III;* Advances in Chemistry Series, 116; American Chemical Society: Washington, D.C.; 1973.
2. Gmehling, J.; Menke, J.; Fischer, K.; Krafczyk, J. *Azeotropic Data, Parts I and II;* VCH: Weinheim; 1994.
3. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry;* 2nd ed.; VCH: Weinheim; 1990.
4. Great Lakes Chemical Corporation Technical Bulletin (2-Methyl-THF).
5. Eastman Chemical Company Technical Bulletin (Diethoxymethane).
6. Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.
7. Riddick, J. A.; Bunger, W. B.; Sakano, T. K. *Organic Solvents, Physical Properties and Methods of Purification;* 4th ed.; Wiley: New York, 1986.
8. Archer, W. L. *Industrial Solvents Handbook;* Marcel Dekker: New York; 1996.
9. *The Merck Index;* 12th ed.; Budavari, S., ed., Merck & Co.: Whitehouse, NJ; 1996.
10. *CRC Handbook of Chemistry and Physics;* 78th ed., Lide, D. R., ed., CRC Press: Boca Raton, FL; 1997–1998.
11. *Industrial Solvents Handbook;* 4th ed., Flick, E. W., ed., Noyes Data Corporation: Park Ridge, NJ; 1990.

solvents that are useful for scale-up operations. Specific applications of solvents are discussed in this chapter, Section IV.

Some of the solvents mentioned in Table 4.3 deserve discussion.

- 1,2-Propanediol (propylene glycol) is a nontoxic substitute for ethylene glycol or methoxyethanol (see Figure 4.8).
- *N*-Methylpyrrolidinone (NMP) is a nontoxic, inexpensive substitute for hexamethyl phosphorictriamide (HMPA, also known as HMPT).
- Dimethylimidazolone (DMI, not covered in Table 4.3) has also been used as a substitute for HMPA [11], but DMI is appreciably more expensive than NMP.
- Methyl isobutyl ketone (MIBK) is a good solvent for extractive work-ups, removes a large amount of water by azeotroping, and is underutilized.
- In some companies, EtOAc is shunned, due to its ease of hydrolysis and problems resulting from the EtOH and AcOH produced.
- Isopropyl acetate (IPAc) is much more resistant to hydrolysis than EtOAc; in the preparation of the methanesulfonate salts **3** (Figure 4.3) significant amounts of the acetic acid solvates were formed when the solvent was EtOAc, and IPAc was preferred [12]. Crixivan intermediate **4** was prepared under Schotten-Baumann conditions by using IPAc at elevated temperatures (Figure 4.4) [13], which suggests the resistance of IPAc to hydrolysis.
- 2-Methyltetrahydrofuran (2-MeTHF) is an inexpensive solvent that is immiscible with water; by substituting 2-MeTHF for THF, work-ups may be eased.
- Diethoxymethane (DEM), an acetal with solubility similar to etheric solvents, may be a good substitute for THF and Et_2O [14]. DEM has a low propensity to form peroxides and can be used for Grignard reactions and organolithium reactions. Methyl lithium is available as a solution in DEM, which is much safer than CH_3Li solutions in Et_2O [15].
- *t*-BuOH is a solid at room temperature, which limits its usefulness; *t*-AmOH melts at −12°C, which extends the operating range of tertiary alcohols.

II.B.1. Solvents Used on Scale with Caution

Table 4.3 lists several solvents that many chemists will think are inappropriate for scale-up, including nitromethane, 1,4-dioxane, and methylene chloride (also

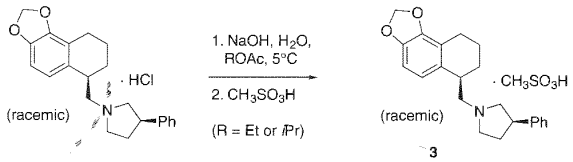


FIGURE 4.3. Salt exchange process using aqueous NaOH and acetate solvents

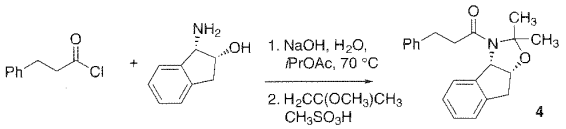


FIGURE 4.4. A Schotten-Baumann reaction in IPAc at 70°C

known as dichloromethane, or DCM). Nitromethane (rocket fuel) forms an explosive sodium salt that can be pyrophoric upon contact with H_2O [16]. Due to its anticipated carcinogenicity 1,4-dioxane is usually avoided [16]. Methylene chloride is in disfavor due to potential environmental impact and the difficulty of completely recovering this volatilized solvent due to its low boiling point. In spite of these concerns, some companies use these solvents for manufacturing operations. For any process development using these solvents, an early assessment should be made to determine whether these solvents can readily be used at the scale-up site and whether there are any acceptable alternative solvents.

Sometimes there is no ready substitute for a solvent, so provisions must be made for safe scale-up. For instance, amine hydrochloride salts often display some solubility in chlorinated solvents, and little solubility in other anhydrous solvents. In this case it may be appropriate to use methylene chloride; otherwise the chemist must consider alternative reagents or conditions. It should be stressed that the electrophilic reactivity of CH_2Cl_2 is often unappreciated [17–19]. Reactions of amines, a mercaptan, and an alcohol are shown in Figure 4.5.

TIP: Minimize contact of methylene chloride with basic compounds or basic aqueous phases. Consider any side reactions that may occur during periods of unnecessarily long contact, such as overnight storage of solutions containing amines that may act as nucleophiles.

III. SELECTED SOLVENT IMPURITIES

Impurities are described in many texts on solvents [4, 5]. Many organic impurities can be identified by GC or GC/MS techniques; for instance, MIBK can be found to contain mesityl oxide, the precursor to the manufacture of MIBK (Figure 4.6) [20]. Common impurities in solvents include H_2O, DMF [21], and AcOH (in EtOAc and other solvents). Some solvents are inhibited with trace amounts of antioxidants, e.g., CH_2Cl_2 (stabilized with amylene or cyclohexane) and THF and 2-Me-THF (stabilized with BHT, "butylated hydroxytoluene"). These impurities can influence the desired chemistry positively [22] and negatively, so and they should be considered.

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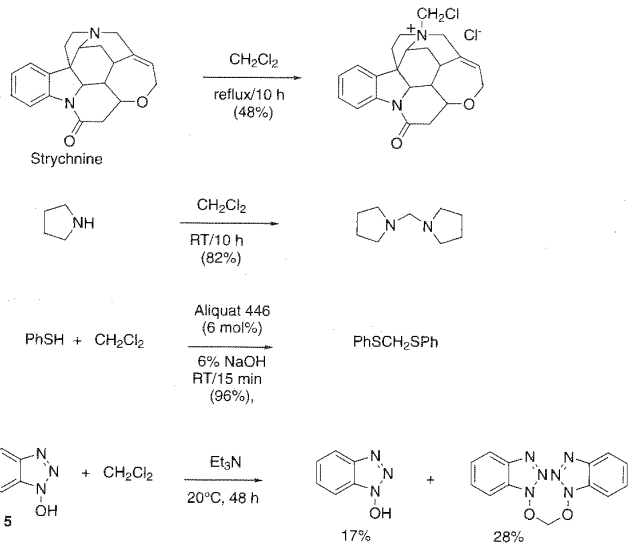


FIGURE 4.5. Some reactions of methylene chloride

TIP: When concentrating stabilized THF or 2-MeTHF, consider BHT as a probable process contaminant. Typically the concentration of BHT in purchased solvents is 0.025%, but with removal of the solvent, the levels of this impurity grow. BHT can be readily detected by reverse-phase HPLC.

Ethyl alcohol is available in many denatured grades. Some of the grades more useful to the pharmaceutical and fine chemicals industries are shown in Table 4.4.

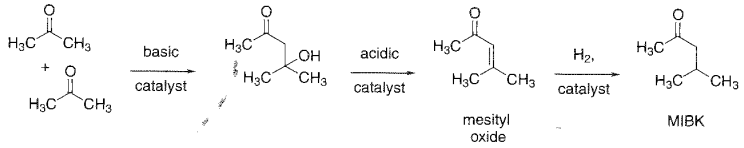


FIGURE 4.6. Manufacture of MIBK

TABLE 4.4. Selected Grades of Denatured Alcohol[a,b]

Grade	Denaturant	Denaturant charge
SDA 3A	MeOH	4.7–4.8 wt%
SDA 12A-3	Toluene	5.1–5.2 wt%
SDA 23A	Acetone	7.2–7.4 wt%
SDA 29-3	EtOAc	1.1 wt%
SDA 30A	MeOH	8.9–9.1 wt%

[a]Solvents are available in 190° and anhydrous conditions.
[b]"Ethyl Alcohol Handbook," U.S.I. Chemicals, © 1981 by National Distillers and Chemical Corporation.

IV. APPLICATIONS OF SOLVENTS

For reliable processing and minimized processing costs, the process chemist may select a solvent for a specific application. Many of these considerations, shown in Table 4.5, are very familiar to the chemist.

Clearly the priorities for solvent choices change with each reaction. Increasing the reaction rate may be less important than the ease of work-up and isolation operations. The best solvent for a reaction may be the one from which the product can be crystallized directly [23].

IV.A. Choosing Solvents for Homogeneous Reactions

In the early stages of developing a process, solvents and reaction conditions are chosen to dissolve the starting materials and reagents. Insoluble starting materials and reagents are less available for reaction than are soluble starting materials and reagents. Insolubility decreases reaction rates and may increase the rate of undesired reactions. For example, in the protection of the amino group of prolines by di-*t*-butyldicarbonate (Boc_2O), yields of 40–60% were found when the reaction was run under standard conditions of NaOH/aqueous dioxane (Figure 4.7) [24]. When the reaction was conducted in an organic solvent to decrease hydrolysis of Boc_2O, solubility of the amino acid starting materials was recognized to be a limiting factor. The solubility of the starting materials in dry CH_3CN was increased by using tetramethylammonium hydroxide as the base, and the derivatization was carried out in excellent yield.

TIP: Scaling up a reaction that is a solution is much easier than scaling up a reaction in which the components are insoluble or poorly soluble.

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TABLE 4.5. Process Design Reasons for Selecting Solvents

Goal	Impact on processing
Increase the desired reaction rate	Increase productivity, often through homogeneous reaction conditions.
Provide homogeneous reaction conditions	Increase reaction rate; decrease by-products.
Provide heterogeneous reaction conditions	Drive reactions by removing products and by-products from solution.
Increase the stirrability of reactions	Minimize localized heating; minimize by-product formation; increase ability to transfer slurries to filters.
Remove impurities by distillation (co-distillation or azeotroping)	Increase productivity, yield, and product quality.
Remove impurities by the addition of an immiscible solvent, usually H_2O, and extraction	Increase productivity, yield, and product quality.
Remove by-products by crystallization or precipitation	Increase productivity, yield, and product quality.
Purify the product by crystallization or recrystallization	Increase productivity, yield, and product quality; prepare the desired crystal form.
Increase the safety of operations	Protect operators, analysts, plant facilities, and communities.
Decrease atmospheric emissions and loss to process streams	Decrease environmental impact; may decrease processing costs.
Use readily available solvents, including those which do not require record-keeping for agencies outside of company	Increase ease of conducting campaigns and long-term operations.
Decrease contributions to overall product cost	THE GOAL: use less expensive solvents and grades of solvents; increase ease of recovery and reuse.

Homogeneous reaction conditions may also be important to minimize further reactions of the desired product, as illustrated by the Fischer indolization in Figure 4.8 [25]. For the first campaign this reaction was run at reflux in methoxyethanol (methyl cellosolve, bp 123°C, TWA of 5 ppm over 8 hours [26]). Under these conditions the reaction mixture was initially homogeneous, and ammonium chloride precipitated as the reaction progressed. A less toxic solvent was sought in subsequent research. Homogeneity and reaction temperatures over 90°C were found to be key for clean generation of the indolyl alcohol **8**. Under heterogeneous

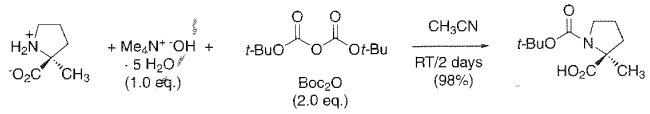


FIGURE 4.7. Increased N-acylation of amino acids in the presence of tetramethylammonium hydroxide

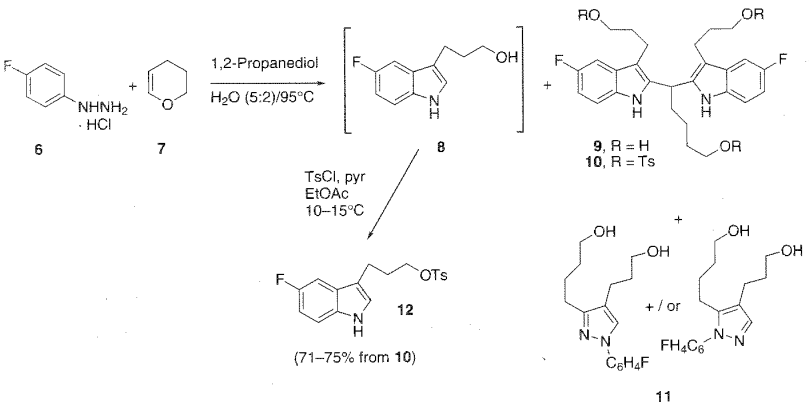


FIGURE 4.8. By-products formed in a Fischer indolization due to heterogeneous reaction conditions

conditions, the desired intermediate **8** reacted further with dihydropyran (**7**) to afford the triol **9**. The pyrazole(s) **11** were probably formed by condensation of two molecules of **7**, with loss of H_2O and reaction with **6**. The oily intermediate **8** was telescoped to the crystalline tosylate **12**, and the presence of tritosylate **10** dramatically reduced the isolated yield of **12**. The formation of **9** increased under conditions where starting material **6** was only slightly soluble. In essence, **8** was reacting with a localized excess of **7** to form **9**. A mixture of water and 1,2-propanediol (available in food grade) was found to dissolve **6** at 95°C. Adding dihydropyran over at least 30 minutes ensured that there was no localized buildup of this reagent. Conducting the reaction under these conditions reduced the formation of **9** to 1%, eliminating the need to use silica gel treatment to remove **9**. Homogeneous reaction conditions for preparing the indolyl alcohol **8** were essential for the development of a simplified, rugged process.

Dissolving larger molecular weight compounds, such as peptides and polycyclic aromatic compounds, may be very difficult, and often a successful approach is to find conditions under which the product is soluble. In such cases solubility may be affected by the reagents used, reaction concentration, and the presence of counter ions and any cosolvents. The octapeptide methyl ester **13** in Figure 4.9 had poor solubility in organic solvents. For rapid hydrolysis of the ester with minimal epimerization, a suspension of powdered **13** in THF was treated with 40% aqueous $(n\text{-Bu})_4NOH$ [27]. The suspension became a solution, and hydrolysis occurred with formation of only 0.8% of the epimer. To achieve good solubility and rapid reaction without significant epimerization, the keys were to match the lipophilic base $(n\text{-Bu})_4NOH$ with lipophilic **13**, and to have the proper concentration of H_2O.

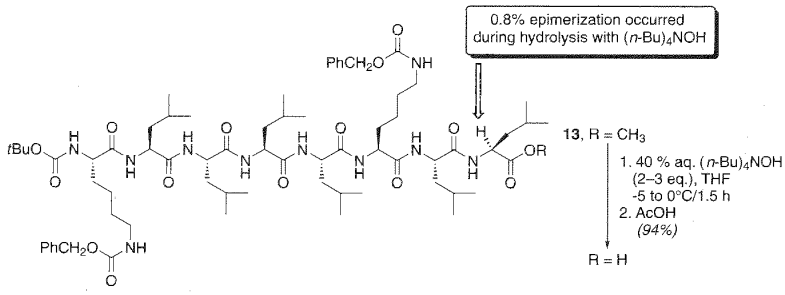


FIGURE 4.9. Hydrolysis of an octapeptide ester with $(n\text{-Bu})_4NOH$

IV.B. Choosing Solvents to Increase the Desired Reaction or Reaction Rate

Solvent polarity can be an important factor in increasing reaction rates. More polar solvents help stabilize the formation of polar transition states leading to products. In S_N1 reactions, charge is concentrated in the polar transition state relative to the starting material, and changing to more polar solvents can markedly increase the reaction rate by solvating and stabilizing the transition state. For instance, the solvolysis of Me_3CBr is 3×10^4 faster in 50% aqueous EtOH than in absolute EtOH [28]. For S_N2 reactions, however, going to more polar, hydrogen-bonding solvents may slightly decrease the reaction rate. Polar, non-hydroxylic solvents will accelerate S_N2 reactions with nucleophiles such as N_3^-, because the nucleophile is not solvated by hydrogen-bonding. Using DMSO instead of MeOH has been shown to accelerate by as much as 10^9 S_N2 reactions with N_3^- [28]. Similar trends have been noted for E_1 and E_2 reactions [29]. For radical addition reactions, solvent effects are less dramatic: A 35-fold deceleration was found when going from cyclohexane to DMSO [30].

TIP: Experimental facts are far more valuable than hypotheses. For instance, in the solvolysis of Me_3CCl, one can see a trend: Using solvents with higher dielectric constants (ε) usually accelerated the solvolysis [31]. *But not all solvents with higher ε accelerated this reaction.* Presenting the data can end discussions quickly, so people can immediately go on to the next problem.

The trend of accelerating reactions by using more polar solvents was demonstrated for the aminolysis of epoxide **14** with *t*-$BuNH_2$ (Figure 4.10). Faster reactions were noted as the solvent was changed from benzene to *i*PrOH to MeOH to H_2O [32]. As shown in Figure 4.10b, the use of more polar solvents greatly improved the yield from amination [33]. Each of these reactions probably involves a polar intermediate or transition state that is stabilized by solvent interaction.

TIP: Consider using excess reagent as a solvent to dissolve starting material. For instance, excess *t*-$BuNH_2$ helped to dissolve **14** in H_2O.

Solvent selection can markedly influence the product ratios of a reaction. In the catalytic asymmetric aminohydroxylation of styrene, the ratio of the acetamide products rose from 0.9:1 to 6.1:1 when the reaction was run in aqueous acetonitrile instead of aqueous *n*-PrOH (Figure 4.11) [34]. Solvent polarity can influence asymmetric induction, particularly during peptide coupling. When the racemic azlactone **15** was condensed with L-lysine methyl ester (**16**, Figure 4.12), the D,L-product predominated in relatively nonpolar solvents, and the L,L-product predominated in polar solvents and at lower temperatures [35].

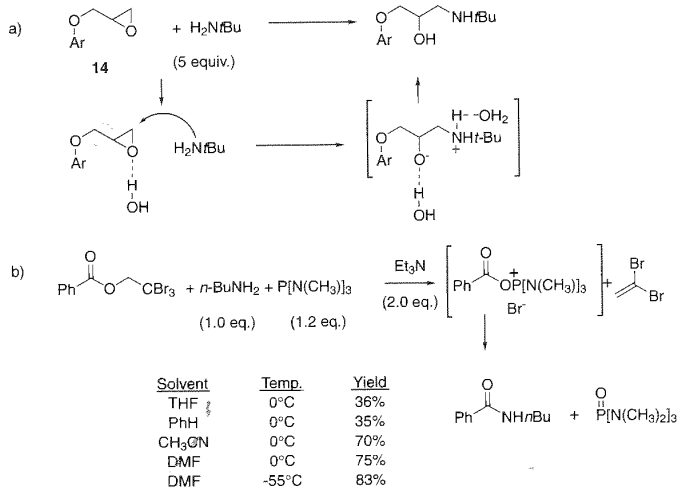
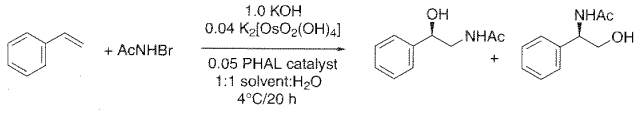


FIGURE 4.10. Improved reaction conditions by use of more polar solvents



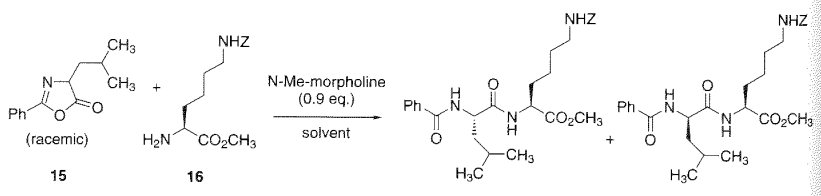
Cosolvent		
n-PrOH	0.9	1
CH_3CN	6.1	1

FIGURE 4.11. Influence of solvent on regiochemistry

Solvents can also inhibit reactions. For example, the deprotection of the benzhydryl ester **17** (Figure 4.13) was found to take place much faster in CH_2Cl_2 than in EtOAc [35]. Perhaps EtOAc acted as a Lewis base and sequestered the protons from the acid reagents, thus inhibiting the desired reaction. CH_2Cl_2 is somewhat more polar than EtOAc (Table 4.3), which would accelerate the solvolysis.

IV.C. Choosing Solvents to Provide Heterogeneous Reaction Conditions

Some reactions can be driven to completion by removing the products physically from the reaction. Products that are out of solution may be protected from further reaction. An excellent example is found for the selective removal of the BOC (*t*-butyloxycarbonyl) group from N-BOC-amino acid *t*-butyl esters [37]. As shown in Figure 4.14, treatment of the L-serine derivative **18** with anhydrous HCl in



	L,L	D,L
THF/23°C	35	65
DMF/23°C	68	32
DMF/5°C	77	23

FIGURE 4.12. Influence of solvent on asymmetric induction during azlactone opening

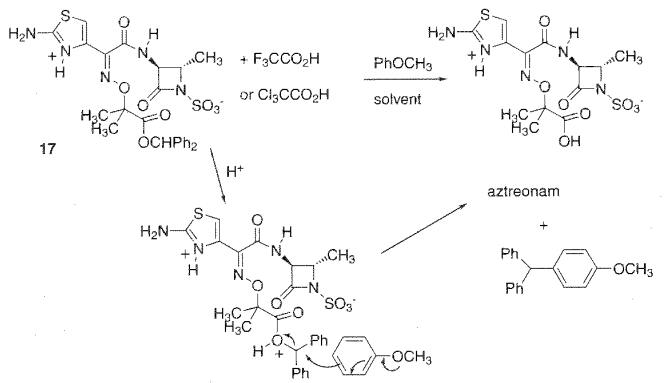


FIGURE 4.13. Deprotection of a benzhydryl ester

EtOAc affords an excellent yield of **19**, which still has two acid-labile protecting groups. The successful conversion is driven by the poor solubility of amine hydrochloride salts in EtOAc, and precipitation of the product limits any significant further reaction of the molecules.

IV.D. Choosing Solvents to Increase the "Stir-ability" of Reactions

Often solvents are selected to increase the fluidity and "stir-ability" of reactions. A heavy, viscous liquid or suspension cannot be readily mixed. Efficient stirring allows for improved heat transfer and minimizes impurity formation from any localized hot spots within the vessel. With efficient mixing, reagents are readily dispersed during additions, thereby decreasing side reactions, where control of reagent stoichiometry is critical to good yields (see Chapter 14, Scale-up Concerns). During crystallizations, readily stirred reactions afford better control of crystallization, produce better crystals, and afford greater ease in transferring a slurry to the filter. Stir-ability at the desired conditions may be limited by the freezing point

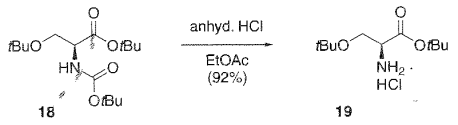


FIGURE 4.14. Heterogeneous conditions to limit acid-catalyzed reactions

and boiling point of a solvent. For ease in crystallizations, it may be useful to find substitutes for some of the more viscous solvents, e.g., *i*-PrOH and *t*-BuOH.

IV.E. Choosing Solvents to Remove Impurities by Azeotropic Distillation

Azeotropic distillation is a convenient means to remove some impurities on scale. A constant-boiling mixture exhibiting a constant ratio of volatile components is known as an azeotrope, or an azeotropic mixture. Azeotropes may be composed of two components (binary), three components (ternary), or more. An azeotrope with a boiling point above that of the highest-boiling constituent is known as a positive or maximum-boiling azeotrope [38]. An example is that of 20.2% HCl in H_2O, which boils at 108.6°C. Most of the azeotropes chemists encounter in process R & D are negative azeotropes, that is, the boiling point of the azeotrope is less than the boiling point of any component. In any case, the chemist knows that most of the minor component of an azeotrope is gone when the temperature of the vapors approaches the boiling point of the major component.

Water is the compound most commonly removed by azeotropic distillation on scale, and some examples are presented in Chapters 5 and 6. Removing water by azeotroping is a convenient operation on scale to reach strictly anhydrous conditions, which may be key for running the reaction or for crystallizing the product. Excellent references are available to describe azeotropes of solvents with water and other compounds [38, 39]. In general, small, unlike molecules form azeotropes, as shown in Table 4.6.

TIPS:

- Try to anticipate the formation of azeotropes when distillation and concentration occur. Unexpected azeotropes may cause unsafe operations. For instance, distillative removal of water from the reaction of an amine with benzyl chloroformate ($PhCH_2COCl$) resulted in formation of an azeotrope of water and benzyl chloride, a common impurity in benzyl chloroformate [40].
- Sometimes small changes in solvents or reagents can greatly improve processing. For instance, formic acid may be preferred over acetic acid in some cases, as formic acid can be removed azeotropically much more readily (see Table 4.6). Hexanoic acid was preferred as a catalyst over acetic or propionic acid, as hexanoic acid does not codistill with the reaction solvent $PhCH_3$ [41].

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TABLE 4.6. Some Binary Solvent Azeotropes[a]

	Heptane (bp 98°C)		Cyclohexane (bp 81°C)		Toluene (bp 111°C)	
	Azeotrope bp	% of polar solvent	Azeotrope bp	% of polar solvent	Azeotrope bp	% of polar solvent
MeOH (bp 65°C)	59.1°C	51.5 wt%	54°C	38 wt%	63.8°C	69 wt%
EtOH (bp 78°C)	70.9°C	49 wt%	64.8°C	31.3 wt%	76.7°C	68 wt%
*i*PrOH (bp 82°C)	76.4°C	50 wt%	69.4°C	32 wt%	80.6°C	69 wt%
*n*BuOH (bp 118°C)	94°C	18 wt%	79.8°C	9 wt%	105.5°C	32 wt%
*t*BuOH (bp 83°C)	78°C	62 wt%	71.3°C	37 wt%	none	none
*t*AmOH (bp 102°C)	92.2	26.5 wt%	78.5°C	16 wt%	100.5°C	56 wt%
Acetone (bp 56°C)	56°C	89.5 wt%	53°C	67 wt%	none	none
THF (bp 66°C)	none	none	[b]	[b]	none	none
CH_3CN (bp 81°C)	69.4°C	44 wt%	62.2°C	33 wt%	81.1°C	78 wt%
CH_3NO_2 (bp 101°C)	80°C	35 wt%	70.2°C	28 wt%	96.5°C	55 wt%
EtOAc (bp 77°C)	none	none	72.8°C	54 wt%	none	none
CH_3CO_2H (bp 118°C)	95°C	17 wt%	79.7°C	2 wt%	104°C	32 wt%
HCO_2H (bp 100°C)	78.2°C	56.5 wt%	70.7°C	30 wt%	86°C	50 wt%

[a]Sources: Loewenthal, H. J. E. *A Guide for the Perplexed Organic Experimentalist* 2nd ed., Wiley: Chichester, 1992, pp. 170–171; Horsley, L. H. *Azeotropic Data–III;* Advances in Chemistry Series, 116; American Chemical Society: Washington, D.C., 1973; Gmehling, J.; Menke, J.; Fischer, K.; Krafczyk, J. *Azeotropic Data, Parts I and II;* VCH: Weinheim, 1994.

[b]Positive-boiling azeotrope.

Reducing distillation pressure can reduce the portion of the minor azeotropic component for some solvents. As shown in Table 4.7, by dropping the distillation pressure from 760 mm to 25 mm the amount of water removed in EtOAc drops by more than 50%. If reducing the pressure results in no azeotrope, these conditions are said to "break" the azeotrope. Reducing the distillation pressure does not always decrease the proportion of the minor component in the azeotrope, as shown in Table 4.7 for the *i*-PrOH-H_2O azeotrope.

IV.F. Choosing Solvents to Remove Impurities by Adding an Immiscible Solvent and Extraction

Often solvents are selected or avoided due to the extent of water miscibility. Solvents with low water solubility readily afford phase separations when extracts are washed with aqueous solutions, and minimal loss of the product to the spent aqueous phase occurs. Product may be lost to the aqueous phase when extracting solutions of solvents with high water solubility. To minimize such losses it may be necessary to partially concentrate the solution before extraction or to dilute with large volumes of water and water-immiscible solvents (see Chapter 10).

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TABLE 4.7. Composition of Water in Solvent - H_2O Azeotropes as a Function of Pressure

Pressure (mm)	bp (°C)	wt% water in azeotrope[a]
EtOAc - H_2O		
25	1.9	3.6
250	42.6	6.3
760	70.4	8.5
iPrOH - H_2O[b]		
67		12
95		13
153		12
190		13
319		12
380		13
760		12

[a]Horsley, L. H. *Azeotropic Data–III;* Advances in Chemistry Series, 116; American Chemical Society: Washington, D.C.; 1973

[b]Data are taken from two studies, and may represent the same composition as measured by two investigators.

IV.G. Choosing Solvents to Remove By-products by Crystallization or Precipitation.

Removing by-products by crystallization or precipitation can ease work-up conditions. Solvent ratios may be adjusted or solvents may be exchanged during work-up to remove by-products. Some examples are shown in Table 4.8. Removing the by-product may also allow for an improved yield by isolating the kinetic product (see Figure 8.11).

IV.H. Choosing Solvents to Purify the Product by Crystallization or Recrystallization

Solvent selection is usually very important in preparing both high-quality product and the desired crystal form. Details may be found in Chapter 11.

IV.I. Choosing Solvents to Increase the Safety of Operations

The chemist must consider the safety of operators during processing and of those who come in contact with the drug substance or intermediates after the processing of a step is complete. Selecting a less hazardous solvent during scale-up preparations not only decreases risks to operators and the community but also simplifies operations and decreases processing time overall. Some solvents are avoided due to

TABLE 4.8. Solvents Useful in Removing Some Reagent By-products

Reagent	Reagent By-product	Solvent to Precipitate or Crystallize By-product
Dicyclohexylcarbodiimide (DCC)	Dicyclohexylurea (DCU)	DMF; THF - H_2O
N-Chlorosuccinimide	Succinimide[a]	CH_2Cl_2; $PhCH_3$
Triphenylphosphine	Triphenylphosphine oxide	Heptane
Amines	Amine hydrochlorides	EtOAc; THF; CH_3CN

[a]Can also readily be removed by extraction into H_2O or aq. $NaHCO_3$.

unpleasant vapors, e.g., acetic acid. The presence of residual solvents may also be a concern for analysts examining isolated compounds.

IV.J. Choosing Solvents to Decrease Atmospheric Emissions and Losses to Process Streams

Many operations—spills, emissions to the atmosphere, contamination of wastewater streams, and disposal of wastes—release solvents and other compounds to the environment. Controlling emissions is particularly important for continued operations on a manufacturing scale. To decrease emissions, reactions may be run at lower temperatures, or higher-boiling solvents may be chosen. Sometimes solvents are avoided if they are difficult to remove or if the chemist anticipates that the presence of this solvent will cause down-stream processing difficulties. DMSO can be considered one of these solvents: Multiple extractions with H_2O may be necessary to satisfactorily remove DMSO, and small amounts of residual DMSO may adversely affect the crystallization of the product.

IV.K. Choosing Readily Available Solvents

Solvents that can be readily purchased in large quantity or that are available on-site are preferred for scale-up. For instance, some sites will have ready access to one type of denatured alcohol. Requiring use of another type of denatured alcohol might cause significant delays if permission from local regulatory authorities is needed. Most sites routinely store and use acetone, but plans to use 2-butanone may meet some resistance simply because of unfamiliarity.

TIP: When developing a process for a new site, consider any regulations that might restrict delivery of a solvent to that site. Regulations can vary from state to state and from country to country.

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IV.L. Choosing Solvents to Decrease Immediate Contributions to Overall Product Cost

Considerable financial gain can be realized by minimizing the volumes of solvent used and by selecting less expensive solvents and grades of solvents, as appropriate. Minimizing the volume of solvent used also helps contain the cost of waste disposal.

> **TIP:** For initial laboratory investigations, whenever possible use solvents from bulk supplies that have been purchased for routine processing. Avoid special grades of solvents, such as HPLC-grade solvents, as processing may change when reactions are run in bulk solvents, due to differing impurities and impurity levels. Using a higher grade of solvent may not be necessary; for instance, water is readily removed from many solvents (and scale-up vessels) by azeotropic distillation, eliminating the need to purchase more expensive "anhydrous" solvents. Once a special grade of solvent has been shown to be necessary, then purchase of the more costly material is readily justified.

Recovery and reuse of solvents may have great financial impact for manufacturing operations. Usually solvents are recovered by distillation, with optional aqueous washes before distillation. High-boiling solvents such as DMF and DMSO are difficult to recover, so they often are used only once, then sent to waste disposal. Solvents may be chosen for decreased water solubility and to decrease the burden on water processing facilities. All waste-water streams that contacted organic solutions should be considered to be contaminated with that solvent and solute, as very few compounds are truly "insoluble."

V. ALTERNATIVES TO CLASSICAL SOLVENTS

There are three alternatives to solvents classically used by organic chemists. Water may be used in place of organic solvents, or no solvent may be added to a reaction. Alternative solvents are also being investigated.

V.A. Water

Although water is the most readily available solvent, classically water has been avoided as a solvent for organic reactions. In many reactions, e.g., those using strong bases, $AlCl_3$, and dehydrations, the use of water as a solvent inhibits or stops the reaction. Often large molecules or molecules with hydrophobic groups do not exhibit enough water solubility to allow for reactions of reasonable concentration.

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Recently there has been a huge amount of research on reactions in water. Many chemical and enzymatic processes are run in water. A number of carbon-carbon bond-forming reactions can be carried out in water, and the thought of such investigations would have been readily dismissed years ago. Two excellent reviews on this subject [42, 43] show the extensive breadth of aqueous reactions.

A wide variety of carbon-carbon bonds can be formed in aqueous conditions (Figure 4.15). An indium-mediated Barbier reaction on unprotected galactose led

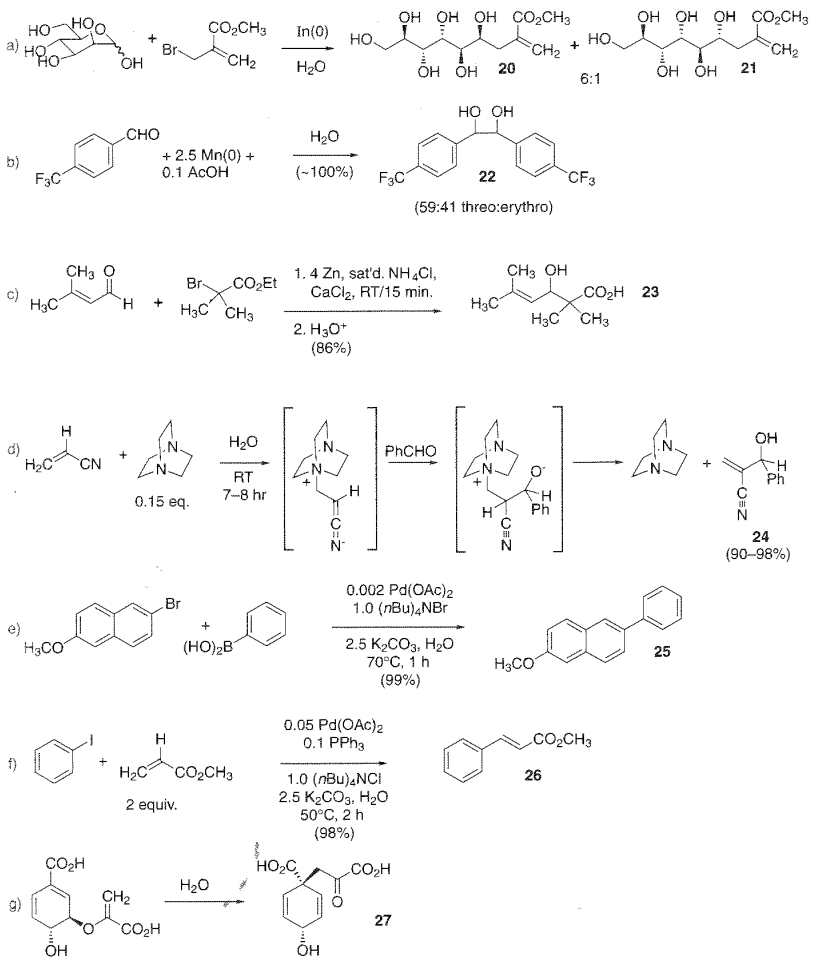


FIGURE 4.15. Selected reactions in water

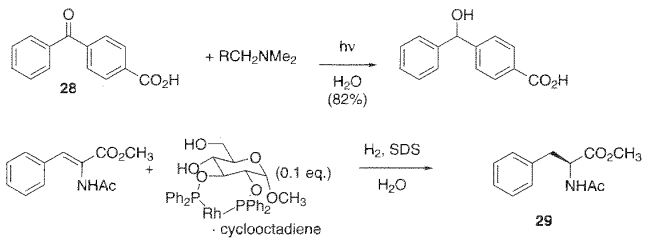


FIGURE 4.16. Some reductions performed in water

to the formation of the two unsaturated products **20** and **21** in a ratio of 6:1 [44]. A McMurry-like coupling using manganese powder produced a quantitative yield of the diols **22** [45]. Reformatsky reaction gave the hydroxy acid **23** in 86% yield [46]. The Baylis-Hillman reaction leading to **24** was found to be accelerated in H_2O [47]. Suzuki couplings in the presence of $(n\text{Bu})_4\text{NBr}$ have also been carried out efficiently in water, as shown with the preparation of **25** in 99% yield [48]. Quaternary ammonium salts were also found to be necessary for Heck-type reactions in water, as for the preparation of **26** [49]. The Claisen rearrangement to afford **27** was 100 times faster in water than in MeOH [50].

Water has been used to accelerate reductions, as in photochemical reduction of the ketone **28** (Figure 4.16) [51]. Surfactants have also been shown to aid reactions in water: when sodium dodecyl sulfate was added, the ee rose from 61% to 94% in the preparation of **29** (Figure 4.16) [52].

Bromination of electron-rich benzoic acids was carried out advantageously in water using N-bromosuccinimide (NBS) or dibromodimethylhydantoin (DBDMH) (Figure 4.17) [53]. For scale-up, either of these reagents was preferred over the toxic Br_2. Water was greatly preferred over $CHCl_3$ or CCl_4, solvents usually employed with NBS brominations. An excellent yield resulted using the conditions in Figure 4.17, with reduced levels of dibrominated impurities relative to those seen with Br_2/dioxane bromination.

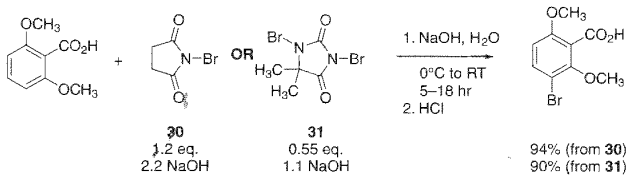


FIGURE 4.17. Bromination of an electron-rich benzoic acid in water

Water has also been judiciously added as a cosolvent to increase reaction rates. In the dehydrobromination of **32** (Figure 4.18), using 6% water as cosolvent was found to give the highest yield of the 1,4-diene **33** and the lowest yield of the undesired 4,6-diene **34** [54]. Water increases the solubility of the base in this reaction. For the deprotection of N-phthaloyl derivatives by $NaBH_4$ (Figure 4.18), the concentration of H_2O in *i*PrOH was examined from 1–20%, and the fastest rate occurred with 14% H_2O [55]. For the oxidation of alcohols using catalytic CrO_3, 0.75% H_2O in CH_3CN was found to give the best yields (Figure 4.18) [56].

> **TIP:** In some reactions a small change in the amount of water charged can have significant effects. Setting up reactions on a "test-tube" scale with the concentration of water varied in increments may be an easy way to assess any potential benefits of water.

Various grades of water available for process R & D are shown in Table 4.9.

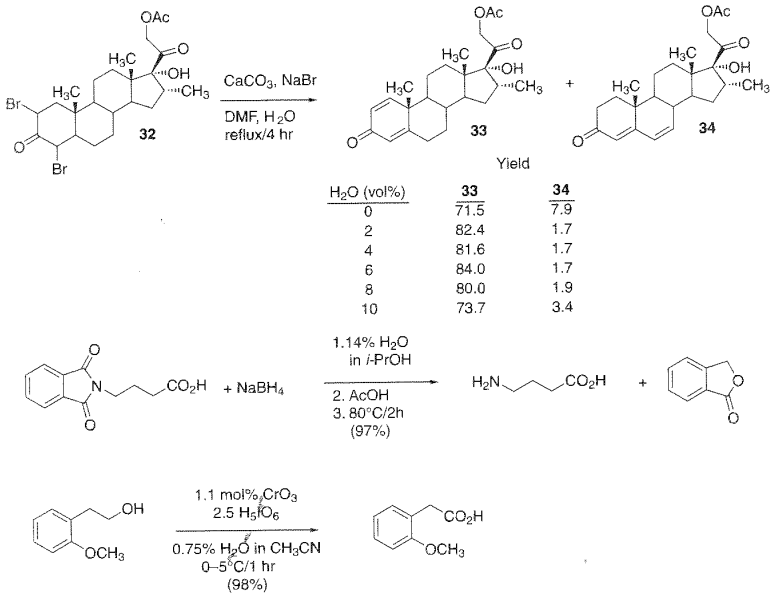


FIGURE 4.18. Water as a cosolvent to increase reaction rate

TABLE 4.9. Grades of Water Used for Chemical Processing

Type	Characteristics
City water	Drinking water from municipal facility. Often contains chlorine, a potential oxidant that can cause side-reactions. Inorganic salts and organic impurities may be present.
Distilled water	Non-volatile components are in principle removed from the condensate. Quality depends on the equipment and technique.
Deionized water	Treated with ion exchange resins to remove ions. Often available on site in large volumes. Caution: pH may vary.
Water for injection, pyrogen-free	Microbes and proteins are usually removed by filtration through filters of < 2 μm. Used to reconstitute drugs prepared as lyophiles. Packed in sterile containers, expensive.
Highly purified water	Contaminants are measured in the ppt levels. Used in the semiconductor industry.

V.B. Neat Reactions

In many industrial settings, no solvent is used for a reaction, i.e., the reaction is conducted "neat." The advantages of this approach are that no expenses are incurred for the purchase and disposal or recovery of solvent. Under such concentrated conditions the reaction proceeds rapidly, and product throughput is very high.

While there are obvious advantages to solvent-free reactions, there may be small savings if organic solvents are used for work-up [57] or if purification of spent aqueous streams is costly. A disadvantage of solvent-free reactions is that controlling reaction temperatures can be difficult, as the heat capacity of a solvent is not available to help dissipate the heat of reaction. For efficient conversions,

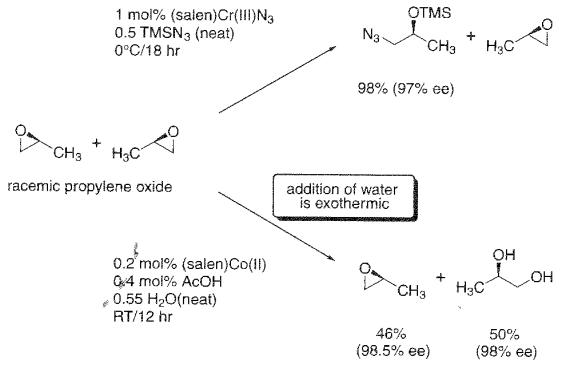


FIGURE 4.19. Kinetic resolution of racemic propylene oxide in solvent-free conditions

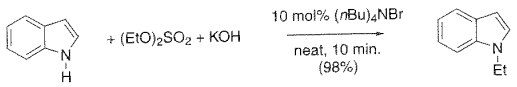


FIGURE 4.20. Alkylation of indole using PTC under solvent-free conditions

thorough mixing may be problematic in solvent-free reactions. In principle, any mixing device can be a suitable reactor, and ball mills [58] may be suitable for some small-scale operations. For large-scale operations, neat reactions are often limited to those with liquid products. Figure 4.19 gives two examples of solvent-free reactions that have been conducted on scale through the kinetic resolution of racemic propylene oxide [59, 60].

Excess liquid reagents can be used as solvents in neat reactions. Many PTC reactions have been conducted without organic solvents (see Figure 3.17). Conversions can be very fast and efficient, as in the ethylation of indole [61] (Figure 4.20). The esterification of amino acids in melted octadecanol was also an effective solvent-free reaction (Figure 4.21) [62].

Formoterol was also prepared through a neat reaction (Figure 4.22). Significantly, the presence of water leads to the formation of undesired regioisomers during the coupling [63]. In another neat reaction, a small amount of dichloromethane was added to decrease viscosity and allow for better mixing [64].

V.C. Possible Future Directions

Reactions in fluorous solvents (usually perfluorinated hydrocarbons) have been described [65], and benzotrifluoride ($PhCF_3$) has shown to be a useful replacement for CH_2Cl_2 [66]. These solvents are significantly more expensive than solvents routinely used today, but prices may drop as applications and demand rise.

Nonaqueous ionic liquids have been used for hydrogenation of arenes and other liquids [67, 68]. By selecting a stable catalyst that is soluble in the ionic phase, purification of products began by separating the liquid products from the ionic liquid containing the catalyst. Because of the expense of nonaqueous ionic liquids, the ability to recover and reuse these materials will be important to control costs if they are to be used on scale.

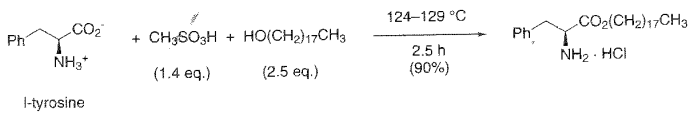


FIGURE 4.21. Solvent-free esterifications of amino acids

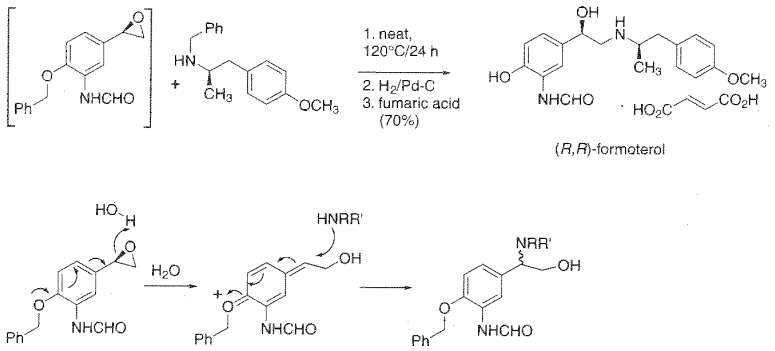


FIGURE 4.22. Solvent-free preparation of formoterol

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CHAPTER 5

Running the Reaction

I. INTRODUCTION

How a reaction is run can determine its success or failure, so details of the operations can be very important. Details of the specific conditions must be thoroughly described before a process can be safely and reproducibly scaled up, especially by someone who did not develop the original process. Few chemists are naturally inclined to describe in detail the conditions that they used. The nonspecific descriptors ("groaners") listed in Table 5.1 are not sufficient to allow for ready scale-up of most processes.

Procedural steps for setting up and running a reaction are shown in Table 5.2. Details are discussed in the sections below.

II. DETERMINING REACTION SAFETY

Before running a reaction, the chemist must ask whether the reaction is safe to run. *Accidents incur great costs.* Potentially at risk are the chemist, coworkers, employees on-site, and members of the local community. People may get hurt,

TABLE 5.1. Nonspecific Descriptors Found in Chemistry Experimental Procedures

Added slowly
Added dropwise
To a dilute solution
Added in portions
Added to a cold solution
Was run overnight
Added at −78°C (was the temperature kept constant during the addition?)
With a slight exotherm
At room temperature (colder in England, hotter in the tropics)
Excess reagent
Vigorous agitation
Worked up in the usual way
Gave a white solid
Sufficiently pure
Yields given without consideration of product quality

and health effects may last far beyond the inconvenience of the incident. Expensive equipment can be damaged. Valuable time can be lost, causing costly delays in the development of new compounds. Severe accidents can have adverse effects on public relations for the offending company.

Each reaction should be considered for possible hazards, including reaction exotherms, gas evolution, and the safety of handling reagents, solvents, and products [1]. Known or anticipated toxicologic hazards of starting materials, reagents, and products should be included in such assessments. Many companies have laboratories to assess chemical reaction hazards, while others contract out such analyses.

To identify possible problems from exotherms and gas evolution, some measure of the magnitude of reaction exotherms is attainable using differential

TABLE 5.2. Step-by-Step Procedure for Setting Up and Running a Reaction

Determine if reaction is safe to run.
Confirm equipment is safe for operations.
Select reaction scale.
Choose equivalents of reagents, starting materials, and solvents.
Determine if inert conditions are needed, and inert reactor.
Charge starting materials and solvents.
Adjust (and maintain) reaction temperature.
Determine optimal addition time and temperature.
Determine optimal addition sequence of reagents.
Adjust reaction pressure.
Adjust stirring.
Monitor reaction progress.

Sun Ex. 1022

scanning calorimetry (DSC) and the reactive system screening tool (RSST). DSC detects heat transitions for solid compounds, typically starting materials and products. For safety assessment, key transitions include endothermic melting and exothermic decomposition. Quantitative and semiquantitative assays are possible. Thus DSC can be used to determine whether a reaction is being run safely below the decomposition temperature of a reaction component. RSST can be used to monitor reaction exotherms and gas evolution. The sample is introduced into a well-insulated, spherical glass cell that can be pressurized. Gas evolution can be noted as the cell pressure increases with heating.

More quantitative measurements are attainable by using an accelerated rate calorimeter (ARC), which is an adiabatic (sealed) calorimeter used to study runaway reactions. The data generated can be directly applied for plant scale-up, e.g., for calculating whether the cooling system for scale-up can safely accommodate the reaction exotherm. Sealed calorimeters show a decreasing boiling point associated with a change in the volatile reaction components [2]. Stirred tank calorimetry can also be used to accurately calculate the heat of reaction [3].

TIPS:

- Not every reaction should be subjected to full chemical hazard analysis, as some reactions, e.g., the hydrolysis of an ester in water, will have little risk involved. When unsure, it is always wise to get the advice of a more experienced person before running a potentially hazardous reaction.
- Any reaction involving air or O_2 should be thoroughly investigated before scale-up.

III. ASSESSING SAFE OPERATING CONDITIONS FOR THE LABORATORY

Safe operating conditions include safe equipment, chemicals, process operations, and personnel safety. Details for safe laboratory operations have been published [4, 5].

The primary key for safe laboratory operations is the fume hood, which removes harmful vapors. The fume hood should be correctly drawing air across the open surface. Clutter within the hood must be minimized for safe operations. Outside the hood, all equipment such as gas cylinders, must be safely secured. Personnel must be protected from any moving equipment, such as belts and wheels of pumps and air compressors. All emergency equipment, such as fire extinguishers and spill containment pillows, must be readily accessible.

Personnel should be trained in safe operations. Safety glasses, gloves, safety shoes, and other protective clothing should be used routinely. Portable safety

shields should be readily available and used if a highly exothermic reaction is expected.

TIP: Safety issues should not be taken for granted. Review safety regularly.

Static sparks can cause explosions. Static buildup occurs during routine operations when poorly conductive materials contact each other, then separate without the chance for rapid discharge to the ground. The relaxation time, or amount of time needed to discharge static charge, varies widely (Table 5.3) [6]. Heptane is preferred over hexane due to heptane's shorter relaxation time. Grounding equipment, including glassware such as large chromatography columns, reduces the risk of static discharge.

Some common chemicals, such as *i*-PrOH, can form peroxides in explosive concentrations [7]. Peroxides can react, sometimes vigorously, with reagents such as alkyllithiums, amines, and other oxidizable compounds. Testing by dip strips containing peroxidase is a convenient means to monitor the peroxides present in chemicals. Guidelines for the use of such strips and purification of solvents containing peroxides have been published [7].

IV. SELECTING THE REACTION SCALE

The scale of a reaction is determined by the amount of chemicals available, how expensive the components are, and how readily more material can be obtained. The size of available equipment can also limit the reaction scale. The amount of time available is another factor: larger runs take longer, and the amount of information obtained is not always commensurate with the time and effort expended. For instance, larger runs will require more time for work-up if a substantial portion of the solvents must be removed by concentration. While the knowledge

TABLE 5.3. Relaxation Times for Static Discharge of Some Common Solvents

Solvent	Relaxation Time	Half-Time Value
Toluene	21 s	15 s
Hexane	46 h 42 min	32 h 26 min
Heptane	0.18 s	0.13 s
Methanol	9×10^{-6} s	6×10^{-6} s
Ethanol	1.6×10^{-4} s	1.1×10^{-4} s
Water	1.4×10^{-6} s	1×10^{-6} s

gained from an extended concentration may be needed, it could be obtained in only one experiment designed to investigate many aspects of scale-up.

In general, a small scale is appropriate as one starts to develop a process, as initial reactions may not produce product that is pure enough for further study without having to resort to purification. Many small-scale "scouting" experiments can be run to determine optimal conditions, and there is no pressure to obtain clean product. As greater confidence is gained in the process, larger scale reactions may be set up to prepare suitable quantities of material for others. Larger scale runs may be necessary to examine physical parameters, e.g., to develop an efficient crystallization of a concentrated slurry or to examine distillation during work-up.

TIP: Premature scale-up wastes valuable time, materials, and money.

V. CHOOSE EQUIVALENTS OF REAGENTS, STARTING MATERIALS, AND SOLVENTS

The charges of reagents, starting materials, and solvents to reactions are minimized to decrease cost of inputs and to optimize vessel throughput. Minimizing these charges also decreases operating times by decreasing the amount of time needed to add these components, to remove solvents by distillation, and to neutralize reactive components. Waste disposal costs are also decreased by minimizing charges of reaction components. Thus this consideration can have considerable impact on overall product cost and productivity.

Undercharging reagents can lead to increased impurities when the desired product has reactivity similar to that of the starting material or a reagent. As shown in Figure 5.1, the desired secondary amine **3** is expected to be more nucleophilic than isobutylamine (**2**), and **3** does react with starting epoxide **1** to afford the dimeric amine **4**. Five equivalents of **2** were charged to minimize formation of the dimer **4**, and a greater charge of **2** would have contributed unnecessarily to costs. [8].

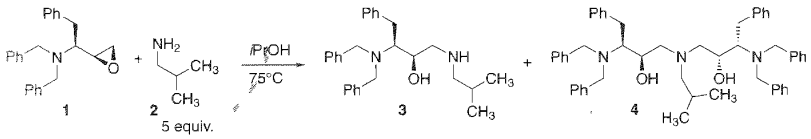


FIGURE 5.1. Overreaction of amines with epoxides

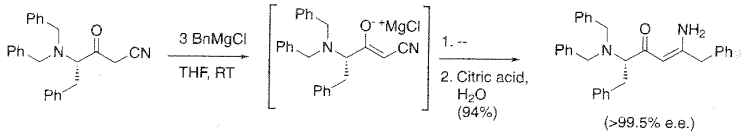


FIGURE 5.2. Grignard addition to a β-keto nitrile

The goals of minimization must be balanced by the drive to use a sufficient amount of reagents to complete the reaction in a reasonable amount of time, thus increasing productivity. In general, 1.02–1.2 equivalents are often charged in order to reach suitably rapid reactions. More equivalents may be charged if the reagents are inexpensive and easy to neutralize, and if increased waste is not an issue. Additional equivalents will be needed if there is more than one reactive group in the molecules, as in Figure 5.2 [9]. Reagents may also be chosen to facilitate work-up (Chapter 10). If many equivalents of a reagent are needed, fewer equivalents may be used by increasing reaction temperature and/or concentration.

TIP: If many equivalents of a reagent are needed to carry out a reaction completely, consider running the reaction at a higher temperature or concentration to decrease the amount of reagent needed.

Particularly hazardous reagents may be charged in limiting amounts. With excess reactants present, the more hazardous reagents should be consumed. This approach is recommended for reactions with the poisonous cyanide reagents and with the explosive sodium azide. The benzyl cyanide **5** was prepared from only 1.05 equivalents of NaCN using PTC (Figure 5.3), and excess NaCN was

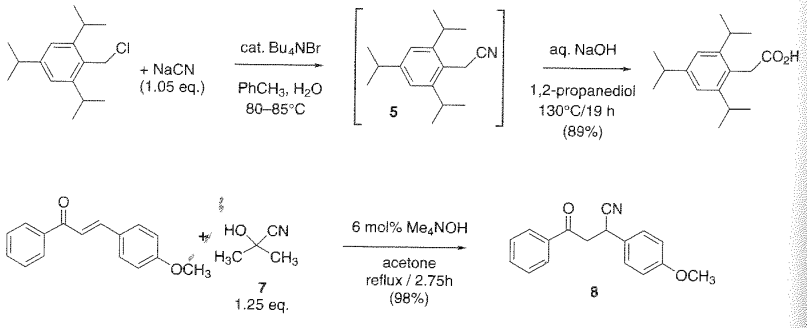


FIGURE 5.3. Reactions with cyanide and cyanohydrin using PTC

destroyed by NaOH treatment [10]. For the Michael addition of cyanide to the chalcone **6**, acetone cyanohydrin (**7**) was employed instead of NaCN. Only 1.25 equivalents of **7** were needed for an excellent yield of **8**, and excess **7** was destroyed by treatment with NaOCl [11]. Both NaN_3 and NaCN were used in the preparation of the tetrazole **9** (Figure 5.4) [12]. In this process the aqueous phases are never acidic and safely contain unreacted NaN_3 or NaCN.

> **TIP:** PTC can provide a safe, highly effective approach to reactions with NaCN and NaN_3. First of all, reaction conditions are usually basic, which safely keeps NaCN and NaN_3 in solution as the anions. Second, because the nucleophiles are less solvated under PTC conditions than in DMSO or similar solvents, PTC provides more reactive conditions. Hence fewer equivalents of NaCN and NaN_3 are needed, and reactions are generally faster.

Excess reagents may be charged to facilitate work-up. In the dialkylation of amine **10**, four equivalents of *n*-PrI were charged (Figure 5.5) [13]. Overalkylation produced the quaternary amine **12**, which was easily removed from the product **11** by aqueous extraction. The product **11** was much more readily freed of **12** than of **13**, which was the contaminant when less *n*-PrI was used.

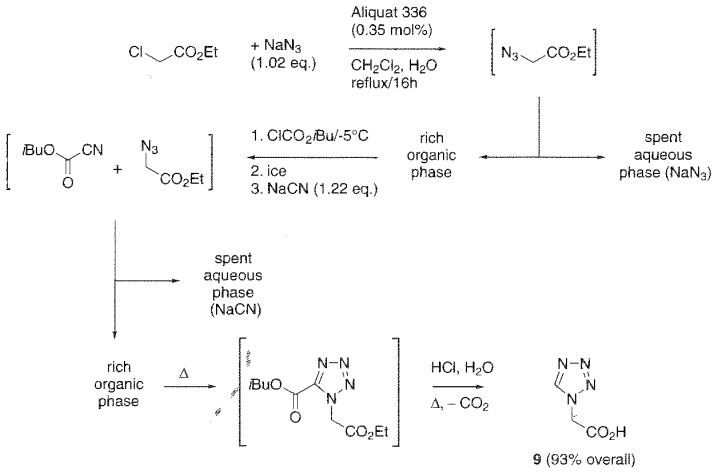


FIGURE 5.4. Reactions with cyanide and azide using PTC

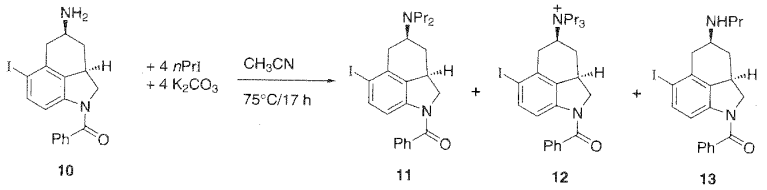


FIGURE 5.5. Beneficial overalkylation of a primary amine

Other factors should be considered when minimizing solvent charges. More concentrated reactions often mean shorter reaction times. However, too highly concentrated reactions can make stirring difficult, and lead to side reactions due to poor mixing and poor heat transfer. With more concentrated reactions there is less solvent available to help dissipate any exothermic reactions, making temperature control more difficult and extending addition times.

For initial laboratory investigations, a reaction concentration of 0.3–0.4 M may be a good starting point. More dilute conditions will be needed to minimize selected intermolecular reactions for some relatively slow reactions, such as β-lactam cyclization and macrolactonization. The optimal manufacturing concentration has been described as greater than 10% [14], and should be adjusted for the process needs.

The preparation of the tolmetin sodium intermediate **17** (Figure 5.6) [15] illustrates several points that apply for running reactions reproducibly, quickly, and safely. Reaction of *N*-methyl pyrrole (**14**) with chloral (**15**) was slower if purified **15** was used; this condensation is acid-catalyzed, and was accelerated by traces of trichloroacetic acid present in aged **15**. Unfortunately when the solvent was removed for the subsequent step, residual acid promoted the decomposition of the chloral adduct **16**. Thorough removal of the acid from the CH_2Cl_2 extract was possible only by extraction with dilute aqueous NH_3; all other treatments were less effective, including aqueous $NaHCO_3$, solid $NaHCO_3$, and Et_3N. The reductive transformation of **16** to the acid **17** was mediated by aqueous sodium

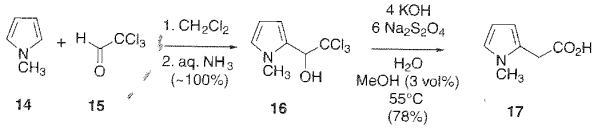


FIGURE 5.6. Preparation of a tolmetin sodium intermediate

dithionite, and **16** was insoluble under the reaction conditions. By adding only 3 vol% of MeOH to break the surface tension, the reaction rate was increased markedly. Such attention to the details of reagents and solvents can greatly increase the reproducibility of reactions.

TIPS: for running the reaction:

- To determine maximal concentration, work backwards. For instance, to hydrolyze ethyl benzoate with aqueous NaOH, determine the saturation concentration of sodium benzoate in H_2O at the desired temperature. Then examine hydrolysis of ethyl benzoate at that concentration.
- Use heterogeneous reactions to drive a reaction to completion and to decrease overreactions (see Figure 4.14.)
- Add small amounts of solvents to break the surface tension of heterogeneous reactions and increase reaction rates.
- Use reagents and starting materials as received. Beneficial impurities may be present. Subsequent optimizations may determine that additional purification is needed.

VI. EMPLOY INERT CONDITIONS IF NEEDED

An inert atmosphere is applied to reactions to remove oxygen and to keep out O_2 and H_2O from the reaction. The reactivity and undesirability of H_2O is presented in Chapter 6. Oxygen may also generate undesired impurities, explosively in some cases.

Removing O_2 is necessary for the safe operations of many reactions, especially hydrogenations. Funtional groups which are readily oxidized with O_2 include mercaptans, tervalent phosphorus compounds, and some amines. Anions may also react with dissolved O_2, leading to the generation of impurities during alkylation of these anions [16].

Several approaches are used to remove oxygen from reactions. Reactors may be flushed with N_2, and solvents in the reactor may be sparged with purified nitrogen in order to displace dissolved O_2. A slight positive pressure of N_2 (a "nitrogen blanket") may be applied to the reactor to exclude the entry of atmospheric H_2O and O_2. Hydrogenators are usually subjected to 4–6 cycles of partial vacuum and flushing with N_2 before H_2 is introduced. Oxygen may also be eliminated by heating a solvent or reaction to reflux under N_2 and cooling under N_2. Oxygen detectors may be installed in reactor headspaces or immersed in aqueous solutions if the absence of O_2 is critical.

Sun Ex. 1022

VII. CHARGE STARTING MATERIALS AND SOLVENTS

The sequence of adding starting materials, reagents, and solvents usually must be optimized for each reaction. In general, adding liquids is easier and safer than adding solids. During scale-up operations solvents and liquids are usually pumped or pressurized into the reactor or are drawn into the reactor by partial vacuum.

Solvent may be added last for safety reasons. Often the solvent is the most flammable and most volatile component of the reaction. Solvent also may be added last to minimize vapor loss. If the solvent is added first, it may splash up toward the operator when additional reaction components are added through open manways.

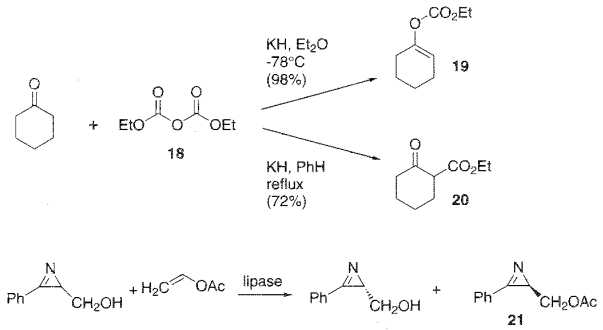
On the other hand, adding the solvent last may cause mixing difficulties, and so solvent is sometimes added before the starting materials and reagents. For instance, a starting material may be poorly soluble in the solvent, so if the solvent is added after the starting materials have been charged, it may be difficult to disperse the solids effectively. This is particularly true if the vessel agitator is situated above the charged solids. In such cases, while the solvent is stirred, the solids may be charged to the reactor, perhaps in portions to ease their dispersal.

TIP: Liquids are generally measured more accurately by weight than by volume, as the densities of liquids and solutions can change significantly due to sample temperature. Thinking in terms of weight of material added is good training for introducing a process to the pilot plant or manufacturing plant, where most measurements also are by weight.

VIII. SELECT REACTION TEMPERATURE

In general, lower reaction temperatures are used to increase selectivity and to avoid side reactions. The reaction of cyclohexanone with diethyl dicarbonate (**18**) led to the O-acylated product **19** at −78°C (Figure 5.7), with the C-acylated product **20** being produced at about 80°C [17]. Cooling a lipase-mediated esterification to −40°C enriched the product ester **21** to 97% ee (Figure 5.7) [18]. Reaction rates slow with decreasing temperatures, and the rule of thumb is that increasing the reaction temperature by 10°C will usually double the reaction rate.

Sun Ex. 1022



Temperature	% yield (% ee) ROH	ROAc
20°C	45 (90)	55 (72)
-40°C	62 (46)	31 (97)

FIGURE 5.7. Effect of reaction temperature on product distribution

TIP: In a pilot plant most reactions can be readily conducted in the temperature range of −40°C to +120°C. Temperatures outside this range may require specialized equipment. To develop processes that can readily be introduced to scale-up facilities, try to run reactions in the range of −40°C to +120°C.

The effects of temperature control on reaction selectivity were shown during hydrogenolysis of an aziridine (Figure 5.8) [13]. Aziridine **23** was prepared by reaction of the amino alcohol **22** with methanesulfonyl chloride and Et_3N. (Curiously, neither the methanesulfonamide nor the mesylate could be isolated from this reaction; reaction of mesyl chloride and analogs of **22** without N-alkyl branching led to the formation of the methanesulfonamides.) Attempted hydrogenolyses in CH_3OH or AcOH led to solvolyses and formation of the corresponding ether **25** or acetate **26** derivative. Treatment of **23** with H_2 in THF/H_3PO_4 at 0–5°C led to regiospecific cleavage of the benzylic aziridine bond, and the temperature was then raised to 55°C to remove the nitrogen-protecting group. The only by-product detected using these conditions was the desamino compound **24**, and formation of this impurity was minimized by initially conducting the hydrogenolyses at 0–5°C.

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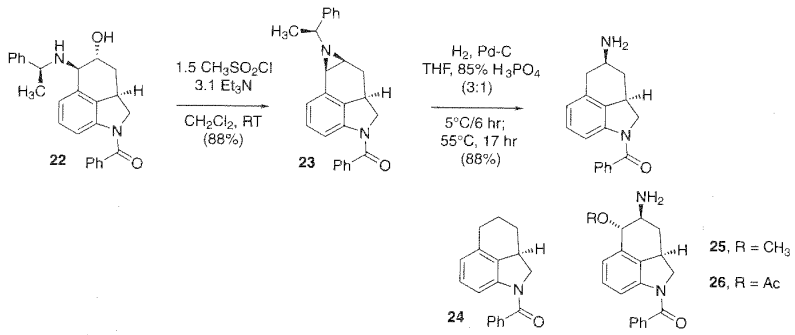


FIGURE 5.8. Minimizing by-product formation during tandem hydrogenolysis by temperature control

IX. SELECT THE DURATION AND TEMPERATURE OF AN ADDITION

Adding a reagent to the reactor containing the starting material often results in an exothermic reaction, and the chemist usually wants to maintain the reaction within a desired temperature range. To reduce the rate heat is evolved, one can add the reagent in portions or at a steady rate over an extended period. Generally the key is to balance the heat generated by the addition against the cooling provided by the vessel utilities. Sometimes the addition is extended to prevent buildup of the reagent and formation of by-products (see Figure 13.9). For convenience in controlling the addition rate, ideally the last reagent is a liquid or is added as a solution.

For good control of reaction temperature and hence reproducible, and safe reactions, additions must be considered as occurring over a defined period of time. During operations on a large scale, addition times commonly range from 0.5–4 hours or even longer. This occurs due to the decreased rate of heat removal for large vessels (Chapter 13).

The chlorination of the hydroxypyrimidine **27** (Figure 5.9) illustrates the importance of carefully investigating addition times in the laboratory before going

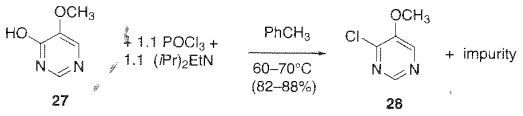


FIGURE 5.9. Chlorination of a hydroxypyrimidine

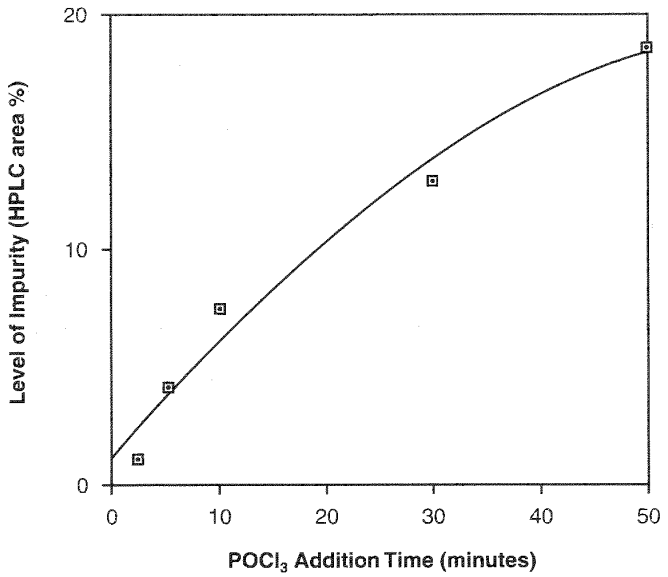


FIGURE 5.10. Formation of an impurity in the chlorination of **27** with extended addition of $POCl_3$. Reprinted with permission from *Org. Process Res. Dev.* **1997**, *1*, 310. Copyright 1997 American Chemical Society and the Royal Society of Chemistry.

to scale-up operations [19]. In early investigations the liquid $POCl_3$ was added last to a hot suspension of **27** and $(i\text{-Pr})_2EtN$ in $PhCH_3$. When addition times were increased from about two minutes to 50 minutes, an impurity rose from about 2% to almost 20% (Figure 5.10), and the yields of **28** decreased similarly. Other investigations showed that the yield decreased as the reaction concentration was increased (Figure 5.11). Since the desired yields would not be expected on scale with addition times anticipated at about 30 minutes, extra time was spent for laboratory optimization before this chlorination was scaled up.

Additional data were generated in the laboratory. The nonlinear yield effect of concentration on yield (Figure 5.11) suggested that the chlorination of **27** might be second-order with regard to one of the reaction components. (All experiments were run with 1.1 equivalents of $POCl_3$.) The chlorination impurity was identified as the dimer **30** (Figure 5.12). HPLC analysis of the chlorination as $POCl_3$ was being charged showed that **30** was primarily formed near the beginning of the addition, when less than 10% of the $POCl_3$ had been added.

The behavior of the chlorination and dimerization reactions can be analyzed by the mental tool called the "snapshot." With the snapshot one mentally freezes the processing at some point in order to assess the tendencies for the desired reaction and side reactions to occur. Consider taking a snapshot of the chlorination

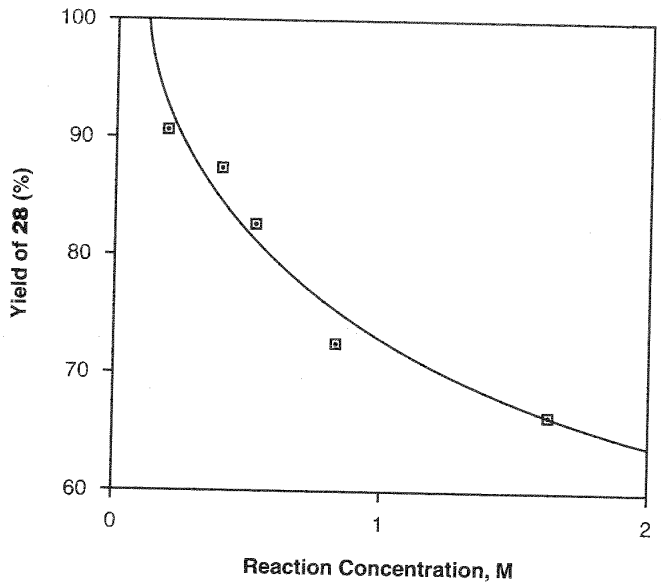


FIGURE 5.11. Yield of **28** as a function of reaction concentration. Reprinted with permission from *Org. Process Res. Dev.* **1997**, *1*, 310. Copyright 1997 American Chemical Society and the Royal Society of Chemistry.

after 10% of $POCl_3$ had been added to the hot suspension of **27**. If the reaction of **27** with $POCl_3$ is assumed to be essentially instantaneous at temperatures over 70°C, then generation of the chloride nucleophile (probably as $(i\text{Pr})_2\text{EtN} \cdot \text{HCl}$) was also essentially instantaneous. Then in the snapshot of the reaction after the addition of 10% of $POCl_3$ there would be 0.1 equivalents of chloride and 0.9 equivalents of **27**, for a mole ratio of 1:9. Under such relatively concentrated

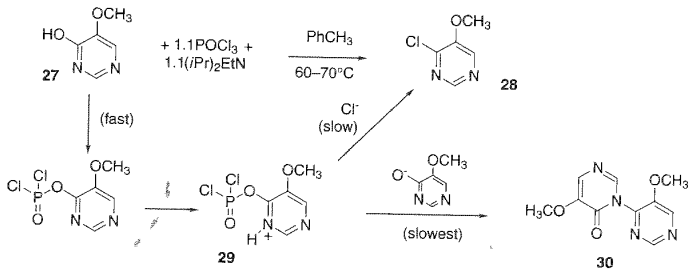


FIGURE 5.12. Mechanism of chlorination and dimerization of **26**

conditions the weakly nucleophilic **27** competed successfully with chloride for reaction with the activated pyrimidine **29**, forming the dimer **30**. Examining the reaction by this "freeze-frame" technique explains the decreased yields of **28**, both as the addition time was extended and as the reaction concentration was increased.

TIP: Use the "snapshot" to anticipate processing difficulties.

A reliable chlorination of **27** was developed for scale-up. $POCl_3$ was added to a slurry of **27** and $(i\text{-}Pr)_2EtN$ in $PhCH_3$ at room temperature over 20–30 minutes, with the reaction being allowed to warm to no more than 40°C during this period. Under these conditions there was little formation of the product **28**, and very little dimer **30** formed. Then the reaction was heated to 60–70°C over 0.5–1 hour, and held at this temperature until the reaction was complete. On scale this procedure generated 2–4% of **30**, and most of this impurity was removed by the aqueous washes during work-up. Yields of **28** were reliably 82–88% [19].

Another approach to minimize the formation of dimer **30** would have been to add $POCl_3$ to a suspension of **27** and ~10 mol% of a chloride salt. A suitable reagent may be $(n\text{-}Bu)_4NCl$, with a solubility in $PhCH_3$ of 19.4 g/100 mL at 25°C [20]. However, this approach was not investigated, as it would have required purchasing another reagent.

Reactions of terminal olefins should be monitored for polymerization. On a scale of up to 10 mol, 4-vinylpyridine was added over 2–3 hours to **31** in order to minimize polymerization and formation of the divinylpyridine adduct **32** (Figure 5.13). [21] For this reaction, CH_3CN/Et_3N displayed moderating effects and good yields, while the reaction using $CH_2Cl_2/(i\text{Pr})_2EtN$ led to extensive polymerization of 4-vinylpyridine and low yields.

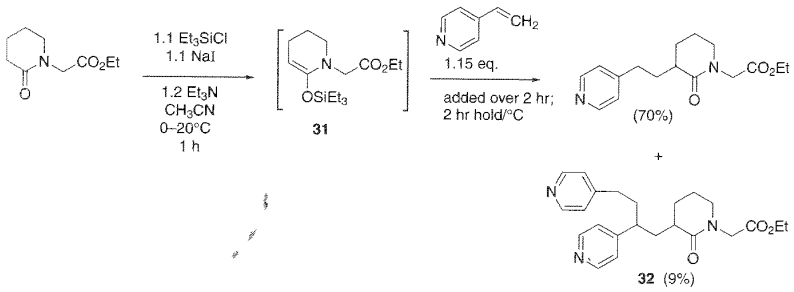


FIGURE 5.13. Minimizing polymerization of olefins through extended additions

TIP: Anticipate probable addition times on scale, and if appropriate add the key reagent in laboratory experiments over this length of time. In the laboratory, syringe pumps are very useful for reliable delivery of small volumes over an extended period.

Adding reagents at low temperatures can create problems if the freezing point of the reagent is above the temperature of the reaction. For instance, oxalyl chloride (mp −10 to −8°C) is often used for Swern oxidations of secondary alcohols. Typically this reaction is conducted at −78 to −70°C, and oxalyl chloride is added to the surface of the reaction. Under these conditions oxalyl chloride may freeze at the point it exits the addition line. Diluting with solvents allows compounds with relatively high freezing points to be added to cold reactions.

X. SELECT THE SEQUENCE OF ADDITIONS

As mentioned in Section IX, the sequence of additions may be determined by safety considerations and the reactivity of components—or simply by the convenience of adding a liquid or a solution. The starting material may be added last in order to control a reaction exotherm. If a key reagent is particularly toxic and special care is needed for its transfer, such a reagent may be added early in the charging sequence.

The addition sequence may determine the primary reaction course or influence impurity formation. For example, condensation of diethyl 3-oxoglutarate **33** with chloroacetone and methylamine is expected to give the 5-methylpyrrole **34**, the Hantzch pyrrole product (Figure 5.14). The isomeric 4-methylpyrrole **35** (a precursor to zomepirac sodium) was prepared in good yield by first treating **33** with methylamine, then adding chloroacetone [22]. The addition sequence was also important for the chlorination of the sulfinate anion **36**: The dimer **37** was produced when N-chlorosuccinimide was added to the reaction, but when **36** was added slowly to excess Cl_2, the desired sulfonyl chloride **38** was produced (Figure 5.14) [23]. The course of these reactions may be predicted if one takes a mental snapshot of them.

In the preparation of amide **42**, a precursor to saquinavir [24, 25] (Figure 5.15), two addition sequences were investigated. The preferred procedure was to add pivaloyl chloride (PivCl) to a solution of carboxylic acid **39** in EtOAc, followed by the addition of Et_3N. This cleanly generated the mixed anhydride **40**, which reacted with L-asparagine (**41**) to afford **42** in 90% yield. When pivaloyl chloride was added to a solution of **39** and Et_3N, some of the symmetrical anhydride **44** was generated, and coupling with **41** led to lower yields of **42** since only half of **44** can form the desired amide.

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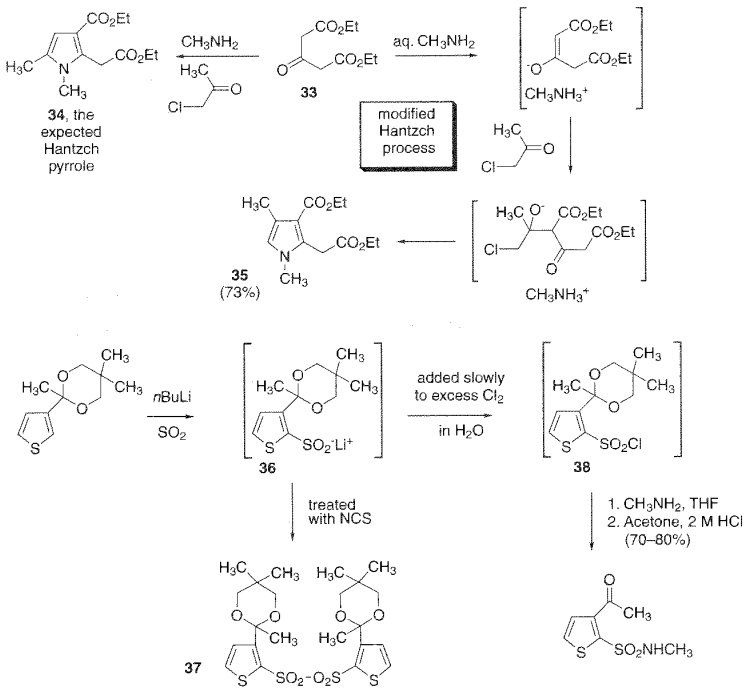


FIGURE 5.14. Reactions determined by addition sequence

Modifying the addition sequence was necessary for successful preparation of the imidazolylpyridine **43** by the Hofmann rearrangement (Figure 5.16) [26]. Treating the reaction with KOH was found to be necessary to minimize bromination of the pyridine ring (**44** and **45**). For optimal yields of **43** it was necessary to age NBS and KOH at −5°C before adding the substrate. This aging formed the reactive brominating agent **46**, which was unstable at room temperature. These mechanistic investigations led to the altered addition sequence [27].

XI. SELECT REACTION PRESSURE

Most reactions in scale-up facilities are conducted at or slightly above atmospheric pressure. Reactors are generally fitted with rupture disks set to release at about 25 psi. This allows a reactor to be sealed and contain toxic or irritating components, thus protecting operators and maintaining suitable levels of volatile reagents

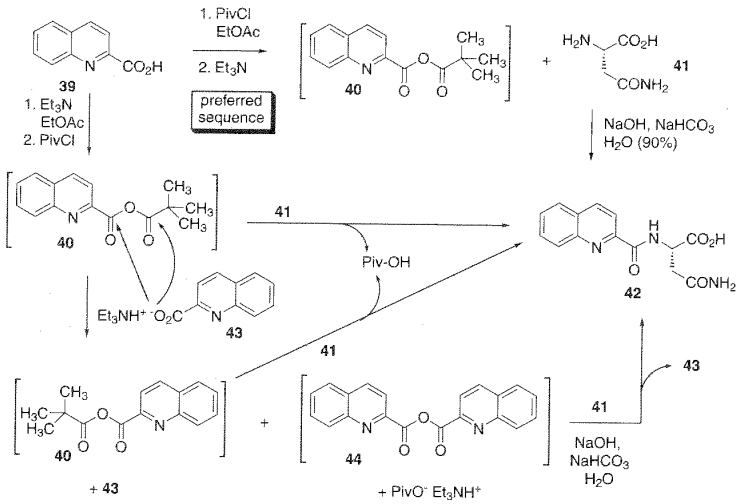


FIGURE 5.15. Two addition sequences for mixed anhydride formation

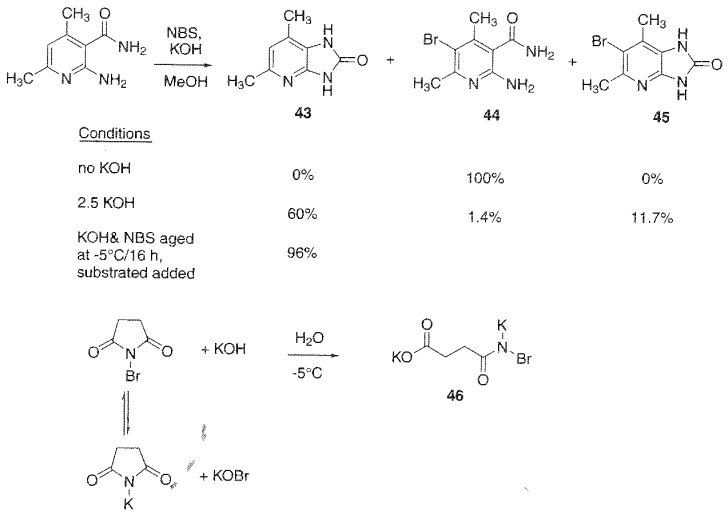


FIGURE 5.16. Optimizing a hoffmann rearrangement by changing the addition sequence

in order to promote reactions. Compounds that may be contained in sealed reactors include H_2, NH_3, HCl, and low-molecular-weight amines, and mercaptans. To minimize emissions, off-gases from reactions using these volatile reagents are "scrubbed" by contact with a medium designed to absorb or neutralize them.

Being able to run a reactor under a slight positive pressure can become important to accelerate reactions with volatile components. For instance, aqueous NH_3 is a convenient reagent for ammonolyses. Heating an epoxide to 60–65°C in CH_3OH with aqueous NH_3 produced a pressure of 10–15 psig, below the release pressure for the rupture disk on the scale-up vessel. Under these conditions the preparation of the amino alcohol was complete in less than 3.5 hours, and there was minimal loss of NH_3 [28].

Hydrogenations are usually run in specialized equipment that can be pressurized. Often this equipment is dedicated for hydrogenations, to minimize the introduction of compounds that could poison future hydrogenations.

TIP: A small increase in the temperature of a hydrogenation (about 10°C) may increase the reaction rate more than a small increase in hydrogenation pressure (about 10 psi).

XII. ADJUST STIRRING

For homogeneous reactions the rate and type of agitation are generally important considerations only during the addition of key reagents. As the reaction progresses, gentle agitation may suffice to allow good mixing and contact of reaction components.

Agitation can be very important for heterogeneous reactions influenced by mass transfer. Hydrogen uptake is faster with high-shear agitation and entry of H_2 as fine bubbles. For example, in the reduction of ethyl pyruvate, the ee of the product **47** increased with higher agitation rates (Figure 5.17) [29].

In other catalyzed reactions agitation can also influence the reaction rate. In the PTC-mediated benzylation of pyrrolidinone (**48**) a marked increase in the initial reaction rate was noted as the stirring was increased from 400 to 1000 rpm (Figure 5.17). Reaction was determined to occur at the interface of the two solvents [30]. For PTC reactions that do not occur at the interface, rapid agitation is not necessary [31].

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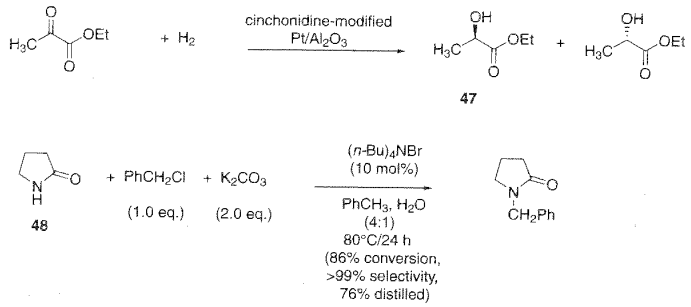


FIGURE 5.17. Reactions influenced by agitation rate

XIII. MONITOR THE REACTION CONDITIONS

For reproducible processing it is necessary to monitor and control conditions used for the reaction and work-up. In-process monitoring will be addressed in Chapter 7. All observations and relevant data should be recorded, such as reaction temperature, pH, equivalents of reagents charged, reaction pressure profile, and duration of reaction.

TIPS: To Efficiently Optimize Process Development in the Laboratory

- Provide a balanced equation for each run.
- Anticipate the goals for each run. Maximize information from each run, and minimize the need to repeat any run.
- Anticipate the operations for each run. Mark any key reactor volumes before charging the reaction components. Locate any necessary equipment and be sure it is in working order.
- Record data on all inputs, including starting materials, reagents, and solvents. Include the molecular weights of starting materials and reagents, the lot number of each component (including solvent), and the amount of material theoretically and actually charged.
- Record all observations as they happen. Keep the laboratory notebook near the fume hood.
- Record the time of day with all observations. After the operations are complete there will be time to calculate the amount of time between steps.

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CHAPTER 6

Effects of Water

I. INTRODUCTION

In developing a process the chemist may encounter water in the roles of impurity, beneficial additive, or solvent. Some examples of water as solvent and cosolvent were discussed in Chapter 4. Water may also be necessary in the crystallization of a desired hydrate (see Chapters 11 and 12). This chapter will examine some of the more subtle effects of water on processing.

TIPS:

- The influence of water on processing is often overlooked until water-related problems arise.
- The key questions are: (1) Is water detrimental or helpful to my reaction? (2) If water plays a role, how much can be tolerated or how much is needed for reliable processing?

Water can prevent many reactions from occurring as the chemist had planned (Figure 6.1). Some reagents react with water very quickly and exothermically,

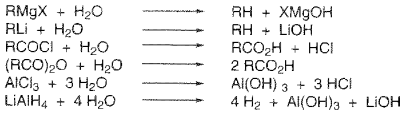


FIGURE 6.1. Some Reactions Quenched by Water

such as the decomposition of an alkyl lithium reagent with water. Other reactions are slower, and more dependent on reaction conditions. For instance, to minimize hydrolysis of the acid chloride during a Schotten-Baumann reaction, the process is usually conducted at 0–10°C, and pH is maintained at pH 8–10 (Figure 6.2) [1, 2]. The chemist uses experience to develop conditions to minimize *in situ* hydrolysis of valuable reagents.

II. DETECTING AND QUANTITATING WATER

Water can be readily detected by gas chromatography, infrared and ^{1}H NMR assay. Quantitation can be straightforward if standard data points have been generated that use known amounts of water in the presence of the primary compound to be assayed. The presence of water may be inferred by thermogravimetric assay; however, any weight loss may not be specific for water.

The Karl Fischer titration is the analytical method most specific for water and is also the most convenient to use. The basis of the Karl Fischer titration is the reaction of water with iodine and sulfur dioxide (Equation I). In the early development of this analytical technique, the solution containing water was titrated

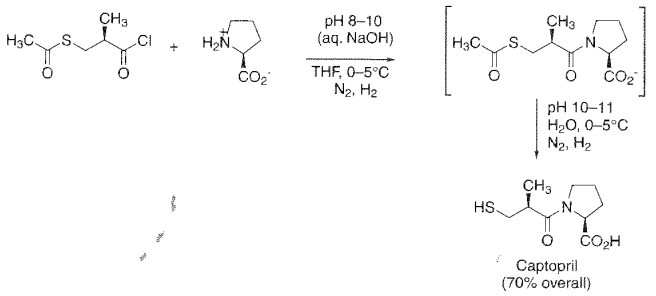


FIGURE 6.2. Use of Schotten-Baumann Reaction to Prepare Captopril

with a solution of I_2 in benzene or MeOH until the I_2 color remained. This provided a sharp, reproducible endpoint for determining the initial water content [3].

$$I_2 + SO_2 + H_2O + 3 \text{ pyridine} + CH_3OH \rightarrow 2 \text{ pyridine} \cdot HI + \text{pyridine} \cdot HOSO_2OCH_3 \quad \text{(Equation I)}$$

Other compounds will react with the Karl Fischer reagent, including those in Table 6.1. Compounds which dehydrate readily by intermolecular or intramolecular reactions, e.g., methyl ketones, must be assayed for water content using specialized reagents.

For convenient automated laboratory assay, two types of Karl Fischer titration are available: the classical, volumetric assay and the more sensitive coulometric assay, which is appropriate for samples containing less than 10 mg of water. In the latter, I_2 is generated electrolytically at the cell anode, and the amount of water is determined by the current required for electrolysis. Coulometric assays are useful for compounds that are available in only small quantities, such as compounds in early development.

III. REMOVING WATER FROM ROUTINE ORGANIC PROCESSING

Water can enter a reaction as part of the air, solvents, reagents, or by-products of a reaction, or it can enter as a contaminant in equipment (Table 6.2). Since water is *the* impurity most likely to be found in all stages of processing, its presence and effects should always be considered.

TABLE 6.1. Compounds Known to React with Karl Fischer Reagent[a]

Ascorbic acid
Hydrazines and substituted hydrazines
Mercaptans
Alkali carbonates
Alkali bicarbonates
Alkali sulfites
Boric acid and oxides
Cupric salts
Ferric salts
Metal hydroxides
Metal oxides
Sodium tetraborate
Sodium thiosulfate
Stannous chloride

[a]Mitchell, J., Jr.; Smith, D. M. *Aquametry;* Interscience; New York, 1948; p. 22.

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TABLE 6.2. Entry of Water into Reactions and Means of Removing Water

Entry of Water into Reactions	Means of Removing Water
Moisture in air	Use dry N_2 or Ar to exclude air
Solvents	Buy dry solvent
	Remove water by azeotroping
	Consume water with excess reagents
	Consume water chemically (pretreatment)
Reagents	Consume water with excess reagents
	Remove water by azeotroping
By-product formation	Remove by water by azeotroping
Equipment	Clean thoroughly
	Rinse with polar solvents and flush equipment thoroughly
	Azeotrope dry
	Monitor moisture before charging starting materials and reagents

III.A. Entry of Water through Processing Air

At 20°C the amount of water in the air we breathe can be as high as 17 g/m^3, depending on the relative humidity. What is important is not the amount of water in air but the amount of water that condenses in the reactors and on key intermediates and products.

When water-sensitive reactions are being run, the easiest means to eliminate the intrusion of water from atmospheric air is to run the reaction under a positive pressure of dry nitrogen or argon. Since argon is denser than N_2 (Table 6.3), argon is sometimes preferred over N_2 in the laboratory. For scale-up operations, N_2 is used more frequently than is argon. A highly detailed description of how to handle air-sensitive reagents in the laboratory has been published by the Aldrich Chemical Company [4].

TABLE 6.3. Density of Gases Used for Chemical Processing[a]

Gas	Density, g/liter
Air, dry, 10°C/760 mm	1.247
Nitrogen	1.251
Argon	1.784

[a] *Handbook of Chemistry and Physics*, 47th ed.; Weast, R. C.; Selby, S. M., eds., The Chemical Rubber Company: Cleveland, Ohio; 1966, pp. B-155, B-201, F-8.

III.B. Entry of Water through Solvents

In some cases small amounts of water in a solvent will change the primary reaction course. Bromination of annulene **1** in anhydrous DMF (Figure 6.3) gave the desired dibromide **2**; bromination in the presence of 1% water gave the undesired diketone **3** in 46% yield [5]. Tosylation of an indole nitrogen in CH_3CN was ineffective unless about 1% H_2O was present in the solvent CH_3CN (Figure 6.3); apparently this small amount of H_2O was necessary to dissolve some of the base KOH [6]. These examples underscore the importance of monitoring water levels in solvents, particularly older bottles of solvent that may have picked up atmospheric moisture.

> **TIP:** Many reagents and solvents are hygroscopic, i.e., they absorb water upon exposure to air. Since the amount of water present can have a considerable influence on the reaction course, it is prudent to know which reaction components are hygroscopic and to assay for water content immediately before running a critical reaction.

The simplest way to obtain a dry solvent is to purchase "anhydrous" solvent. Examination of chemical catalogs quickly shows that while buying "anhydrous" solvent is convenient for small-scale operations, purchasing large quantities for

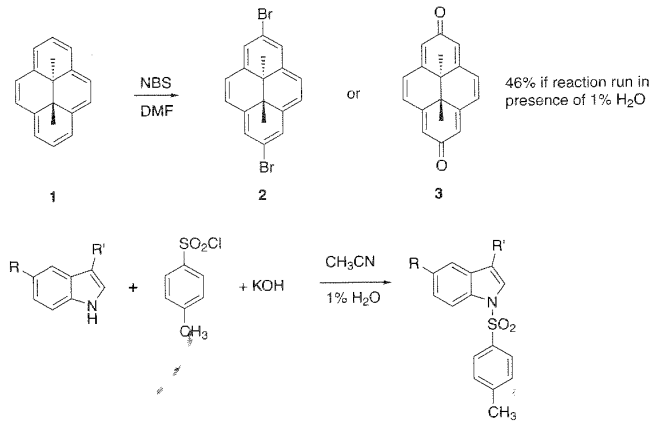


FIGURE 6.3. Reactions Mediated by the Presence of Water

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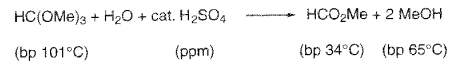


FIGURE 6.4. Reaction of Water with Trimethyl Orthoformate

scale-up will be expensive. The most economical alternative is to dry solvents azeotropically. Treatment with molecular sieves may be appropriate for solvents that do not form azeotropes with water. Ortho esters can be used to treat solutions containing water, with the advantage of generating volatile by-products (Figure 6.4) [7]; such treatment is appropriate if the subsequent reaction can tolerate the presence of any unreacted trimethyl orthoformate. Treating solvents with Na_2SO_4 or $MgSO_4$ is an inefficient means of removing water from solvents. For solvents with dielectric constants less than 15, water and other contaminants can be readily removed on a laboratory scale by filtration through Al_2O_3 (activity I) or SiO_2 (activity I) [8].

III.C. Entry of Water through Reagents

Water is an inherent part of some stable crystalline compounds, both organic and inorganic. Examples of hydrated inorganic compounds include $NaOAc \cdot 3\ H_2O$; $Fe(C_2O_4) \cdot 2\ H_2O$; $Zn(OAc)_2 \cdot 2\ H_2O$; $CaCl_2 \cdot 2\ H_2O$; $SnCl_2 \cdot 2\ H_2O$; and $K_2CO_3 \cdot 1.5\ H_2O$. Trying to remove water from these compounds and combatting resorbtion of water is difficult. "Anhydrous" $(n\text{Bu})_4NF$ was found to contain 1.6 equivalents of H_2O, and the attendant H_2O was proposed to cause the unwanted equilibration of ylides (Figure 6.5) [9, 10]. The presence of water in compounds such as these must be accepted, with additional treatments as necessary to eliminate the effect of the attendant water. The presence of water is not

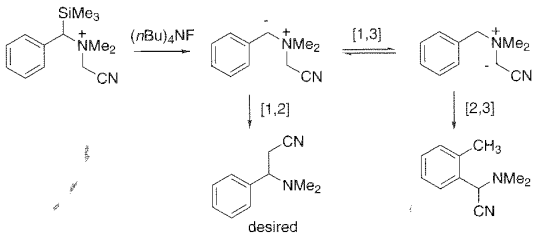


FIGURE 6.5. Ylide Isomerization Due to Water in "Anhydrous" $(n\text{Bu})_4NF$

always detrimental; water may influence the activity and lifetime of some systems, as was noted for methyltrioxorhenium-catalyzed epoxidations (Figure 1.5).

Using anhydrous solvents and reagents may not be necessary if the reaction can be treated inexpensively with excess reagents that consume the water. For instance, excess acetic anhydride may be added to consume H_2O for an acetylation. In the case of the Mitsunobu reaction to make the sulfonate **5** (Figure 6.6), water reacted with triphenylphoshine and diisopropyl azodicarboxylate (DIAD), thus destroying these relatively expensive reagents [11]. The water contribution from solvent was very low since toluene was used, which can dissolve only 0.05% water. The other primary entry for water was from the starting ester **4**, and specifications were set to control the amount of water in **4** at no more than 0.1%. When the solvent and starting material had been charged on scale, the amount of water in the reactor was determined by Karl Fischer titration. The charge of triphenylphoshine and DIAD could then be adjusted if necessary. A slight overcharge of these reagents was employed so that processing was rarely interrupted to calculate and adjust the charges. In the case of this reaction, having to add a small amount of additional reagent was more convenient than azeotroping or other operations to remove water.

TIP: Whenever possible, conduct reactions in solvents that absorb only small amounts of H_2O. For example, run a dehydration reaction in $PhCH_3$ instead of EtOAc.

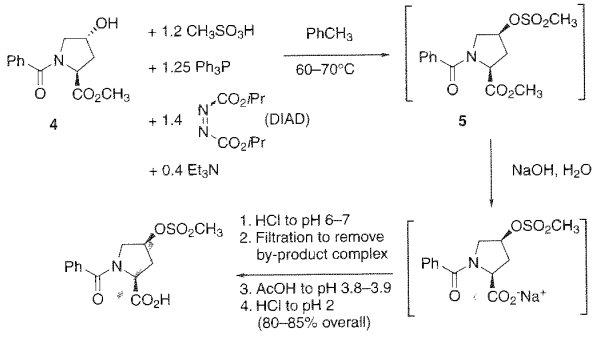


FIGURE 6.6. A Mitsunobu Reaction Using Triphenylphoshine and DIAD

III.D. Formation of Water as a By-product and Its Removal

Many reactions are essentially dehydrations, and the water generated can inhibit the desired reaction. Solvents may be selected to remove water azeotropically during the reaction. In the formation of the pyrrole ring in **7**, water was removed as the CH_3CN-H_2O azeotrope (Figure 6.7). Lower yields were found when the by-product H_2O was allowed to stay in the reaction, perhaps due to the hydrolysis of **6** [12]. In the Ullmann reaction to produce **8**, removing water by azeotroping with the solvent (pyridine) was found to improve the yield (Figure 6.7) [13]. The water may have been generated by the reaction of HBr with K_2CO_3. The authors suggested that the copper catalyst was deactivated by H_2O formed by reaction of the byproduct HBr and K_2CO_3.

III.E. Removing Water from Processing Equipment

Small-scale laboratory equipment can be readily cleaned and dried in an oven. Glassware can then be quickly assembled hot and allowed to cool under a stream of nitrogen or argon, thus excluding atmospheric moisture. But large-scale equipment cannot readily be dismantled, dried in hot ovens, and reassembled quickly. Therefore it is essential that water be flushed from all portions of equipment.

On scale, cleaning equipment demands thought and time. Since not all internal surfaces can be reached by a cleaning brush, residues are usually dissolved with an appropriate solvent. It may be necessary to reflux the solvent throughout the system and collect some distillate to ensure that solvent contacts all surfaces of the equipment train. Particularly important are the "dead legs," process lines that may contain volumes of liquid that are difficult to displace. (Often dead legs are found

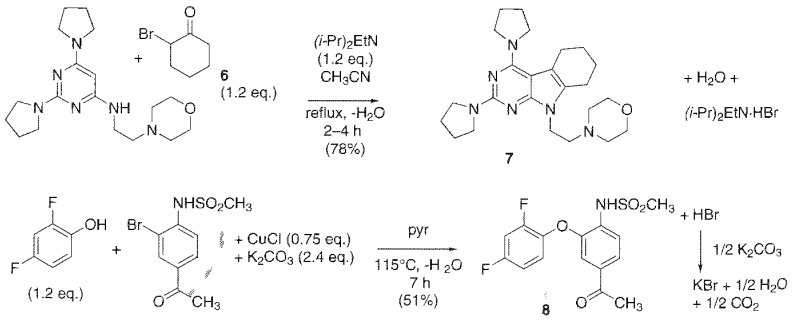


FIGURE 6.7. Removing Water as It Forms to Improve Processing

in inconvenient locations, such as pipes near the ceilings of process facilities. The best approaches are to insert a drain in such places, or avoid using this part of the equipment train.) The solution is drained, usually while it is hot. Optionally, the equipment may be rinsed with water, and the water drained off. Then a water-miscible solvent may be used to rinse the equipment, and this solvent is drained off. Then the vessel is rinsed out with a small volume of solvent to be used for the reaction and charged with the reaction solvent. A Karl Fischer titration is carried out to determine if the level of residual water is acceptably low. Operations not involving rinsing with water may be carried out under a slight pressure of N_2 in order to exclude atmospheric moisture.

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CHAPTER 7

In-Process Controls

I. INTRODUCTION

In-process controls (IPCs) are used to confirm that the processing of an intermediate or final product has been completed as expected. If analysis shows that processing is not suitably complete, actions are taken to drive processing to the desired end point before processing is continued to the next step. IPCs ensure that material of suitable quality is prepared efficiently, thus reaching expected outputs by the timeline. Reliable IPCs ensure high productivity. Without IPCs, one can only hope to meet development and production goals.

In-process controls are used to verify that all stages of processing have been completed as expected, including

- Completion of reaction. This may mean complete or nearly complete consumption of starting material, generation of the suitable level of product, or generation of a maximum level of impurities. A reaction may be checked by techniques such as GC, HPLC, IR, TLC, and others.

- Maintenance of suitable levels of H_2O. This can be important for running a reaction, crystallizing an intermediate, and other steps. Starting materials, reagents, and solvents may be checked before being charged to a reactor. The most convenient quantitation is usually a Karl Fischer titration.
- Charging the desired levels of reagents. For instance, a solution of NaOH may be titrated before being added to a reaction to ensure that the proper number of equivalents will be added.
- Conducting extractions at the desired pH. A pH meter may be used to verify that the desired pH has been reached. This may be used to confirm that the desired amounts of all components were added or that all impurities have been removed from a rich organic phase.
- Complete displacement of a solvent by a higher-boiling solvent, often important to reach the expected yield and product quality from a crystallization. Reaching a target temperature may signify that a distillation is complete. The reactor contents may then be assayed by GC to confirm that the lower-boiling solvent has been reduced to an acceptable level.
- Thorough washing of a filter cake. The filtrate streams may be assayed for the appropriate level of a key impurity, for instance, by HPLC (in the case of an organic impurity) or conductivity (for salts present in an aqueous crystallization). The product cake may also be analyzed for thorough washing. For instance, a sample of the filter cake of an amine hydrochloride API was slurried in H_2O; then the pH was measured to determine whether washing had been sufficient to remove excess HCl [1]. Obtaining a sample of the product from the filter may be operationally difficult on scale.
- Complete drying of product. On a multikilogram scale it may be very inconvenient to dry to a constant weight, especially if the product has to be removed from the dryer for weighing. Products may be analyzed for residual solvents by KF, GC, or differential scanning calorimetry (DSC). Rapid loss-on-drying (LOD) assays may also be developed to determine if drying is complete.

If analysis indicates that the desired endpoint has not been reached, operators are faced with a series of choices before proceeding to the next processing stage. Usually processing is extended. For instance, a reaction may be allowed to continue under the initial processing conditions, or concentration may be continued to remove additional solvent. More reagent may be added in order to drive a reaction to completion or to adjust an aqueous phase to the desired pH before processing is resumed. As processing continues, the batch will be checked again by IPC until the desired endpoint is reached; then processing is allowed to progress to the next phase. As a last resort, material may be reworked to reach compliance with the filed purity specifications.

TIP: IPCs must be developed during the early stages of process development to ensure future successes. It is important to gather data thoroughly during early development, and as processes are developed not all points of processing need to be measured in detail. For instance, it may be unnecessary to confirm that a lower-boiling solvent has been removed from a reaction once the temperature of the pot mixture is significantly above the solvent's boiling point. However, for at least the first two or three runs, it may be wise to confirm by GC that suitable residual levels of this solvent have been reached at the desired processing temperature and pressure. What seem to be excess data at the early stages of process development may be used to justify later processing.

A simple hypothetical example will serve to demonstrate the value of IPC. Suppose that a reactor is charged with a hydrogenation catalyst, an unsaturated compound, and solvent. Air is then replaced with H_2, using a suitable evacuation protocol. Then the reactor is charged with H_2 to the desired pressure, and the reactor is sealed (the pressure is "locked in"). When the starting material is reduced and H_2 is consumed, the pressure is expected to decrease. For any given run, however, an anticipated drop in pressure does not guarantee that the desired reaction is complete. A leak may have occurred, enabling a loss of H_2. The wise chemist notes the drop in reaction pressure, then confirms by a second assay that the reduction is complete. Since processing time and materials are very valuable, IPC is used to ensure that the desired processing endpoint has been reached before proceeding to the next step. Choosing the appropriate IPC and collecting dependable data are challenging, often unappreciated aspects of process development.

TIP: "What else could happen?" is usually not an acceptable attitude when considerable resources and time are invested in scale-up operations.

I.A. The Importance of IPC for Processes Filed with the FDA

When a New Drug Application (NDA) is filed with the FDA, in-process controls must be included as part of the CMC (Chemistry, Manufacturing, and Controls) section. Data in the CMC section demonstrate that the company has suitable

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controls in place to prepare API of reliable, high quality. Included in the CMC section are descriptions of the processing, the yields and quality expected, and identification of the impurities and routine impurity levels in the API. If the yields of the filed intermediates and API drop significantly below those given in the filed documents, the FDA must be notified. Decreased yields indicate that processing is no longer controlled and thus the quality of the API may have dropped. Similarly, new impurities or heightened impurity levels found during IPC analyses suggest that the quality and safety of the API is not at the expected level, making this batch of API unsafe for formulation. There are many risks, financial and ethical, in using substandard API. The health of those taking the drug may be at risk, which could lead to significant legal repercussions. The FDA has the power to suspend sales of this drug and other drugs if significant departures from the CMC section have occurred.

II. CHOOSING THE APPROPRIATE IPC

Suitable in-process controls must perform three functions:

- Allow key aspects of processing to be unequivocally examined, including starting material, product, and any impurities formed during or affected by that stage of processing.
- Produce accurate, reliable assays for the desired process step. Assays must tolerate variance in operator technique.
- Provide convenience when used either in the lab and on scale.

Table 7.1 (p. 150–151) lists analytical methods used for in-process control. Some of these applications may be adapted for in-process controls other than those listed. In considering transferring methods to other sites, the ability to perform some assays may be limited by the relative cost of the instruments, as indicated in the last column. Some of the less-often used IPCs can be useful and are mentioned in the following pages.

Some IPCs can be very simple, e.g., determining whether a condensate contains two phases. For example, a homogeneous distillate may indicate that the azeotropic removal of water from a toluene extract is complete. At this point it may be appropriate to test the contents of the distillation vessel to confirm that all water has been removed. Other IPCs will require relatively rigorous quantitation and sophisticated, expensive instrumentation. Often an IPC is chosen for convenience and dual use. For instance, the method used to follow a reaction may also

be used to assess final product purity. Generally the simplest analytical method is preferred, as long as it is suitably accurate and reliable.

Thin layer chromatography (TLC) can be a very useful IPC, especially in the early stages of process R & D. A benefit of TLC is that in principle all reaction impurities can be detected, from those traveling at the solvent front to those that never moved from the baseline. Although quantitation of reaction components can be much easier using HPLC or GC instead of TLC, it is difficult to know whether all compounds eluted from HPLC and GC columns. Even with solvent and temperature gradients, elution of all compounds cannot be guaranteed. In addition, gas chromatography usually carries with it the concern that thermal degradation during chromatography may have led to decomposition of the compounds of interest. TLC may give a clue to the presence of a troublesome impurity.

TIPS:

- TLC can be semiquantitative for low levels of impurities by spotting known concentrations onto the TLC plate. With consistent technique, the level of an impurity can be judged to be less than one concentration, e.g., 1.0%, and greater than another, e.g., 0.5%.
- For consistent application of solutions to a TLC plate, gently touch a microcapillary containing the analyte solution to the surface of the plate and allow a small portion of the aliquot to flow out. Moving parallel to the baseline of the plate, apply the solution in a narrow band about 0.5 cm long. Upon development of the plate, tight, narrow bands are formed, making visualization of trace impurities easier [2].

Visual in-process controls can prove very useful and should be employed when appropriate. Color changes are usually assessed qualitatively, that is, by the presence or disappearance of a specific color. More than one equivalent of reagents is charged in order to completely consume the species causing the color or to allow the buildup of the reagent that causes the color. Color changes can be accurate and convenient for monitoring low-temperature reactions. To rely on a color change as an in-process control, color changes must be shown to be effective assays by corroboration with results from other assays, such as IR, HPLC, or isolated yield of product.

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TABLE 7.1. In-process Controls Useful in Process Research and Development

Analytical method	To monitor[a]	Quantitative[b]	IPC Suitability	Comments
HPLC: UV detectors	rxn., wash	++	++	Very useful. Review[c]
Electrochemical (redox)	rxn., wash	++	+	Specific uses.
Refractive index (RI)	rxn., wash	+	+	For general use.
Gas chromatography (GC)	rxn., S.C.	++	++	Rapid assays.
GC-mass spectrometry (GC-MS)	rxn., S.C.	++	+	Instr. cost, available on site?
Thin-layer chromatography (TLC)	rxn.	+	++	Inexpensive, portable.
IR and near-IR	rxn.	++	++	Good for in-line assay.
UV and visible spectrophotometry	rxn.	++	++	Rapid assays.
^{1}H NMR	rxn.	+	+	Instr. cost, available on site?
^{13}C NMR	rxn.	−	−	Instr. cost, available on site?
^{31}P NMR	rxn.	+	+	Instr. cost, available on site?
Moisture meters (KF titration)	solv., reag., cryst., drying	++	++	Rapid assays.
Titration: acid-base	reag.	++	++	Rapid assays.
Iodometric (redox)	reag.	++	++	Rapid assays.
Alkyl lithium reagents	reag.	++	+	Assay before charging vessel.
Grignard reagents	reag.	++	+	Assay before charging vessel.
pH meter: pH measurement	rxn. cond., extn.	+	++	Rapid assays; aq. systems. Good for in-line assays.
Dissolved oxygen	rxn. cond.	++	+	Rapid assays; aq. systems.
Density: hygrometers	S.C.	++	++	Rapid assays.
Volumetric flasks and balance	S.C.	++	+	Rapid assays.
Refractometer	S.C., product	++	+	Need solvent-free sample for liquid product.
Chloridometer	extn., wash	++	++	Assays halides. Rapid assays.

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Conductivity meter	extn., wash	++	++	Assays salts. Rapid assays.
Ion-liquid chromatography	extn., wash	++	++	Assays ions.
Capillary electrophoresis	extn., wash	++	++	Assays primarily ions.
Atomic absorption (AA) & Inductively Coupled Plasma MS (ICP-MS)	wash, product	++	+	[Metals]. Instr. cost, available on site?
Loss on drying (LOD)	drying	++	++	Rapid assays.
X-Ray powder diffraction	product	+	+	Detection limit ~10% for polymorphs
Optical rotation	product	++	−	Need solvent-free sample.
Melting point	product	+	−	Need dry sample
Differential scanning calorimetry (DSC)	product	++	+	Could use for LOD.
Impregnated paper, e.g., metals	extn., wash	++	+	Very rapid assays.[d]
pH strips	rxn. cond.	++	+	Very rapid assays.[d]
Peroxides	solvents	++	+	Very rapid assays.[d]
NH_3	extn., wash	++	+	Very rapid assays.[d]
Spot tests: organics, e.g., pyrroles	Impurities	+	+	Mostly qualitative tests.
Metals, e.g., Cu and Pd	extn., wash	+	+	Mostly qualitative tests.
$AgNO_3$ test	wash	+	+	Halides.
Visual: indicators (pH and others)	rxn. cond.	+	+	Rapid assays.
Liquid-liquid phase splits	extn.	−	+	Rapid assays.
Polymorph may float or sink	cryst.	−	+	Rapid assays.
Microscope	cryst.	+	++	Crystal size & polymorph.

[a]Abbreviations: *rxn.,* reaction progress; *S.C.,* solvent chasing (by distillation); *extn.,* extractions during work-up; *wash,* washing a solid cake on a filter; *rxn. cond.,* reaction conditions; *cryst.,* crystallization conditions; *drying,* drying isolated solid product.

[b]"Quantitative" implies that this technique can be readily used with standards to obtain an accurate purity or concentration of the desired compound.

[c]Weston, A.; Brown, P. R. *HPLC and CE: Principles and Practice;* Academic Press: San Diego; 1997.

[d]A selection of test strips may be purhcased from EM Science.

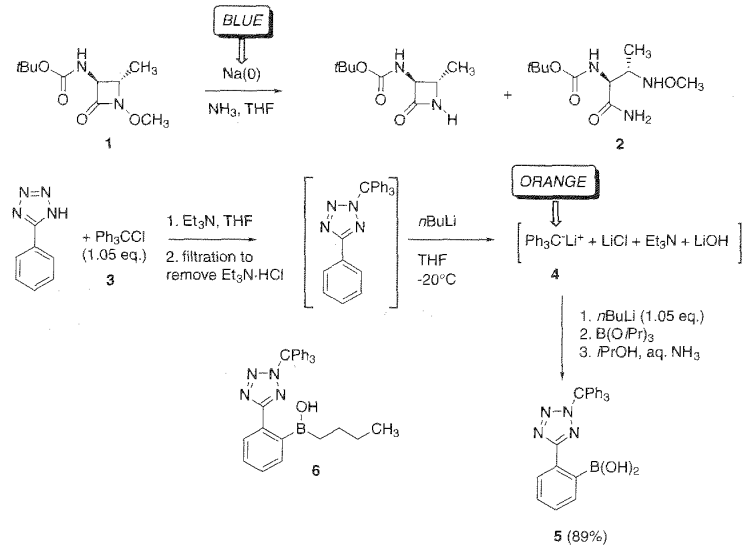


FIGURE 7.1. Examples of reaction colors used as in-process controls

Two examples show the utility of visual in-process controls. In the demethoxylation shown in Figure 7.1 it was essential to add the starting material to a solution of excess Na(0), or significant ammonolysis resulted to give **2** [3]. The addition of **1** was halted when the deep blue color of Na(0) solvated with NH_3 disappeared; then more Na(0) was added, and the addition of **1** was resumed. In the preparation of the losartan intermediate **5**, *n*-BuLi was added in two portions in order to minimize the generation of **6** formed by excess *n*-BuLi (Figure 7.5) [4]. The first portion was "titrated" into the reaction until an orange color appeared. The initial portion of *n*-BuLi reacted with any H_2O and $Et_3N \cdot HCl$ remaining in the filtrate. When these were consumed, excess trityl chloride (**3**) reacted with *n*-BuLi and generated an orange color due to the presence of **4**. Subsequently 1.05 equivalents of *n*-BuLi was added to effect the lithiation with minimal formation of **6**. Color changes that are characteristic of reaction progress should be monitored whenever possible.

Visual assays include "spot tests," in which aliquots of a reaction are treated with chemicals to determine based on color changes whether compounds are present or absent [5]. The name "spot test" is probably derived from running the tests in small wells on white porcelain plates; small colorless glass vials also work well. The generation of dimethylsulfoxonium methylide (**8**) by using excess iodide **7** was monitored by adding aliquots of the reaction to solutions of iminostilbene (**9**, Figure 7.2): KO*t*-Bu is basic enough to deprotonate **9**, but **8** does not react with **9** [6]. With consumption of KO*t*-Bu the reaction changes from purple to

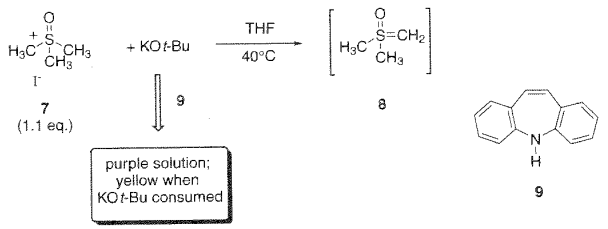


FIGURE 7.2. A color test to monitor the consumption of KO-*t*-bu

orange-yellow. Reagents for spot tests can also be applied to spots on TLC plates to help in the identification of impurities.

Color change indicators may be used for rapid analyses of reactions. Perhaps the most familiar is the addition of dyes such as phenophthalein to aqueous systems as pH indicators. For accurate pH measurement, pH meters are usually preferred over pH indicators. The addition of any indicator to a reaction will be curtailed if these indicators carry through to product, and the need to detect the presence of such indicators poses an additional analytical burden.

A useful application of indicators is to monitor reactions at very low temperatures (Figure 7.3). A trace of 4-phenylazodiphenylamine (**10**) was added to monitor

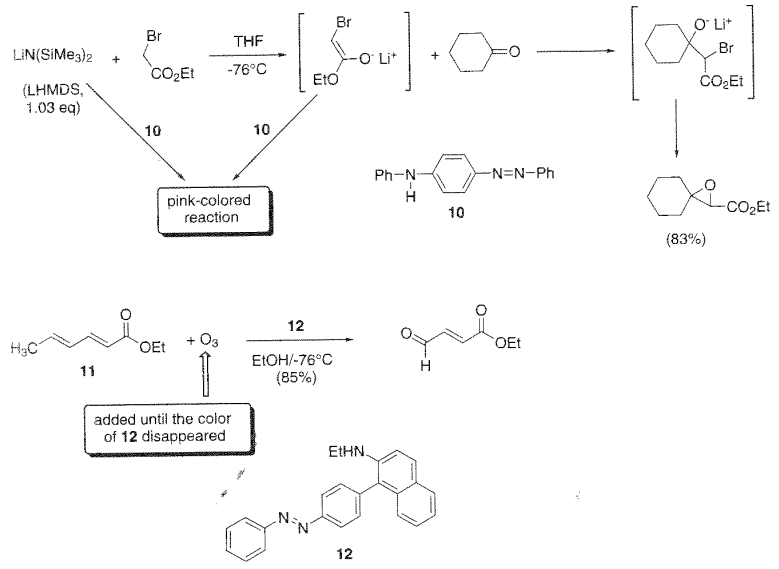


FIGURE 7.3. Use of color indicators to follow reactions

a Darzens condensation carried out at −76°C: with consumption of the base and/or ester anion, the solution reliably changed from pink to yellow [7]. Dyes such as sudan red 7B (solvent red 17, **12**) have been used to avoid over-ozonolysis of dienes or enynes [8]. Ozone was introduced into a solution of ethyl sorbate (**11**) containing a trace of **12** until the red color dissipated. This indicated that the consumption of **11** was complete and that excess O_3 was reacting with **12**. Various dyes can be used to "tune" the reactivity of the indicator relative to the olefin substrate [8].

III. GENERATING REPRODUCIBLE IPCS

Reactions can be analyzed almost instantaneously through in-line analyses, i.e., by analyzing the reaction using a probe inserted into the reactor or a reactor stream. In-line assays may be used for analyzing reactions run in dedicated equipment, which is often the case in manufacturing, or to assay reactions that are difficult to assay by conventional external methods (see below). Relatively few analytical techniques have been adapted for in-line assay.

In the early stages of development, and often during scale-up operations, samples are withdrawn from the reaction streams and assayed. External assays are usually preferred since they offer more flexibility in choosing the suitable analytical technique.

III.A. Obtaining a Representative Sample of the Process Stream

The first step in developing accurate IPCs is to obtain a representative sample of the reaction, one that accurately reflects the extent of reaction and the profile of impurities in the reactor at the time the sample was withdrawn. Two sets of parameters must be considered: whether the reaction is homogeneous or heterogeneous, and the temperature of the reaction relative to the temperature of the sample preparation. All samples must be taken safely, with precautions where appropriate to protect operators and to exclude atmospheric moisture and O_2 from both the reactor and the sample.

A heterogeneous reaction is often more difficult to sample than a reaction that is a solution. A solution can be sampled from any point in a reactor, and all portions of the sample are expected to give identical assays. With heterogeneous reactions, care must be taken to ensure that the sample withdrawn can be assayed to truly indicate the contents of the reactor.

An example of the difficulty inherent in assaying a heterogeneous reaction is shown in Figure 7.4. Chlorination of the hydroxy pyrimidine **13** in $PhCH_3$ with $POCl_3$ required a base [1]. Toluene was a safe, effective solvent and was

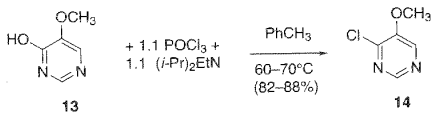


FIGURE 7.4. Chlorination of an hydroxypyrimidine using $POCl_3$ and diisopropylethylamine

convenient for telescoping the preparation of **14** into the next step. Using Et_3N as the base led to the formation of a viscous oil (probably amine salts) that clung to the walls of the laboratory glassware. HPLC assay of each phase showed that the product **14** was formed in the fluid phase as a $PhCH_3$ solution, while the immobile viscous phase entrapped **13**. Analyzing only the $PhCH_3$ solution could show when the production of the product **14** had leveled off but would not detect any unreacted **13**. Obtaining a representative sample of the immobile phase of this reaction was difficult on a large scale, where access to reactor contents was restricted through small handholes. When the process using Et_3N was scaled up, 23–34% of unreacted **13** was recovered. To eliminate difficulties in running this reaction, $(i\text{-Pr})_2EtN$ was used in place of Et_3N, and a fluid dispersion resulted that did not entrap starting material. By in-process HPLC assay, each phase contained both **13** and **14**, and either phase could be used to analyze the progress of the chlorination. The process was reliably scaled up when $(i\text{-Pr})_2EtN$ was used in the chlorination of **13**.

> **TIP:** Reactions that lead to the formation of a viscous oil may be difficult to scale up. For rapid scale-up, design conditions that do not generate any viscous oil.

For a heterogeneous reaction, sampling is easier if the phases are not viscous. If the reaction is a dispersion of two liquids, samples can be taken from the top and bottom of the reactor, or increasing the agitation may provide a suspension of both phases that can be readily withdrawn. For a reaction that forms a suspension of a liquid and a solid, samples can be withdrawn as well-dispersed suspensions, or either phase may be withdrawn for assay.

Temperature is a concern when the reaction temperature is not the same as the temperature at which the sample is prepared for assay. With high-temperature reactions, safely withdrawing a sample is a concern. Reactions that are solutions at higher temperatures may become heterogeneous when cooled for sample preparation, in which case it may be necessary to assay each phase or to warm the aliquot to generate a solution for sampling. Reactions at very low temperatures also pose sampling difficulties: By warming a reaction aliquot to room

Sun Ex. 1022

temperature, the reaction may progress significantly beyond the extent of the reaction in the reactor, providing erroneous analyses. Under these conditions it may be necessary to study the temperature and time constraints for sample preparation. For low-temperature reactions, in-process assay using infrared (IR) spectroscopy may be used (see Section III).

III.B. Reproducible Sample Preparation

Reproducible assays are the second key in developing reliable IPCs. Consistent sample preparation and rugged assay methods are crucial. Samples should be promptly prepared after aliquots are withdrawn from the reactor, as any extended processing can change the temperature of a sample and affect the product distribution and impurity profile. (This may be more important than is at first obvious, because it may take time to transfer the sample from the scale-up floor to the analytical lab!) Diluting a sample into solvent or mobile phase also ensures a rapid quench and a more accurate analysis of the current reaction state. Guidelines are summarized in Table 7.2 [9].

TIP: Consistent sample preparation can eliminate questions about the validity of assay results and may eliminate the need for duplicate assays. This can save valuable time during scale-up runs.

TABLE 7.2. General Guidelines for Reproducible Sample Preparation for IPC

1. Dilute sample promptly. Dilution effectively slows or quenches reactions, allowing for reliable assays.
2. Consistently measure volume of diluent. Use volumetric flasks to prepare dilutions.
3. Accurately measure sample to be diluted. Deliver aliquot for dilution by a microliter syringe or volumetric pipette. Quickly weigh solid samples. If it is necessary to deliver quantities larger than those a pipette can accommodate, weigh the aliquot and dilute.
4. Be consistent about order of dilution.
5. Be sure that the sample is completely dissolved. This is particularly important if the sample purity is to be assessed.
6. Note if dilution of the sample significantly changes the microenvironment of the analyte sample relative to the conditions of the surrounding solvent. For instance, dilution of a reaction aliquot into an HPLC mobile phase may change the pH of the mobile phase as the analyzed sample travels through the column, resulting in changes in retention times or peak shapes.

The first purpose of sample preparation is to stop the reaction in order to determine the current state of the reaction. Dilution of a small aliquot into a large volume of solvent, e.g., 20 μl of a reaction diluted into 10 ml of HPLC mobile phase, effectively stops most reactions. Dilution is a necessary part of sample procedure for today's sensitive analytical techniques, such as GC and HPLC. For reactions run at high temperature, cooling may slow down the reaction and effectively stop it. More reactive aliquots may be quenched prior to assaying. In heterogeneous reactions that are limited by mass transfer, reaction may be stopped by stopping agitation. The reactions of most samples are stopped by dilution into another solvent.

TIP: If reaction solvent must be removed before the sample is diluted for analysis, solvent removal should be very fast, and all conditions (time, temperature) should be closely monitored and reproduced. This step may introduce significant variability, and results may not be accurate for the reaction.

When preparing samples for IPC, reactions that are solutions are inherently easier to prepare than are heterogeneous samples. With a suspension it is difficult to generate a sample containing liquid and solids in the same proportion as found in the reactor. As a result, assaying a suspension may not indicate the current state of the reaction. In assaying a suspension both solid and liquid phases need to be assayed individually to determine whether suitable assays can be obtained from just one phase.

TIP: Centrifugation in laboratory minicentrifuges or filtration through filters attached to syringe barrels are convenient ways to remove solids from a suspension and ease sample preparation.

A consistent dilution procedure may be necessary for reproducible assays. The order of adding reaction aliquot to diluent or vice versa may produce significantly different results. For instance, in the preparation of **18** by modified Arbuzov reaction (Figure 7.5) [10], the phosphonic acid by-product **17** was detected at

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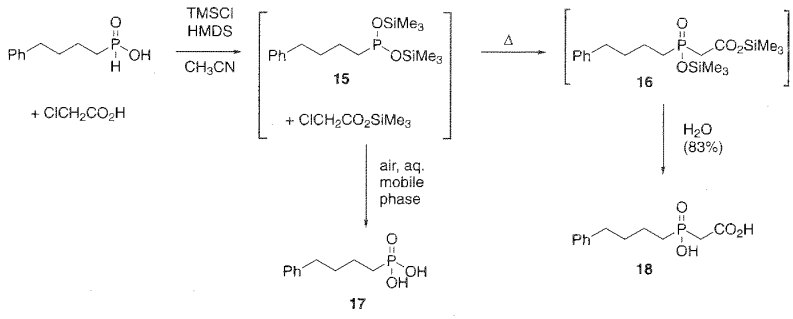


FIGURE 7.5. A by-product formed by air oxidation during sample preparation

significant levels during the start of the reaction and at decreasing levels as the reaction progressed. Analysis showed that **17** was formed by exposure of silylated intermediate **15** to air during the sample preparation, which initially involved adding HPLC mobile phase to a volumetric flask containing an aliquot of the reaction. As **15** was consumed by conversion to **16**, the levels of **17** in the in-process sample also decreased. Formation of **17** during the sample preparation was minimized by quickly transferring reaction aliquots into flasks that contained the desired amount of HPLC eluant as quench and diluent.

Diluting a sample can significantly change the assay conditions at the point the sample preparation is assayed. For instance, diluting an aliquot of a reaction run in AcOH into an HPLC mobile phase may acidify the sample preparation relative to the mobile phase. Injection of the mobile phase then changes the microscopic environment of the eluent during analysis of that sample, and this may change the HPLC performance. In this case sample preparations and mobile phase were made similar by increasing the concentration of the buffer in the HPLC mobile phase, and in-process assays gave HPLC peaks similar to those of standards that were not dissolved in AcOH. It is worthwhile to ascertain that sample preparation has not perturbed the nature of the analytical system.

Even more attention must be paid to details when a reaction aliquot is derivatized before analysis. This may be illustrated by the reaction of chloroethylamine with 2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl isothiocyanate (GITC, Figure 7.6), a reagent used to derivatize amines. Reaction of GITC with chloroethylamine hydrochloride and Et_3N in Et_2O (0.05 M) produced the thiazoline **19** [11]. When the reaction was carried out in pyridine (0.17 M) instead of Et_2O, the dimeric compound **20** was produced. Treatment of **19** with an equimolar amount of GITC in CH_2Cl_2 immediately led to the formation of **20**. Thus the type of solvent used, the number of reagent equivalents (GITC in this case), and

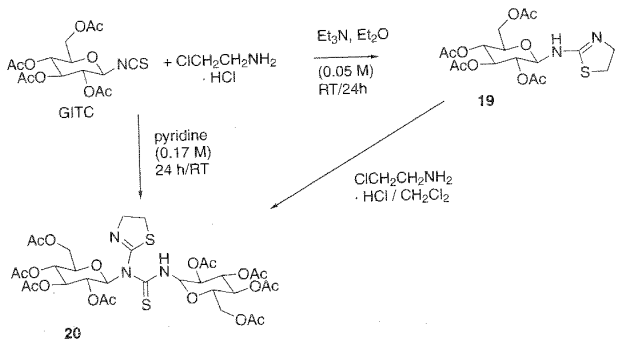


FIGURE 7.6. Reaction conditions affecting derivatization by GITC

perhaps concentration influenced the product formation. These considerations can play crucial roles in reproducibly derivatizing compounds to be assayed.

III.C. In-line Assays

Fourier-transform infrared spectroscopy (FTIR) and pH measurements are the techniques most often adapted for in-line IPC. pH measurements are used for reactions that are run in water or have an aqueous component, e.g., an aqueous extraction. FTIR is especially good for monitoring continuous reactions [12] and reactions that would be dramatically changed by exposure to the atmosphere and temperature of the laboratory. Suitable reactions include low-temperature reactions, reactions run under pressure, reactions with gaseous or toxic materials (e.g., ethylene oxide), and reactions run under inert atmosphere. Further advantages of in-line assays are that no samples need to be prepared, and assay results can be generated within minutes.

Some applications of FTIR are shown in Figure 7.7. The classic example of using in-line FTIR is the Merck investigation of β-lactam formation [13]. The reaction was shown to proceed through the ketene intermediate **21**. FTIR was also used to determine optimal conditions for the low-temperature alkynylation of the ketone **22** [14] and for the methylation of indole **23** [15]. The conversion of phenol **24** to carbamate **25** and isothiocyanate **26** was conveniently monitored by FTIR [16]; due to the hot temperature and reactive nature of the reaction components, special handling would have been required to withdraw reaction aliquots and prepare samples.

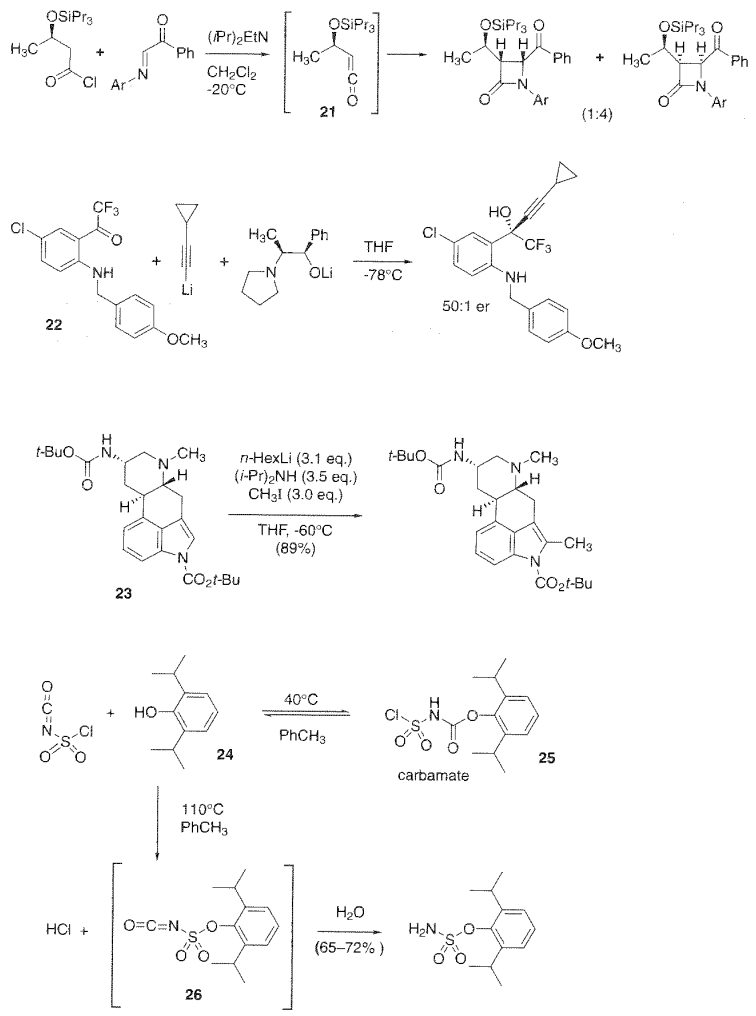


FIGURE 7.7. Some reactions monitored by FTIR

Any probe that is inserted into a reaction must be rugged enough to withstand the reaction conditions and be able to operate reliably under those conditions. For instance, a pH probe may dissolve in hot organic solvents or may break under conditions of vigorous agitation. Many pH probes will not work reliably outside

a particular temperature range. Bubbles or particles in suspension may lead to erroneous analyses by infrared assay. Rugged probes are commercially available.

III.D. Generating Reproducible Assay Data

Once samples have been prepared consistently, it is possible to prepare reproducible assay data. If an assay is reproducible, analysis of a reaction aliquot will give identical results when two portions of this aliquot are sampled and assayed. The true value of a rugged IPC assay is demonstrated when a skilled coworker can readily reproduce the assay. Tips for generating reproducible assay data are shown in Table 7.3.

> **TIP:** Thoroughly describing an IPC assay in writing may also be very important. In this case, all aspects must be described in detail, including reaction sampling, sample preparation, applying the sample to the analytical system, and system parameters for analysis.

One of the keys for generating reproducible data is to consider a system's lower detection limit and the upper limits for linear detector response (Beer's law). For instance, coulometric moisture analysis is accurate for samples containing $\geq$10 μg of H_2O. Injection of a particularly dry sample may deliver $<$10 μg of H_2O, in which case the amount of water measured may not be accurate. Similarly, injecting a dilute sample aliquot may not allow the detection of an impurity present at low levels, so a more concentrated sample preparation may be required. The analysis of a sample preparation more concentrated than those routinely prepared may give detector area count responses beyond the linear response for that compound, making the calculated concentration lower than the true concentration. The injection of a highly concentrated sample may also saturate the detector

TABLE 7.3. Generating Reproducible Assay Data

1. If possible, develop assay method to detect starting materials, products, and maximal number of impurities.
2. Routinely assay standards to ascertain expected behavior of system.
3. Run assays at concentrations above the minimum detection limits.
4. Assay the same amount of sample each time.
5. Design systems with clean separation of peaks. Avoid systems that generate key peaks as shoulders.
6. Use software supplied with analytical method for quantitation.
7. Bias assays in favor of the impurities, not the desired product.

during the elution of a major component, often solvent or product. Under these conditions the area count response for the off-scale peak indicates that less material is present than is actually there, and so the relative area % of a smaller peak in this chromatogram will appear to be increased for this injected sample. An easy solution to this problem is to consistently prepare samples of the same concentration, which may avoid the need to determine Beer's law.

TIP: Autoinjectors provide reliable injection of the desired volume of sample to HPLCs, GCs, and other instrumentation. This equipment allows assays to be readily standardized, eliminating many potential questions about assay reproducibility. The stability of sample preparations in the injector queue must be considered when examining data from an extended run.

The most accurate assays require good separation of the peak under examination. This may not always be possible with the equipment at hand, and usually it is necessary to invest time to develop good analytical methods. Although software is available to integrate peaks that appear as shoulders, analyses may no longer be accurate if the peaks become closer as the analytical system degrades. (For instance, HPLC column performance may deteriorate as more samples are applied.)

Using the software supplied with analytical equipment will make analyses more reliable because it decreases variability due to different operators. Even so, some calculations are more sensitive than others, depending on the analyte. For instance, quantitating very low levels of an impurity by NMR integration will be dependent on how nearly colinear the flat lines of the integral are before and after the key peak in the spectrum.

TIPS:

- When developing a chromatographic separation to monitor a reaction, inject a mixture of unequal amounts of starting material, reagents, product, and by-product. When the chromatogram shows separation of the components, identification of the components can be aided by correlating the peak area counts to the relative amounts of the components charged to the synthetic mixture.
- Bias all analyses in favor of impurities, not the final product. This allows the chemist to detect potential problems in a reaction more readily. For instance, adjusting the HPLC detector wavelength to the λ_{max} of the starting material, not the product, may more readily show the disappearance of starting material and more readily indicate complete reaction.

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CHAPTER 8

Optimizing the Reaction by Minimizing Impurities

1. INTRODUCTION

The goals of process optimization change with the successful development of a project from early process research through scale-up into dedicated manufacturing (Figure 8.1). This general order of optimization may differ according to the nature of the process being considered; for instance, a process generating an inordinate amount of waste may be optimized to decrease waste before scaling up to the pilot plant. The initial goal of all process research and development is to maximize the amount of product generated under the reaction conditions. This is done by driving the reaction to completion, that is, by consuming any starting material that is charged in limiting amounts and by generating product with a minimal amount of by-products. Once the in-process yield has been optimized, the maximum yield of isolated product is expected.

The presence of impurities can complicate purifications and decrease isolated yields. Impurities that are difficult to remove are particularly costly for the final step in making a drug substance. For example, the condensation of amine **1** and

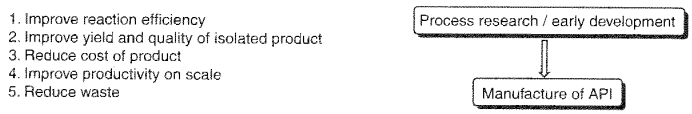


FIGURE 8.1. Goals of process optimization

carboxylic acid **2** with carbodiimides was not efficient, generating high levels of unreacted **2** (Figure 8.2). The presence of more than a few percent of **2** made purification of the drug substance **3** very difficult, and isolated yields decreased significantly. To avoid this purification problem, a more efficient coupling that used the acid chloride **4** was developed [1].

Each 1% of an impurity will often hold back the crystallization of 1–2% of the desired reaction product, as can be seen in Table 8.1. The major impurity in the preparation of aztreonam (Figure 8.3) was the E-isomer, **4** [2]. By adding $CuSO_4$ during the oximation, the ratio of the E:Z isomers increased from 85:15 to 95:5, with the crystallized yield rising from 70% to 80%. This optimization increased the output of aztreonam by 14%, compared to the yield of the initial process! In the preparation of enalapril maleate (**8**) the major impurity is the diastereomer **7** (Figure 8.4) [3]. Optimization of the reaction conditions increased the ratio of **6**:**7** from 87:13 to 94.5:5.5, raising the crystallized yield from 76% to 81% [4]. Introduction of these optimized conditions would be expected to raise the output of enalapril maleate by 6.6%, compared to the initial process. Such process improvements have tremendous benefits by reducing the cost per kilo of drug substance and reducing the amount of intermediates needed to make drug product for the market.

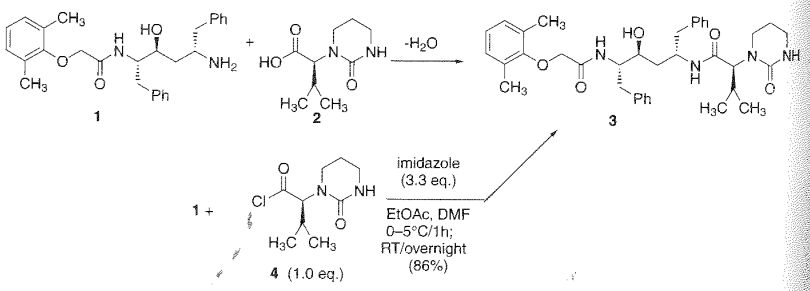


FIGURE 8.2. Amide formation by acid chloride coupling

TABLE 8.1 Comparison of Theoretical and Expected Yields from Optimization of Two Processes

Drug substance	Ratio of drug substance: major impurity	Expected yield[a]	Isolated yield
Aztreonam (Figure 8.3)	85:15 (aztreonam : **5**)	55–70%	70%
Aztreonam (Figure 8.3)	95:5 (aztreonam : **5**)	85–90%	80%
Enalapril (Figure 8.4)	87:13 (**6** : **7**)	61–74%	76%
Enalapril (Figure 8.4)	94.5:5.5 (**6** : **7**)	83.5–89%	81%

[a]Calculated as a range of (amount of drug substance less amount of major impurity) to (amount of drug substance less twice the amount of major impurity). A better prediction of product yield would be reached by subtracting 1–2× the total amount of impurities from the amount of product generated.

Optimizing one step can have significant impact on the remaining steps of a process (Figure 8.5). Investigations into changing the proportion of reaction components are readily undertaken and generally take the least amount of time, with minimal impact on other steps. Rapid optimization is possible by judiciously changing solvents, reagents, catalysts, and ligands; investigations in this area allow

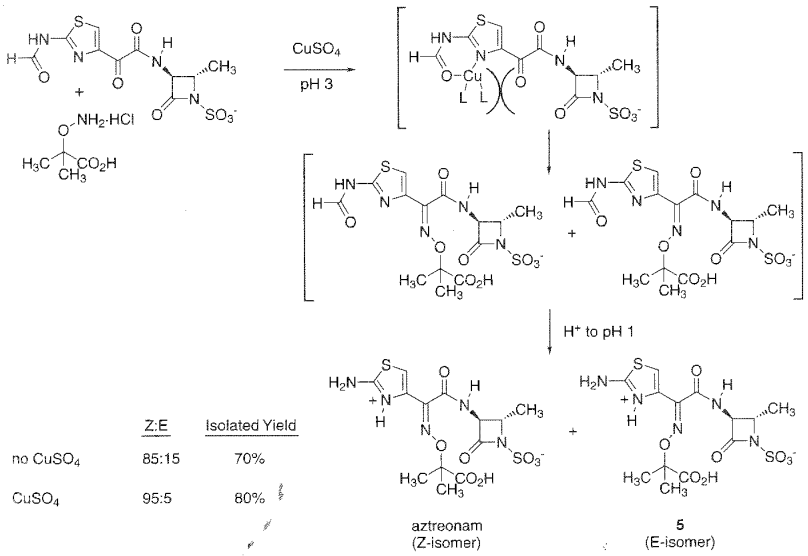


FIGURE 8.3. Improved oxime ether formation in the presence of copper sulfate

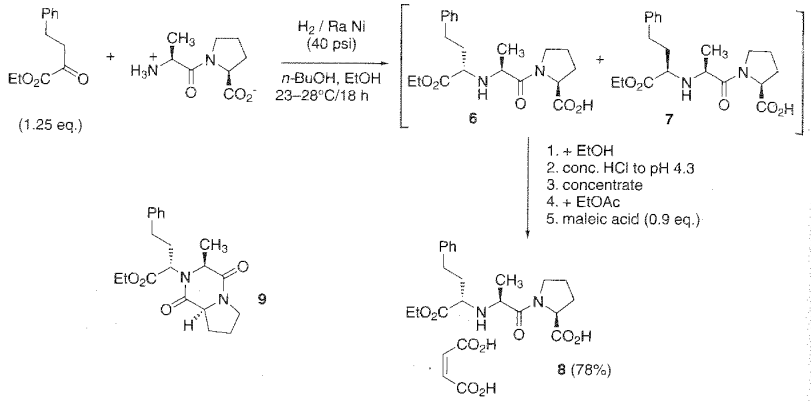


FIGURE 8.4. Preparation of enalapril maleate

the chemist considerable room for creativity and simplifying a process. Such changes may generate different impurities in the isolated intermediates, and it may be necessary to examine the tolerance of subsequent processes for the new impurities. Changing functional groups may greatly improve processing but will require changes in other steps if it is necessary to optimize the preparation and isolation of new compounds downstream from this step. Modifying a route, which includes reordering steps and introducing new steps, may be the best means to minimize impurity formation, particularly in the final product. This last approach will have the greatest impact on other steps and may require the most time overall for optimal process development.

TIP: Optimizing a reaction into a reliable process requires time and money. It is important to know how much time is available for optimization, and to continually assess progress toward meeting the goals of the development timelines.

II. STEPS TO OPTIMIZING REACTIONS

One of the first steps in optimizing a reaction is to examine the initial, or baseline, reaction conditions. These may be provided from the literature or from the

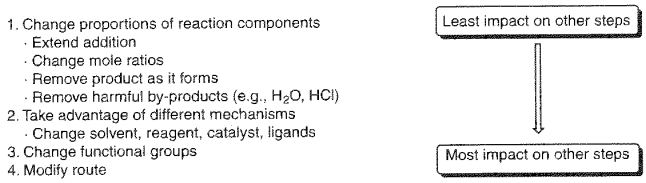


FIGURE 8.5. Impact of process optimization on other steps

chemist's intuition. Varying the reaction conditions and comparing the results to the baseline results allows the chemist to select conditions that lead to complete reactions while generating minimal impurities. A sequence for optimizing a process is shown in Table 8.2.

TIPS:

- Save time in optimizing a process by first examining the reaction under the conditions that have been described by another worker. Use the observations, not just projections of experimental results, to begin optimization.
- For rapid process optimization, monitor the results of process changes using the appropriate in-process assay, not by comparing yields of isolated product.

In monitoring a reaction it is important to know the reaction "kinetics." When developing a process, "kinetics" refers to the rate of formation of the product and

TABLE 8.2. Conditions to Vary for Optimizing Reactions

1.	Temperature: baseline +20°C, baseline −20°C, more as appropriate
2.	Equivalents of reagents
3.	Addition of reagents: sequence and duration of addition
4.	Solvents, cosolvents
5.	Concentration: 50% and 200% of baseline
6.	Change reagents.
7.	Catalyst, [catalyst]; ligand, [ligand]
8.	Stirring, particularly important for heterogeneous reactions
9.	Extend operating conditions, to examine for product decomposition.
10.	Examine other operating conditions, such as pressure, pH, etc.

the amount of time needed to reach the desired process endpoint. The goals of knowing reaction kinetics are to complete processing efficiently and to limit degradation from overreaction. Periodic in-process monitoring generates the relevant kinetic data.

Changing a parameter can have more than one effect on a process. For instance, pH is a critical factor in Schotten-Baumann reactions (see Figure 6.2). Acid chlorides are readily hydrolyzed under strongly acidic or strongly basic conditions, so neutral conditions would minimize hydrolysis. Most primary and secondary amines exhibit pK_as of 10–11.5, so that maximal reactivity would be found at high pH and poor reactivity would be expected under neutral conditions, where the amines would be predominantly protonated. Schotten-Baumann reactions are conducted under weakly basic conditions, pH 8–10, by balancing the hydrolysis of the acid chloride with the decreased reactivity of the amine. In many cases it is wise to examine changes to a process instead of rejecting such conditions on a theoretical bias.

While optimizing a process the chemist usually learns its tolerance limits, the ranges of process parameters at which a process will operate successfully. Knowing these ranges is very helpful for guiding scale-up operations under suboptimal conditions, such as overcharging or undercharging components and exposing the reaction to temperatures above the optimal ranges.

II.A. Optimizing Reaction Temperature

The ideal reaction temperature generates a high-quality product within an acceptable time frame. Increasing a reaction temperature usually increases the reaction rate, but with increased temperature there is usually decreased reaction selectivity. The ideal amount of time will depend on the balance between suitable reaction profiles and the desire to minimize the time any reaction occupies scale-up equipment.

TIPS:

- Running a reaction at or near room temperature offers many potential advantages for scale-up operations. First, operations on scale are extended if large masses of chemicals and equipment must be heated or cooled. Second, running under extreme levels of heating or cooling requires increased energy expenditures. Third, reactions run at an excessively high temperature may generate unacceptably high amounts of by-products, including colored impurities that may be difficult to remove from the product.
- The rule of thumb is that increasing a reaction by 10°C will double the reaction rate. In practice the reaction rate may decrease or even quadruple.

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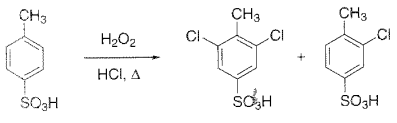
The chlorination of 4-methylbenzenesulphonic acid illustrates the importance of varying temperature range in order to optimize overall conversion and reaction selectivity (Figure 8.6) [5]. In this study, all chlorinations were run for 4 hours at the reaction temperature. The highest yield was obtained at 60°C; increasing the temperature to 80°C led to reduced yields, as the decomposition of H_2O_2 at this temperature was faster than the reaction of H_2O_2 with HCl. There was no appreciable change in selectivity when the reaction temperature was raised from 60°C to 80°C.

II.B. Optimizing Number of Reagent Equivalents

As discussed earlier, minimizing the reagents charged to a reactor decreases the time to charge reagents, cost of raw materials, and waste disposal. But decreasing the number of equivalents can lead to undesirably long reaction times, as the final 10% (or less) of starting material is converted to product. The wise chemist will home in on suitable charges of reagents, as shown for the data in Table 8.3 for the chlorination in Figure 8.6 [5]. No significant increase in conversion was seen when the mole ratio of H_2O_2:**10** was raised from 2.2:1 to 2.5:1, and on this basis the smaller charge would probably be used for scale-up operations.

II.C. Optimizing Addition of Reagents

An extended addition increases the effective mole ratio of reaction components, which can have a beneficial impact on reaction selectivity. This is particularly true for reactions using catalysts. In the dihydroxylations in Figure 8.7, olefin **13** was added over 6 hours in order to ensure high enantiomeric purity of the product [6]. Excess olefin, which accumulates if the addition rate is faster than the reaction rate, is thought to coordinate with the catalyst in a fashion that leads to non-enantioselective dihydroxylation [6]. In the osmium-mediated dihydroxylation of



Temperature	Conversion to **11+12**	Selectivity for **11**
30°C	15%	91%
40°C	46%	87%
50°C	65%	88%
60°C	82%	96%
70°C	79%	96%
80°C	54%	97%

FIGURE 8.6. Chlorination of 4-methylbenzenesulphonic acid

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TABLE 8.3. Effect of Increasing H_2O_2 Charges in the Chlorination of **1**

Mole ratio H_2O_2:**10**	Conversion to **11** + **12**	Selectivity for **11**
1:1	68%	8%
2:1	75%	89.3%
2.1:1	78%	95.9%
2.2:1	82%	96.3%
2.5:1	84%	96%

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14 (Figure 8.7), the addition sequence was critical for effective scale-up [7]. Charging OsO_4 last produced an exotherm of 50°C, and adding the bulk oxidant NMMO last gave only 70–80% conversion. The best sequence was to add the OsO_4 catalyst to the starting material and then add NMMO at reflux over 2.5 hours. Addition sequence and duration should be examined for optimization on a case-by-case basis, especially for catalytic reactions.

II.D. Optimizing Use of Solvents and Cosolvents

Tremendous improvements in yields can be realized by selecting the most appropriate solvent (see Chapter 4). Extensive examination of solvents was undertaken

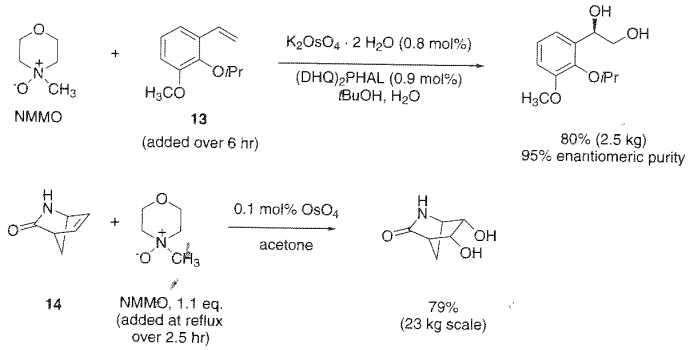


FIGURE 8.7. Dihydroxylation of olefins

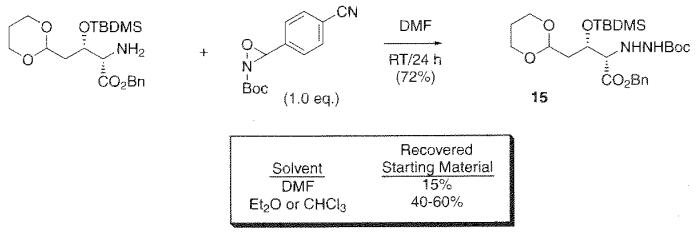


FIGURE 8.8. Hydrazide formation in DMF

for the preparation of hydrazide **15** (Figure 8.8) [8]. The use of more polar solvents gave increased yields, as might be expected for a reaction involving a polar, activated intermediate.

Equilibrium reactions may be optimized by solvent selection if one component of the equilibrium is removed from the reaction, as occurs with crystallization. The raloxifene intermediate **18** was prepared in 80% yield by the sequence in Figure 8.9 [9]. Studies showed that at thermal equilibrium the ratio of **17**:**18** was 10:90, but by adding heptane near the end of the isomerization, the desired product **18** crystallized out of solution affording a final ratio of 2:98.

Equilibration in a Michael reaction led to the crystallization of the desired amino acid derivative **19** in 90% yield (Figure 8.10) [10]. Under these conditions the Michael addition was readily reversible, and the reaction was driven by the

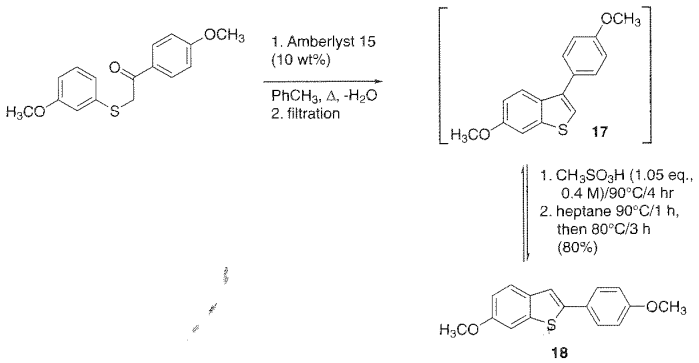


FIGURE 8.9. Equilibrium isomerization driven by solvent selection

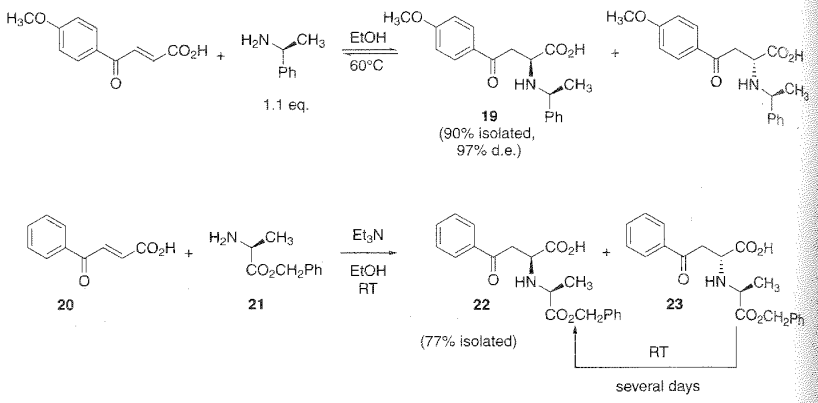


FIGURE 8.10. Diastereoselective Michael reactions

solubility of the undesired diastereomer and the insolubility of the product. To encourage rapid equilibration of the two diastereomers, the authors charged a 10 mol% excess of the chiral amine. Reaction of ketone **20** with L-alanine benzyl ester (**21**) produced the amine **22** in good yield. The undesired, oily diastereomer **23** was noted to be unstable, being converted to crystalline **22** after standing at room temperature for several days [11]. By heating, perhaps the tranformation of **20** and **21** to **22** could have been effected more completely.

Solvents may be chosen to crystallize a by-product and produce a cleaner reaction. When the acetalization in Figure 8.11 was conducted using *p*-methoxybenzaldehyde and *p*-toluenesulfonic acid, the product acetals **25** and **26** were generated in a ratio of 3.4:1, respectively, due to isomerization catalyzed by the soluble acid [12]. Treatment of the diol with DDQ and *p*-methoxybenzyl methyl ether in CH_2Cl_2 produced the desired acetal **25** in good yield as a 39:1 mixture with the unwanted diastereomer **26**. Under the latter conditions the only acid present was the weakly acidic **27**, resulting from reduction of DDQ, and isomerization was minimized by the extremely low solubility of **27** in CH_2Cl_2.

TIP: In equilibrium reactions examine the stability of the products. If the desired product is thermodynamically favored, extend reaction conditions. Yields may be raised by crystallizing the product from the reaction.

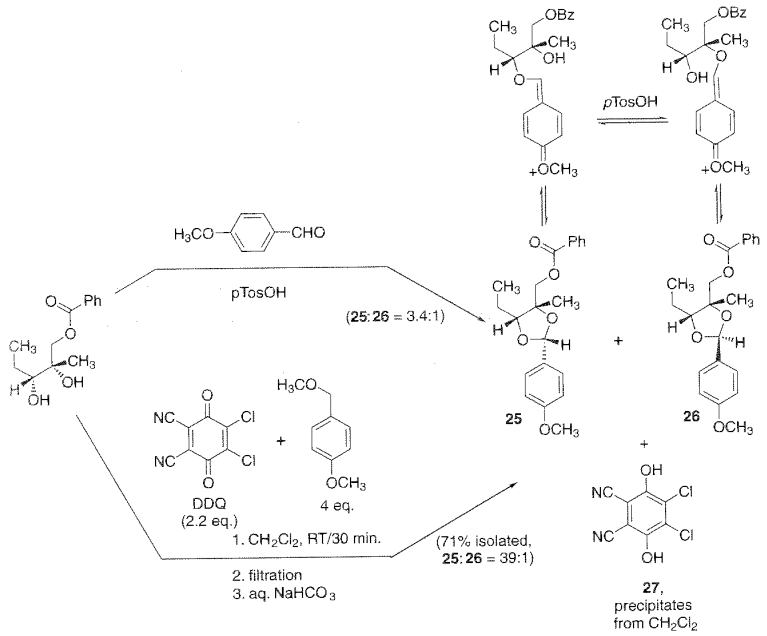


FIGURE 8.11. Minimizing isomerization by precipitating a reaction by-product

II.E. Optimizing Reaction Concentration

In optimizing the concentration of a reaction (see Chapter 5), achieving homogeneous reaction conditions is often a goal. Very few processes are solutions throughout the reaction. A slurry may become a solution as the reaction progresses and the product dissolves in the solvent. Dissolution of the product may help dissolve the starting materials. Alternatively a product may crystallize as it is formed in the reaction, allowing for a very convenient isolation. Reaction concentrations may be optimized in order to facilitate the isolation of pure product in good yield.

Beneficial results may be found by varying the reaction concentration if time allows. For instance, at 1.5 M the addition of NaO*t*-Bu to the adenine derivative **28** afforded a solution, but at 0.8–1.0 M the sodium salt **29** precipitated as a viscous resin (Figure 8.12) [13]. Dissolution at higher concentrations at first seems counterintuitive; perhaps the increased concentrations of the salt **29** and the by-product *t*-BuOH are key to dissolving the intermediate.

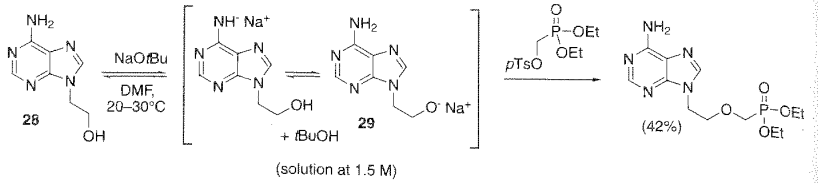
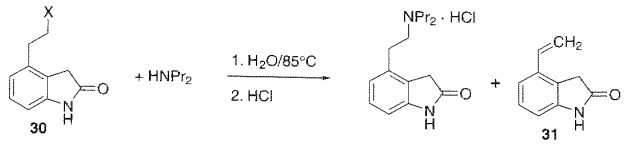


FIGURE 8.12. Dissolution of a sodium salt at higher concentration

II.F. Changing Reagents and Intermediates

By changing reagents and intermediates the chemist is able to use some creativity to optimize a process and apply trends that may be known in the literature. In the preparation of ropinirole (Figure 8.13), attempted displacement of the leaving group in **30** led to the formation of varying amounts of the elimination by-product **31**. Elimination was minimized by the reaction of Pr_2NH with the tosylate derivative of **30** [14].

Sometimes in a group of similar reactions with different starting materials the results are not as expected for each starting material. In this case it is wise to examine the structural differences of the outlying starting materials: perhaps functional groups interfere with the desired transformation. For instance, in the arylation of **32** Cs_2CO_3 was found to be necessary for a good yield (Figure 8.14) [15]. Treatment with NaO*t*-Bu, an effective base for other anilines not substituted with



X	Reaction Time	Ropinirole:**31**
I	<15 min.	1:6
Br	2 h	1.5:1
Cl	48 h	6:1
OTs	1.5 h	40:1

FIGURE 8.13. Using a tosylate to minimize elimination in a substitution reaction

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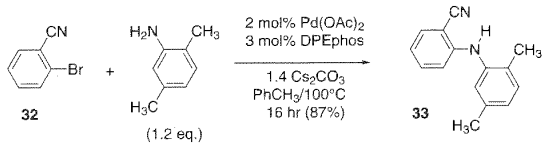


FIGURE 8.14. Improved arylation in the presence of cesium carbonate

a nitrile, produced **33** in only about 30% yield. The authors reasoned that the weakly acidic product **33** deactivates the catalyst in the presence of the stronger base NaO*t*Bu, but not in the presence of Cs_2CO_3.

Some reactions can be optimized by the addition of the appropriate reagent to "tune" the reactivity. Knowing the reaction mechanism is important for efficient optimization using this approach. Bromination of **34** in the presence of the radical initiator azo-bis-isobutyronitrile (AIBN) produced the bromomethyl indole **35** in excellent yield (Figure 8.15). When the bromination was conducted in the

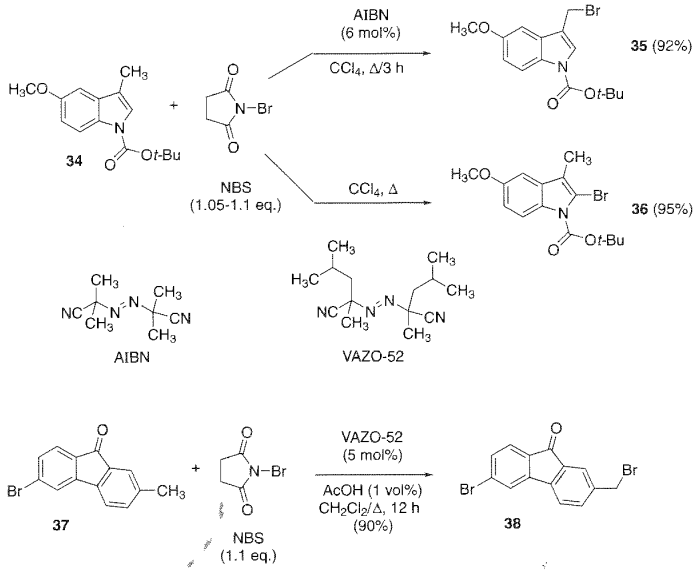


FIGURE 8.15. Using radical initiators to "tune" reactions

absence of AIBN, the 2-bromoindole **36** was produced in excellent yield [16]. The bromination of **37** in the presence of the radical initiator VAZO-52 led to the formation of the benzylic bromide **38** in excellent yield (Figure 8.15) [17]. Radical initiators decompose at different temperatures and may be selected based on the half-life of the reagent at the desired reaction temperature [18].

II.G. Optimizing Catalysts and Ligands

The selection and concentration of catalysts and ligands can determine the success or failure of a process. Considerable effort may be necessary for such optimization. This subject is addressed in Chapter 9.

II.H. Optimizing Stirring

For homogeneous reactions agitation is usually not crucial, but agitation rates can have a dramatic influence on reaction rate for viscous or heterogeneous reactions (liquid-liquid, solid-liquid, gas-liquid). Some aspects of mixing are discussed in Chapters 9 and 13. Agitation can also be very important as a scale-up consideration, particularly during crystallization and transfer of a product slurry to the filter (Chapter 11).

II.I. Importance of Extending Reaction Times

Since most reactions take longer on scale, reaction conditions should be extended in the laboratory to anticipate decomposition or other problems on scale. In particular, extended conditions for preparing the drug substance should be examined. Enalapril (**6**, Figure 8.4) is relatively stable in EtOH, the processing solvent from the reductive amination. After partial concentration of the hydrogenation mixture, EtOAc is added, followed by maleic acid to prepare the maleate salt **8**. Enalapril forms a diketopiperazine (presumably **9**) in EtOAc at the rate of about 1% per hour [3]. Thus to optimize the yields of **8** there should be no delay in charging maleic acid.

II.J. Examine Other Operating Conditions

Effective and optimal operating conditions need to be established for other key variables, which may not have been encountered in the investigations outlined above. Such conditions may include reaction pH, the hydrogen pressure for

a hydrogenation, residence time of a reaction in a continuous flow reactor, and others.

III. MINIMIZING IMPURITY FORMATION BY IDENTIFYING IMPURITIES FIRST

If impurities cannot be minimized readily, it may be necessary to first identify the impurities (Table 8.4). Once the structure of the impurities is known, the mechanism of formation can generally be elucidated, and conditions to avoid forming these impurities may be designed.

For impurities formed at relatively high levels, ^{1}H NMR and ^{13}C NMR spectroscopy may be suitable for identification. If the impurities are enriched in a stream of the reaction, for instance in a wash extract or in the mother liquor, one can identify the impurities simply by comparing the spectra to those of known reaction components. At relatively high levels of impurities, signals from known compounds may be mentally subtracted from the spectra to ease impurity identification. This approach is usually very convenient for the organic chemist.

Mass spectroscopy (MS) may be used to identify impurities whose structures are not obvious or to corroborate the structural assignment. Identification is facilitated by HPLC-MS or GC-MS, which can be used to assign molecular weights to impurities seen in the chromatograms. If access to such equipment is limited, these services can be provided on a contractual basis by other firms.

TABLE 8.4. Steps to Optimize a Reaction If Impurities Cannot Be Minimized Readily

1. Identify impurities (structural elucidation, or comparison to known compounds).
   - HPLC or GC analysis and comparison with those of suspected impurities
   - LC-MS or GC-MS analysis
   - Spectroscopic investigations: NMR, IR
   - Preparative chromatography, then spectroscopy or MS analyses
     Preliminary enrichment for isolating impurities
     - Extraction
     - Isolation from mother liquor and washes
     - Slurry product in solvent ("swish")
   - Unambiguous chemical preparation of proposed impurity, then confirmation by spectroscopic or chromatographic analysis
   - Single-crystal X-ray analysis
2. Propose mechanism to form impurities.
3. Optimize conditions to minimize impurities.
4. Statistical design of experiments

To facilitate the identification of compounds by spectroscopic or MS-related analyses, enriched process streams may be prepared for analyses. Aqueous extracts and mother liquors can provide convenient enrichment. In some cases a solid product may be slurried in a solvent in order to leach out an impurity that has slightly different solubility ("swish" purification [19]). Such enrichment eases isolation of an impurity by preparative chromatography.

Once an impurity has been identified, conditions for forming this impurity can be proposed. The goal is to decrease the formation of the identified impurity by modifying the reaction conditions. If the modified reaction conditions do not prove to decrease or eliminate the formation of this impurity, it may be wise to further secure the structural assignment. Corroborating evidence from other analytical methods is very helpful, and if enough material is available, elemental analysis may be revealing [20]. Single-crystal X-ray analysis is the most definitive structural elucidation, but the process may require considerable time and equipment. Preparing the impurity from an unambiguous route and comparing its spectral or chromatographic behavior to that of the impurity in the reaction can be a rapid means to secure identification.

TIPS: The importance of analytical support and teamwork.

- Often the analysis of a compound is best left to specialists. Analytical chemists may be very helpful in developing an in-process assay for the laboratory or pilot plant and in purifying an impurity. Quality control (QC) chemists may be key in recognizing a new impurity in a manufacturing batch. Spectroscopists know how to get the best performance from their instruments. Good teamwork among the analysts and other chemists is essential to the efficient development of a process.
- To best support the efforts of analysts, thoroughly explain the nature of the reaction and the expected outcome of the analyses. Definitive results are generated more quickly when the analyst is enrolled in helping with a project.

IV. STATISTICAL DESIGN OF EXPERIMENTS

Intuition is usually a chemist's first resort for optimizing a reaction. When intuition fails to guide the chemist to finding suitably optimized reaction conditions within a reasonable time, the chemist usually delves more deeply into the experience of others and the chemical literature, then renews investigations. In spite of vigorous effort, optimizations still may not be satisfactory.

Investigations may fail because the classic approach is to modify one variable at a time, the OVAT approach [21]. Unfortunately many processes are complex, and the OVAT approach may cause investigators to ignore potential optimizations from inter-dependent variables. A more organized approach, employing statistical design of experiments (DOE), may be necessary to optimize conditions involving many parameters [22, 23]. Statistical approaches are usually undertaken to optimize reactions that do not readily yield to intuition-based optimizations or to optimize manufacturing operations where small changes in yields or productivity can have substantial impact on manufacturing costs.

Some of the approaches included in DOE include factorial design, simplex optimization (self-directed optimization), and response surfaces [24]. In factorial design, two (or more) values are assigned to key variables, and experiments are selected at random and run to determine the optimal results. Thus for a system comprising five variables at two settings each, the total number of runs would be 2^5, or 32. Usually 2^{n-1} runs will allow effective optimization from only half the number of runs, 16 in this case [25]. If a variable can be eliminated because it probably has little impact, the number of experiments can be reduced further to 2^{n-2}, or only eight runs for initial optimization. Computer programs are available to assist in DOE optimization [21].

Factorial design was used by workers at DSM-Andeno to optimize the hydrolysis of **40** and crystallization of the diacid chloride **41** (Figure 8.16) [26]. Initial scale-up of the laboratory procedure gave batches of **41** that crystallized poorly and were not easily isolated by centrifugation. Appreciable laboratory experimentation had established that the optimal conditions probably lay in relatively narrow parameter ranges. Conditions for the hydrolysis/crystallization were selected from homogeneous solvent combinations that dissolved **40** but would not dissolve **41,** and aqueous acetone was chosen. Key criteria for the optimization studies were the purity of **41** (above 97%), the level of residual **40** (less than 1%), the ease of isolating the product by crystallization, and low moisture content. Seven variables were examined by factorial design: levels of residual solvent ($PhCH_3$) from the workup of the chlorination, amount of acetone used to dissolve the residue of crude **40**, the temperature for hydrolysis/crystallization, the dosing time for addition of aqueous acetone, the final [H_2O], the agitation rate, and the amount of time between the addition of aqueous acetone and isolation. For optimization, 16

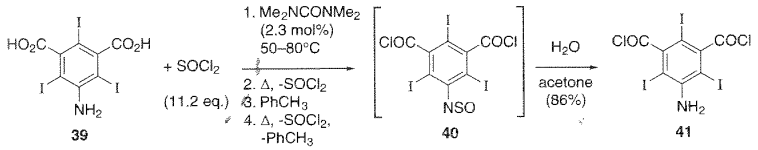


FIGURE 8.16. Preparation of 5-amino-2,4,6-triiodoisophthalic acid dichloride

experiments were run at combinations of the high and low values, as well as two runs at the center points of the ranges. The results indicated not only the optimal conditions but also the conditions at which interaction of variables produced higher levels of impurities (in this case, hydrolysis to regenerate **39**). The optimal process was readily scaled up into manufacturing, producing **41** in very good yield with high purity and high productivity.

In the preparation of epoxide **43**, investigators at Searle resorted to a fractional factorial DOE of eight experiments to optimize four variables (Figure 8.17) [27]. The yields of epoxide **43** were 40–87%, with the butyl adduct **42** being generated at 1–27%. Better yields and purities were obtained at higher temperatures (−20°C vs. −70°C) when $ClCH_2Br$ was used instead of $ClCH_2I$. Halogen-metal exchange at −70°C may have been slower for *n*-BuLi and $ClCH_2Br$ than for *n*-BuLi and $ClCH_2I$. The optimal conditions determined from this study ($ClCH_2I$, −70°C, high agitation) were not used for scale-up, due to the equipment available for scale-up and the more ready availability of $ClCH_2Br$. A continuous process was developed in which a solution of the aldehyde and $ClCH_2Br$ were combined in a static mixer at −35°C with a solution of *n*-BuLi. The continuous process reduced the cycle time, simplified operations, and eliminated the need to cool a large reactor.

V. ROBOTICS AND AUTOMATED PROCESS OPTIMIZATION

Robotics and automated process development are emerging as efficient tools for optimization [28, 29]. The ease of running large numbers of experiments will allow more investigators to take advantage of DOE to optimize experiments efficiently [30].

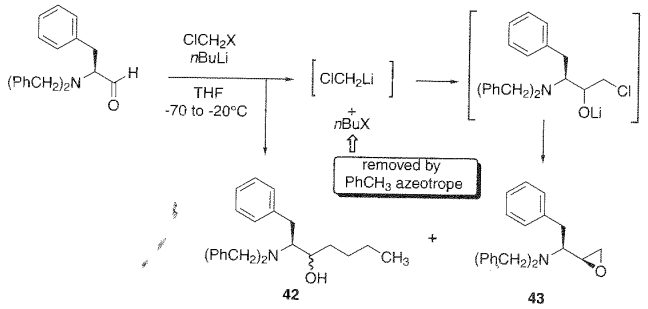


FIGURE 8.17. Low-temperature preparation of an epoxide

TIPS: Optimizing Processes:

- When beginning a reaction, have in hand an assay certain to distinguish starting material and product.
- After the reaction has been optimized, optimize work-up and isolation.
- Whenever possible, split experiments, varying processing on each stream, and compare. This is particularly useful for optimizing work-up and crystallization.
- Minimize duplication, unless that is the goal.
- Reactions causing by-products with extended processing require more attention to scale up.
- Robotics/automation may afford efficient optimization.

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CHAPTER 9

Optimizing Catalytic Reactions

I. INTRODUCTION

Catalytic reactions are becoming increasingly important to increase productivity and minimize waste disposal costs. Examples of catalytic reactions are provided in Chapters 3 and 5. There is a broad diversity of catalysts and means to remove catalysts from reaction products (Table 9.1).

In order to optimize a catalytic system, the important performance parameters must first be defined. These may include optimizing the reaction rate, increasing the yield, increasing selectivity, and increasing the ease of work-up. Catalysts, especially phase-transfer catalysts, may also be used to eliminate the use of polar, high-boiling solvents that are difficult to recover. Product costs may be decreased by developing catalytic processes using alternative raw materials.

The importance, and occasionally the difficulty, of separating catalysts from reaction products must not be overlooked. Catalysts may be selected to avoid the presence of even trace amounts of them in the product. For instance, trace amounts of chlorides are undesirable in monomers to be used for making semiconductors [1], and even 10 ppm of palladium in a drug substance is undesirable

TABLE 9.1. Examples of Catalysts and Catalyst Removal from Reactions

Catalysts	Typical Means of Removing Catalysts from Products
Organic catalysts: DMAP, phase-transfer catalysts, N-hydroxybenzotriazole (HOBt), 2-pyridone[a], and others	Dilution, crystallization, or extraction
Soluble polymer-supported catalysts: ligands attached to polyethylene glycol (PEG) supports	Dilution with antisolvent, precipitation and filtration
Inorganic catalysts: H_2SO_4, BF_3, and others.	Extraction into H_2O, often with neutralization
Transition metals: Pd, Pt, Ru, Rh, Zr, Cu, and others, with associated ligands	Absorption to filter aids or activated carbon, extraction, precipitation, or crystallization of product
Insoluble polymer-supported catalysts: ion exchange resins, poly-DMAP, poly-vinyl pyridine, and others	Filtration
Zeolites	Filtration

[a]2-Pyridone has been found to be superior to DMAP as an acylation catalyst: Calter, M. A.; Guo, X., "One-Pot, Catalytic, Asymmetric Syntheses of all Four Stereoisomers of a Dipropionate Synthon." *J. Org. Chem.* **1998**, *63*, 5308.

[2]. Filtration is the easiest method of removing a catalyst, sometimes by absorption to filter aids or activated carbon (Table 9.1). Recrystallization is often used to purify a product, with the hope that the catalyst will be removed in the mother liquor.

One key in optimizing catalytic reactions is to maximize the catalyst efficiency, or turnover. Low levels of catalyst poisons, which are competing ligands, can have great effects on a process. Some impurities are detrimental to reactions, and some are helpful. By understanding the influence of factors such as the presence and amounts of impurities, co-catalysts, and catalyst decomposition, a rugged catalytic process can be designed. In addition to the considerations discussed in Chapter 8 for optimizing reactions, other factors are important. These are outlined in Table 9.2 and discussed on the following pages.

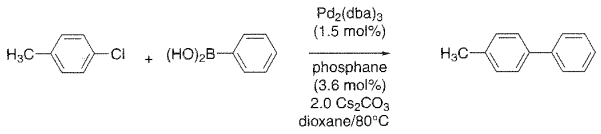
TIP: There can be considerable variability of catalysts from batch to batch [3]. Record the lot number of any catalyst used for reactions and any catalyst pretreatment. It is prudent to use-test every batch of catalyst before scaling up a reaction.

TABLE 9.2 Considerations for Optimizing Catalytic Reactions

1. Catalyst selection/ligand selection
2. Concentration of catalyst
3. Presence of precatalysts
4. Need for extended additions
5. Influence of co-catalysts and impurities
6. Catalyst decomposition
7. Nonlinear catalyst effects

II. CATALYST SELECTION/LIGAND SELECTION

The selections of transition metal catalysts and ligands are often inextricably connected. Ligands and catalysts may be selected to optimize a synthetic transformation or to optimize process productivity (see the example of the TPPTS ligand in Figure 3.21). Many catalytic reactions are highly substrate-specific. Extensive ligand screening may be necessary to develop a reliable, efficient process. For instance, in the development of a reaction for a palladium-catalyzed Suzuki cross-coupling of aryl chlorides (Figure 9.1), at least eight phosphanes were examined, five of which displayed no activity [4]. The optimal ligand for the cross-coupling was $P(t\text{Bu})_3$, which was also the best ligand for the Heck reactions studied by Fu's group [5].



Phosphane	Yield (GC)
—	0%
PPh_3	0%
BINAP	0%
dppf	0%
$P(o\text{Tol})_3$	10%
$Ph_2(CH_2)_3PPh_2$	0%
$Cy_2P(CH_2)_3PCy_2$	0%
PCy_3	75%
$PtBu_3$	86%

FIGURE 9.1. Suzuki Cross-coupling of aryl chlorides and arylboronic acids

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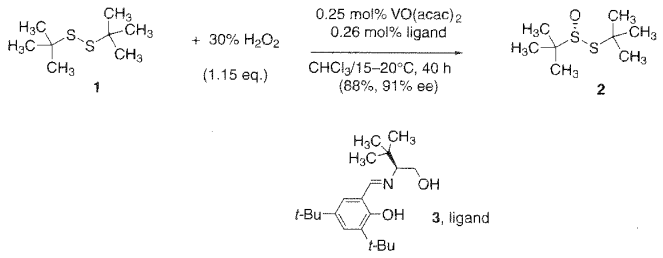


FIGURE 9.2. Chiral oxidation of a disulfide

In the development of a system to efficiently oxidize the disulfide **1** to the chiral thiosulfinate **2** (Figure 9.2), Ellman's group first examined reaction concentration [6]. With 1 mol% of the initially selected catalyst at 0.5 M reaction concentration, there was only 38% oxidation with 71% ee. By increasing the reaction to 1.5 M, there was 89% conversion to **2** with 81% ee. Reactions at higher concentrations led to precipitation of the catalyst. Extensive ligand screening using reaction concentrations of 0.8–1.5 M in **1** led to the selection of the chiral ligand **3**. The oxidation was also optimized for solvent and temperature. One limitation for scale-up of this reaction is the need for very gentle stirring so that the aqueous-organic interface is not broken. This excellent paper describes optimization of a catalytic process in detail.

Other examples show the importance of ligand selection in optimizing reactions (Figure 9.3). In the cobalt-mediated oxidation of cyclohexene with oxygen, ligand selection allowed the choice for epoxidation or allylic oxidation [7]. In a modified McMurry coupling using *in situ*-generated Ti(0), addition of urea **4** increased the formation of the *d,l*-product [8]. In a Heck reaction, Ph_4PCl and dimethyl glycine were necessary for excellent conversion to stilbene **5** [9]. For the Suzuki cross-coupling reaction to prepare **6**, a ligand-free system was found to increase reactivity and decrease impurity generation from protodeboronation [10]. The catalytic system developed by Buchwald's group showed relatively broad applicability for room-temperature Suzuki couplings, as in the preparation of **7** [11]. Some of the other examples in Figure 9.3 may well be substrate-specific.

III. OPTIMIZING CATALYST CONCENTRATION

Adjusting the catalyst concentration can have a great effect on the reaction rate and product distribution, depending on whether the reaction mechanism requires activation by one or more molecules of catalyst per reaction. In the chiral

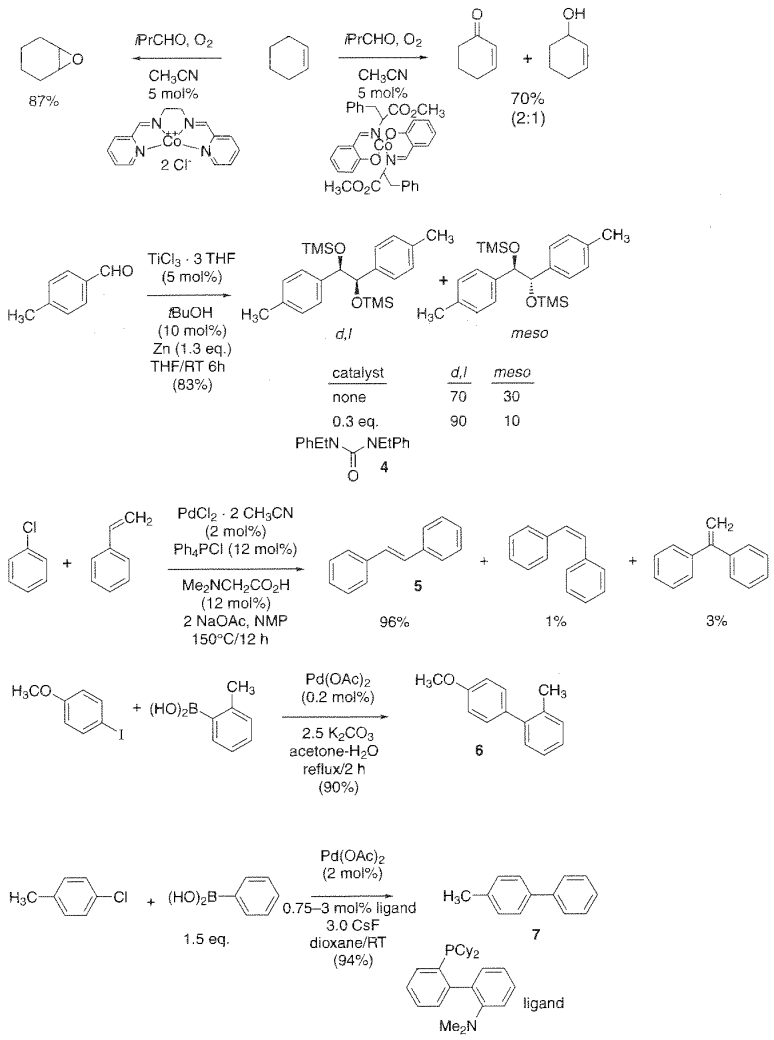


FIGURE 9.3. Reactivity determined by ligand selection

methylation of indanone **8** using the chiral phase-transfer catalyst **9** (Figure 9.4), increasing the concentration of the catalyst both increased the reaction rate [12] and decreased the ee of the product [13]. Physicochemical data indicated that **9**

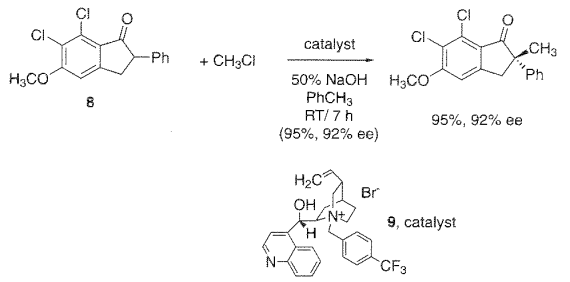


FIGURE 9.4. Chiral methylation using a chiral PTC catalyst

existed in solution as a dimer and dissociated to a monomer during chiral phase-transfer catalytic activity. In this work the fastest conversion was observed using 50% NaOH as the aqueous phase, probably because the amount of H_2O partitioned into the organic phase is minimized with this high concentration of NaOH.

Efficient agitation has been noted as crucial for good reaction rates with **9** and other similar phase-transfer catalysts [12, 14, 15].

Two metal-based catalyst molecules often act in concert for catalysis. In the ring-opening of epoxides by H_2O (see Figure 4.19), two molecules of the cobalt salen catalyst **10** (Figure 9.5) are necessary, one to activate the epoxide, and one to activate the nucleophile H_2O [16]. Opening epoxides by azide using the chromium salen catalyst similarly proceeds through the action of two catalyst molecules [17]. Increasing the charge of cobalt catalyst **10** to 7.5 mol% gave faster opening of epoxides with azide; the catalyst was recycled, effectively decreasing the catalyst charge [18]. A similar mechanism has been proposed for chiral zirconium catalysts [19].

Sometimes an additional phase is seen with catalyzed reactions, although under more dilute conditions such a phase may not form. This phase may be an interface ("rag layer") between an organic and aqueous phase, or an additional layer in

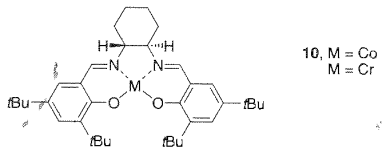


FIGURE 9.5. Metal-salen catalysts in ring-opening of epoxides

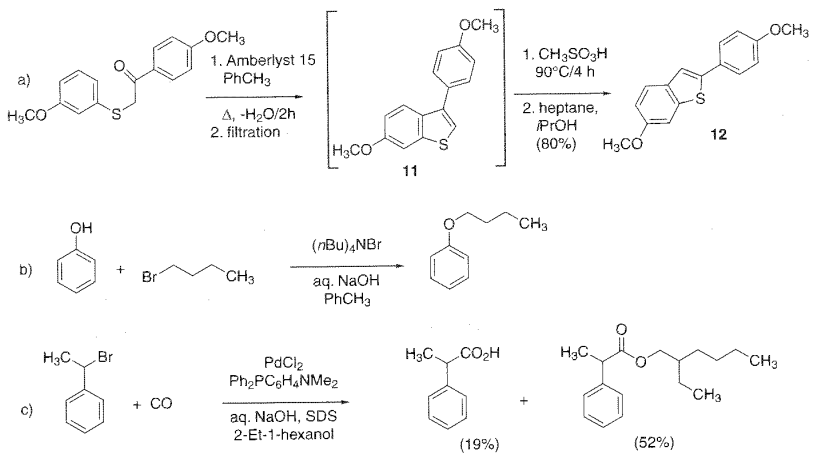


FIGURE 9.6. Reactions accelerated by the presence of an additional phase

an organic reaction. When this occurs, reaction rates are usually markedly increased, as the reaction occurs in this phase. These reactive phases can also be recycled to a subsequent reaction. The rate of methanesulfonic acid-catalyzed isomerization of **11** to **12** increased by a factor of 15 when the concentration ofmethanesulfonic acid was increased from 0.2 M to 0.4 M, with the concomitant formation of a second phase (Figure 9.6a) [20]. A continuous-flow, stirred reactor was used to contain the active third phase in a model PTC alkylation of phenol (Figure 9.6b) [21]. Carbonylation using surface-active catalysts was accelerated by the addition of SDS, and the active interface was recycled to subsequent reactions (Figure 9.6c) [22].

The metal component of catalysts, solvent selection, and reaction concentration can influence aggregation and affect reactivity. The titanium catalyst **13** forms monomeric complexes in solution, but the analogous zirconium catalyst **14** forms polynuclear aggregates (Figure 9.7); this may explain why the chirality induced by oxidation of the sulfides is opposite for these two catalysts [23].

IV. GENERATING ACTIVE CATALYSTS

Many metal-based catalysts are in fact precatalysts. The Mn (III) salen catalyst used for the production of a Crixivan® intermediate proceeds through generation of

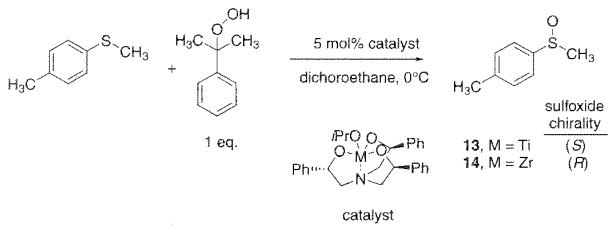


FIGURE 9.7. Sulfoxidation with titanium or zirconium catalysts

the Mn(V) species [24]. The active cobalt salen catalysts used in epoxide openings are Co(III) species, generated by contact with air [25]. In the case of the Cr(III) salen catalyst, the active species is the one with azide as ligand (**15**, Figure 9.8). As pointed out by Jacobsen, the Cl-based catalyst can be used as readily as the azide-based catalyst, but by using the azide-based catalyst, no additional nucleophile was added to the reaction [26]. The added step of preparing the active catalyst species may not be cost-effective on scale, depending on the tolerance of the process for impurities generated from the precatalyst.

Catalysts may need to be aged for optimal activity. This was noted with the Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate catalyst used for asymmetric epoxidation and kinetic resolution [27]. Both addition sequence and aging are essential for proper preparation of the catalyst. Experimentation is necessary to determine if catalytic activity benefits from aging.

V. IMPORTANCE OF EXTENDED ADDITIONS

Extended additions effectively provide reaction conditions with greater concentrations of catalyst and can be important for reliable scale-up (see Figure 8.7). The mental concept of taking a snapshot can be useful in predicting the effect of an extended addition. In the asymmetric reduction of ketones using chiral

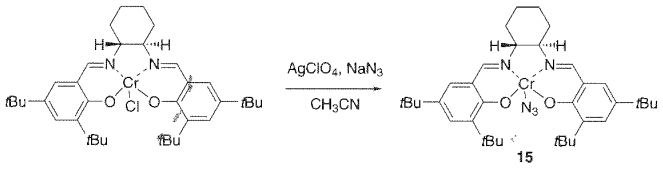


FIGURE 9.8. Conversion of co salen precatalyst to catalyst

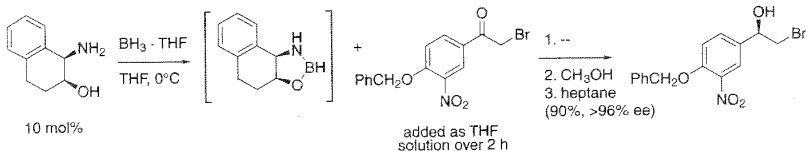


FIGURE 9.9. Asymmetric reduction of a ketone using chiral oxazaborolidines

oxazaborolidines, a Sepracor group used an addition time of two hours for good enantioselectivity (Figure 9.9) [28].

VI. INFLUENCE OF CO-CATALYSTS AND IMPURITIES

Many catalyzed reactions are markedly influenced by co-catalysts and impurities. Co-catalysts may be added to a reaction or may be charged inadvertently with reagents or solvents. Knowing the reaction mechanism is very helpful in anticipating problems. Treatment of a reaction with conditions that disrupt the catalytic cycle—for instance, by removing a bromide through addition of a silver salt—may impede the catalytic reaction. Once the impurities (beneficial and detrimental) have been identified, the impact on the catalyst and reaction may be assessed.

In TEMPO-mediated oxidations, bromide ions are key to the efficient catalytic cycle (Figure 9.10) [29, 30]. Rychnovsky found that TEMPO-catalyzed oxidation of alcohols using *m*-CPBA was also dependent on bromide ions for rapid reaction [31]. Any compounds that sequester bromide ions in these catalyzed reactions should be avoided.

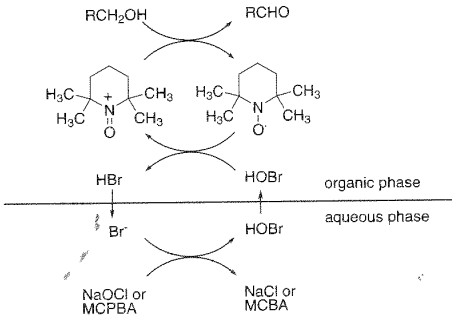


FIGURE 9.10. Catalytic cycle in the TEMPO-mediated oxidation of alcohols

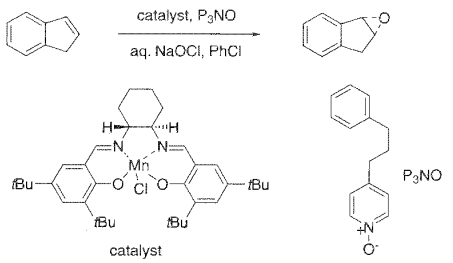


FIGURE 9.11. Use of a co-catalyst in the epoxidation of indene

Merck researchers designed the ligand P_3NO for Mn salen catalysis (Figure 9.11). P_3NO increases the epoxidation rate, stabilizes catalyst, and transports bulk oxidant HOCl into the organic phase [24]. The use of P_3NO allowed for a decreased charge of the Mn salen catalyst, making for a less costly preparation and more reliable processing on scale.

The beneficial effects of impurities may not be evident at first. Trace amounts of Na(0) in Li(0) are useful in the preparation of alkyl lithium reagents [32]. Catalytic Pb has been shown to be useful in Zn-mediated reductions (Figure 9.12a) [33] and in Wittig-like olefinations mediated by Zn (Figure 9.12b) [34]; catalytic amounts of nickel salts and palladium salts have been shown to accelerate Cr(II)- and Cr(III)-mediated reactions (Figure 9.12c) [35, 36]. A catalytic amount of HCl was important for chiral reduction using a ruthenium catalyst (Figure 9.12d) [37]. The importance of trace beneficial impurities may become evident only by failure of the reaction when using different lots of starting materials, reagents, or solvents.

TIP: In investigating reactions, first try reagents that are not highly purified. The garden-variety reagent may contain beneficial impurities that act as co-catalysts.

Detrimental impurities may be formed during a reaction or inadvertently added to a reaction as impurities in starting materials. In the Suzuki cross-coupling reaction to prepare losartan intermediates, two key impurities were identified (Figure 9.13). The phenyl tetrazole salt **16** was formed during the coupling reaction, and **17** was present at the level of about 0.1% in the starting material. Identifying these impurities allowed process tolerance tests to be run to

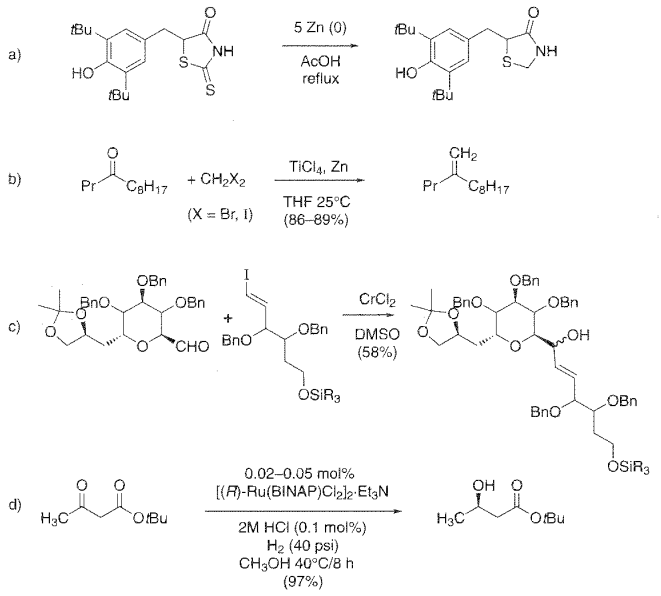


FIGURE 9.12. Co-catalysts found to be useful with metal-catalyzed reactions

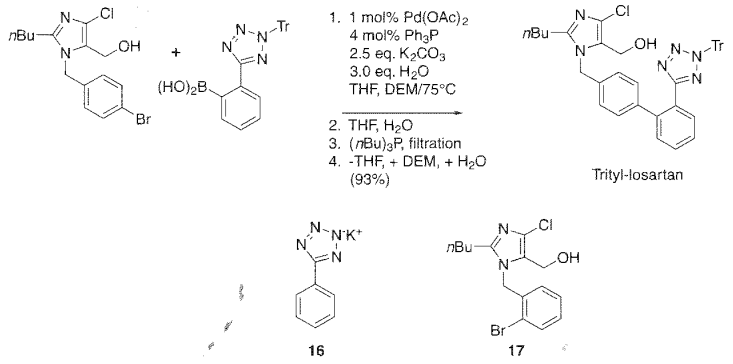


FIGURE 9.13. Impurities in the Suzuki cross-coupling reaction to prepare a losartan intermediate

determine how little catalyst could be used for a reliable process [38]. Detrimental impurities may be present in catalytic amounts of intermediates, and their presence may be noticed by use-tests (see Figure 14.6).

> **TIP:** Often hydrogenations require a second charge of catalyst (usually Pt/C or Pd/C). In effect, impurities are being absorbed to the carbon support. To avoid multiple charges of a valuable metal-based catalyst, pretreat by slurrying the reaction with charcoal.

Phase-transfer catalysts can also be "poisoned" by the presence of halides. Quaternary ammonium cations may form salts with iodide that is generated during reactions. Such salts do not partition well into aqueous phases, disrupting the catalytic phase-transfer cycling mechanism [39]. The presence and generation of iodide (and sometimes bromide) during PTC reactions should always be considered.

VII. CATALYST DECOMPOSITION

Catalysts can decompose under reaction conditions, and it may be necessary to assess the amount of active catalyst remaining, especially near the end of a reaction. Decomposition is often unavoidable, as with the reaction of $Mn(OAc)_3$ with the solvent acetic acid [40] during oxidations (see Figure 2.15). In this case the amount of catalyst was assessed by iodometric titration. Under routine PTC conditions of heat and exposure to NaOH, quaternary ammonium salts used as phase-transfer catalysts decompose, albeit relatively slowly compared to the rate of most PTC reactions. The primary decomposition route is through Hofmann elimination, producing an alkene and tertiary amine as by-products (Figure 9.14) [41]. ß-hydroxyammonium salts can decompose by additional pathways, as shown for the chiral catalyst **9** [13]. Since most quaternary ammonium salts are relatively inexpensive, practical approaches are either to charge additional catalyst as needed or to charge more catalyst at the beginning of a reaction.

VIII. NONLINEAR CATALYST EFFECTS

The use of enantiomerically impure chiral ligands can sometimes lead to products with significantly higher or lower enantiomeric excesses [42]. When there is increased enantioselection, such nonlinear effects have been termed asymmetric amplification. Asymmetric amplification has been noted for the hydroborating

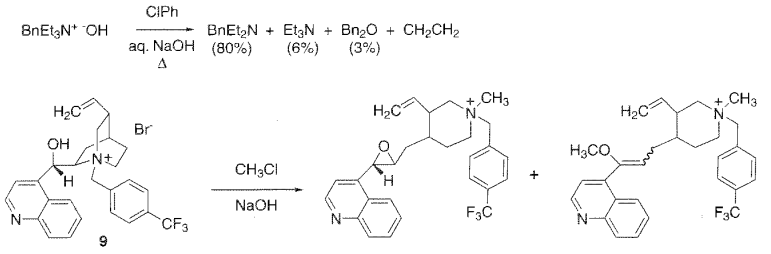


FIGURE 9.14. Decomposition of some quaternary ammonium salts used for PTC

reagents derived from chiral α-pinene [43]. Researchers at Lilly found that extensive purification of the ligand **18** (Figure 9.15) was not necessary in order to obtain product with an acceptable enantiomeric excess [44]. The catalyst charge for this reaction was chosen based on generating acceptable quality product within a short reaction time and minimal catalyst loading.

> **TIP:** Extensive purification of ligands will not be necessary if asymmetric amplification is in effect for the reaction system.

VIII. THE DIFFICULTY OF OPTIMIZING A CATALYTIC REACTION

The use of catalytic reactions is very alluring, but optimization can be very difficult. The success of a catalytic reaction is influenced by the choice of catalyst, ligands, solvents, concentration, temperature, aging, and stirring rate. Catalyst decomposition and the influence of impurities, both co-catalytic and inhibitory, can play big roles. Furthermore, conditions that are optimal for one substrate may not be optimal for another. The interplay of all these parameters can make

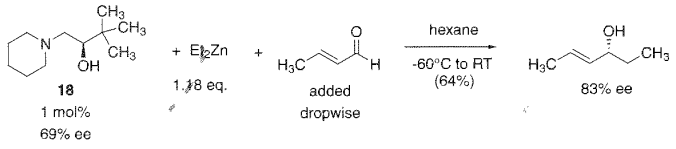


FIGURE 9.15. Asymmetric amplification in an alkylation with diethyl zinc

searching for optimal conditions very time-consuming. For instance, the quest for general catalytic conditions to asymmetrically dihydroxylate olefins was the focus of the Sharpless group for many years [45].

The development of the zinc reagent shown in Figure 9.16 illustrates many of these points. While this reagent was not used catalytically, details of its development are similar to the development of many catalytic reagents. An earlier alkynylation required protection of the amino group of **20** and deprotection to afford **21** [46]; the goal of developing the zinc reagent was to eliminate these two steps. Earlier screening had demonstrated that chiral pyrrolidinylnorepinephrine **19** was a superior chiral ligand to effect the desired enantioselective alkynylation. The presence of *achiral* alcohol auxiliary ligands influenced the enantioselectivity of the alkynylation (Figure 9.16). Optimal enantioselectivity was optimal with 1.2 equivalents of the acetylenic Grignard reagent, at least when neopentyl alcohol was used as the achiral auxiliary. Studies on different substrates showed that an unprotected amino group *ortho-* to the trifluoroacetophenone functionality was necessary for good reactivity. After what was undoubtedly a significant amount of work, an elegant process was developed [47].

Multivariate screening has allowed identification of catalytic conditions that most likely would not have been uncovered by traditional searching [48]. Rapid, multivariable, automated screening will accelerate the development and optimization of catalytic reactions [49].

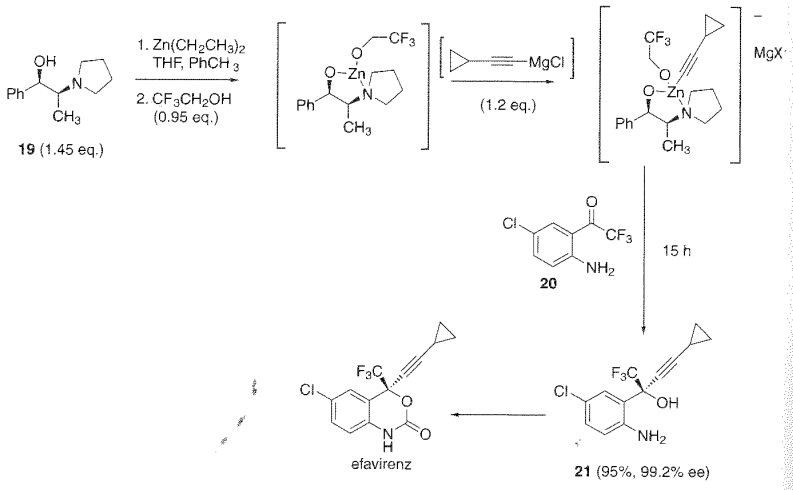


FIGURE 9.16. Alkynylation by zinc aminoalkoxide reagents

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CHAPTER 10

Work-up

I. INTRODUCTION

Work-up is the collective term for the treatments applied to processes after the reaction has been declared complete and before the product is isolated. The purposes of work-up include

- quenching the reaction, or treating the reaction mixture to prevent or minimize any subsequent side reactions;
- providing safe conditions for personnel to continue processing;
- removing impurities;
- providing the product in a form convenient for purification; and
- safely neutralizing waste streams.

The best work-up includes the fewest steps, the smallest number of vessels, the minimal number of extractions, and the minimal volume of solvent needed for extractions. Minimizing these considerations can increase productivity, as long as product quality does not suffer. The person who is responsible for the results of the process operations is usually responsible for process productivity and may reasonably demand justification for every step in the process.

Understanding or anticipating product stability is key to avoiding problems and creating successful work-ups. For instance, many β-lactam antibiotics are hydrolyzed by treatment with concentrated hydroxide, so conditions of high pH are to be avoided for these molecules. Extended solvent removal at high temperatures may decompose a product. It may be appropriate to stress products at extreme conditions in order to identify any processing risks.

The solubilities of products and reagents must be considered, or problems can occur from formation of emulsions or unwanted precipitates that add extra steps and delay processing. The product may be extracted into a waste stream and not recovered. Solubilities can be obtained or anticipated from literature data and anticipated from parameters of hydrophilicity/lipophilicity and the presence or absence of ionizable functional groups.

To generate high-quality reaction products after a work-up, one should exploit all phase separations, both liquid-liquid and solid-liquid. Insoluble impurities in a rich extract can inhibit the subsequent crystallization of the reaction product or become occluded in the product crystals. Small amounts of solids may be removed by a "polish filtration" (Section II.D). Removing small amounts of liquids that separate during extractions can also speed processing overall and improve the quality of the isolated reaction product. For instance, when a product is extracted from an aqueous stream using an organic solvent, diluting the first rich extract with the second, less concentrated extract may lead to the formation of a small amount of an aqueous phase. If this phase contains a significant amount of dissolved impurities, the chemist may choose to remove it by a simple phase split to preclude carrying these impurities along with the product. On the other hand, if this small aqueous phase contains little more than water, and if azeotropic concentration is used to dry the extract, then splitting off this small phase may not be worth the time and effort.

TIPS:

- Eliminate unnecessary operations during work-up. Strive for elegance in simplicity.
- Understand and anticipate product stability.
- Anticipate solubilities of product and reagents.
- Exploit any phase separation.

II. ASPECTS OF WORK-UP

Various aspects of work-ups are shown in Table 10.1 and are discussed in the sections below.

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TABLE 10.1. Aspects of Work-ups

1. Quench
2. Extraction
3. Activated Carbon Treatment
4. Filtration
5. Concentrating Solutions and Solvent Displacement
6. Deionization and Removing Metals
7. Destruction of Process Streams
8. Derivatization
9. Solid-Supported Reagents

II.A. Quench

By quenching a reaction, reactive components are neutralized, thus preventing or minimizing degradation of the product or formation of other troublesome by-products. These components may be unreacted reagents, intermediates that lead to product after work-up, or by-products of the reaction. Diluting a reaction will decrease the reaction rate but not stop the reaction, unless by dilution the reaction becomes heterogeneous and the reactive components separate. Some typical quenches are shown in Table 10.2.

Several modes are possible for quenching a reaction. A common practice is to add the quench reagent directly to the reaction. This method minimizes the volume change for the reaction, keeping vessel productivity high. Adding the quench reagents as a solution to the reaction dilutes vessel productivity. Often quench reagents are delivered as an aqueous solution, which is convenient for subsequent extraction.

Controlling reaction exotherms during quenching may be key to avoiding decomposition and may have safety implications. For highly reactive reagents, quenching may proceed in stages. For instance, dissolving metal reductions in liquid ammonia are often quenched by first adding NH_4Cl, followed by H_2O (Figure 10.1) [1], since quenching with H_2O alone often is highly exothermic. Similarly, $LiAlH_4$ reactions may be quenched by first adding acetone before

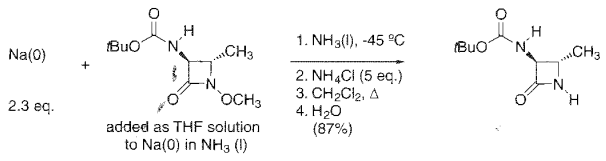


FIGURE 10.1. Dissolving metal reduction of an n-methoxy-ß-lactam

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TABLE 10.2. Examples of Typical Quenches

Reagent to be neutralized	Treatment[a]	Comments / Example
HO^-, RO^-	Neutralize with AcOH or inorganic acids	
H^+	Neutralize with MOH, $MHCO_3$, M_2CO_3 (M = Na, K)	Neutralization with $MHCO_3$ or M_2CO_3 may generate CO_2 and foaming
H_2O_2	H_3PO_2	Oxidation of R_2S[b]
HOCl, Cl_2, NCS, Br_2, I_2	$NaHSO_3$, $Na_2S_2O_3$, $Na_2S_2O_5$	
I^-	$NaHSO_3$, $Na_2S_2O_3$, $Na_2S_2O_5$	To reduce I_2 formed *in situ*
H_2NNH_2	NaOCl	Hydrazide formation[c]
^-CN	NaOCl; NaOH, Δ	PTC can accelerate reactions and safely contain ^-CN under basic conditions[d,e]
$AlCl_3$ and other Lewis acids	H_2O, then perhaps H^+	Insoluble metal hydroxides can impede work-up at pH >7
Ozone / ozonides	H_3CSCH_3, Ph_3P, $NaBH_4$	
Os (VI) / Os(VIII)	Na_2SO_3	
$(Ipc)_2BCl$, other boron reagents	Diethanolamine, triethanolamine	Chiral reduction of a ketone[f], generation of BH_3[g]
BH_4^-	Acetone; H^+; ROH	Caution: H_2 forms with H^+ and ROH
AlH_4^-	Acetone; H_2O, aq. NaOH, H_2O; Rochelle's salt (sodium potassium tartrate)	Caution: H_2 evolution with ROH addition. NaOH work-up gives insoluble granular salts[h]

$(i\text{-Bu})_2AlH_2$ (DIBAL)	CH_3OH, then HCl/>40 °C	Caution: H_2 evolution with ROH addition[i]
Na(0) / NH_3 and other dissolving metal reductions	NH_4Cl, then H_2O	
RMgX (Grignard reagents)	Aqueous citric acid, Rochelle's salt	Facile extractions[g]
RLi, R_2NLi	Acetone, R'OH, RCO_2H	Protonation of RLi forms flammable RH

[a]All quenching operations should be performed cautiously mininize impact of any exothermic reactions.

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adding H_2O. When H_2O is used to quench a $LiAlH_4$ reaction (see Table 10.2), H_2O must be added slowly with good agitation to encourage ready dispersion of the quench reagent and to avoid rapid exotherms. Caution should be taken when adding a quench to a reaction, as the situation is analogous to adding acid to water. It may be easier to control an exothermic reaction during quenching by adding the reaction to a stirred solution of the quench reagent. The reaction temperature can be controlled by precooling the quench solution, cooling the quench vessel during the addition, and by limiting the addition rate to the quench solution.

To optimize yields it may be preferable to add the reaction mixture to the quench solution. Such "inverse quenches" (or "reverse quenches") are valuable when by-products from quenching are particularly reactive. When aqueous quenches are added to the acetylenic aldehyde precursors in Figure 10.2, dimethylamine is generated, which reacts with the desired product **1** [2]. By adding the reaction mixture to aqueous KH_2PO_4, the dimethylamine generated is quickly neutralized by the excess acid, minimizing formation of by-products **2**–**4**. Another option for this and similar reactions is to combine the reaction and the quench solution using a continuous flow reactor for good control (Chapter 13).

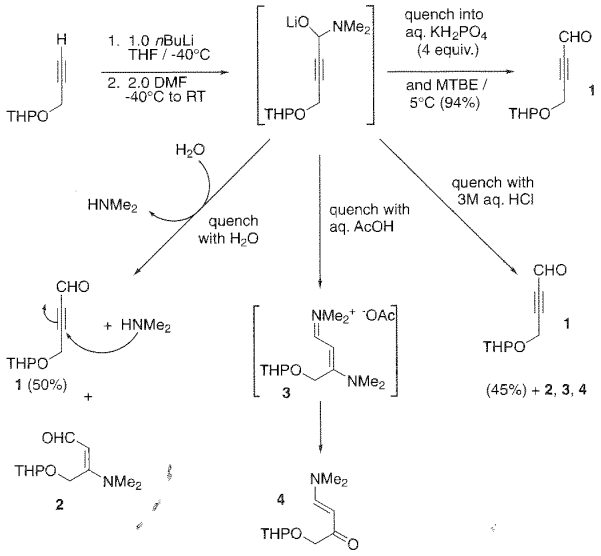


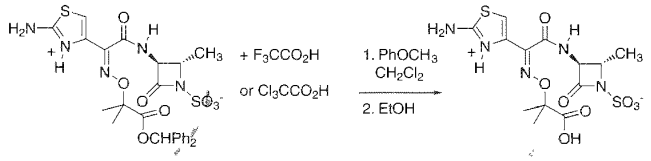
FIGURE 10.2. Optimal quenching of a reaction using an inverse quench

TIP: Apply the snapshot mental tool to predict when an inverse quench will be helpful.

Practical considerations may disallow an inverse quench. For the reduction in Figure 10.1, it was more convenient to add the NH_4Cl quench to the reaction in the pilot plant vessels; otherwise additional considerations would have been necessary to contain the volatile solvent ammonia while transferring to another vessel. In a dedicated facility used for dissolving metal reductions, equipment trains would be designed for an inverse quench if that were advantageous. For the deprotection of the benzhydryl ester **5** (Figure 10.3), the reaction using F_3CCO_2H was fluid, and the reaction could be quenched either by adding EtOH to the reaction or by adding the reaction to EtOH. (In the presence of EtOH the deprotection was very slow, and the product crystallized.) When this deprotection was conducted using Cl_3CCO_2H, the viscous reaction was difficult to transfer, making an inverse quench impractical [3].

TIP: The speed of transferring a reaction into a quench solution may be important in minimizing by-product formation. Transferring through a larger diameter line may be necessary, and the transfer may be quicker by pressurizing than by pumping. These considerations may be important if the reaction is sensitive to temperature, pH, and time. Quenching into a continuous flow reactor may afford the best control.

Often many choices are available in neutralizing a reaction stream, and the primary consideration may be the solubility of the salts formed during neutralization. Solubilities of selected inorganic salts are shown in Table 10.3. For instance,



5 Aztreonam (Azactam®)

FIGURE 10.3. Deprotection of a benzhydryl ester

TABLE 10.3. Solubilities of Selected Inorganic Salts Formed During Work-up

	cold water g/100 mL	hot water g/100 mL	other g/100 mL	cold water g/100 mL	hot water g/100 mL	other g/100 mL	cold water g/100 mL	hot water g/100 mL	other g/100 mL
Anion	Li^+			Na^+			K^+		
Acetate	300 $LiOAc \cdot 2\ H_2O$	vs	21.5 alc	119 (0 °C) NaOAc	170.2 (100°C)	sl s alc	253 (20°C) KOAc	492 (62°C)	33 alc 24.2 MeOH (15°C)
Benzoate	33 (25°C) $PhCO_2Li$	40 (100°C)	7.7 alc (26°C)	66 (20°C) $PhCO_2Na$	74.2 (100°C)	1.6 alc (25°C)	52 (25°C) $PhCO_2K \cdot 3\ H_2O$	112 (100°C)	s al
Bromide	145 (4°C) LiBr	254 (90°C)	73 alc (40°C)	79.5 (0°C) $NaBr \cdot 2\ H_2O$	119 (81°C)	2.3 alc (25°C)	53.5 (0°C) KBr	102 (100°C)	0.14 alc (25°C)
Carbonate	1.54 (0°C) Li_2CO_3	0.72 (100°C)	i alc	7.1 (0°C) Na_2CO_3	45.5 (100°C)	sl s alc	112 (20°C) K_2CO_3	156 (100°C)	i alc
Hydrogen carbonate	—	—	—	6.9 (0°C) $NaHCO_3$	16.4 (60°C)	sl s alc	22.4 $KHCO_3$	60 (60°C)	i alc
Chloride	63.7 (0°C) LiCl	130 (96°C)	25.1 alc (30°C) 42.4 MeOH (25°C) 4.1 acetone (25°C)	35.7 (0°C) NaCl	39.1 (100°C)	sl s alc	34.4 KCl	56.7 (100°C)	sl s alc
Citrate	74.5 (25°C) $Li_3C_6H_5O_7 \cdot 4\ H_2O$	66.7 (100°C)	—	92.6 (25°C) $Na_3C_6H_5O_7 \cdot 2\ H_2O$	250 (100°C)	sl s alc	167 (15°C) $K_3C_6H_5O_7 \cdot H_2O$	199.7 (31 °C)	sl s alc
Hydroxide	12.8 (20°C) LiOH	17.5 (100°C)	sl sol alc	42 (0°C) NaOH	347 (100°C)	v s alc	107 (15°C) KOH	178 (100°C)	v s alc
Iodide	165 (20°C) LiI	433 (80°C)	251 alc (20°C) 43 acetone (18°C) 343.4 MeOH (20°C)	184 (25°C) NaI	302 (100°C)	42.6 alc (25°C) 40 acetone (25°C)	128 (6°C) KI	208 (100 °C)	1.88 alc (25 °C) 1.3 acetone (25°C)
Oxalate	8 (19.5°C) $Li_2C_2O_4$	—	i alc	3.7 (20°C) $Na_2C_2O_4$	6.3 (100°C)	i alc	33 (16°C) $K_2C_2O_4 \cdot H_2O$	—	—
OrthoPhosphate	0.04 (18°C) Li_3PO_4	—	—	1.5 (0°C) $Na_3PO_4 \cdot 12\ H_2O$	157 (70°C)	i alc	90 (20°C) K_3PO_4	—	i alc
Hydrogen Phosphate	—	—	—	4.15 $Na_2HPO_4 \cdot 12\ H_2O$	87.4 (34°C)	i alc	167 (20°C) K_2HPO_4	vs	vs alc
Dihydrogen Phosphate	— LiH_2PO_4	—	—	59.9 (0°C) $Na\ H_2PO_4 \cdot H_2O$	427 (100°C)	i alc	33 (25°C) $K\ H_2PO_4$	—	i alc
Sulfate	26.1 (0°C) Li_2SO_4	23 (108°C)	—	4.8 (0°C) Na_2SO_4	—	—	12 (25°C) K_2SO_4	24.1 (100°C)	i alc
Hydrogen Sulfate	34.9 (25°C) $LiHSO_4 \cdot H_2O$	29 (100°C)	—	28.6 (25°C) $NaHSO_4$	100 (100°C)	sl s alc	36.3 (0°C) $KHSO_4$	122 (100°C)	i alc

Adapted from *CRC Handbook of Chemistry and Physics,* 74th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL; 1994, pp 4-69 through 4-101.

many acids would neutralize a NaOH-mediated hydrolysis of an ester, and the corresponding sodium salts of acids would be formed. If 0.5 molar equivalents of concentrated H_2SO_4 were used, most of the by-product Na_2SO_4 might be expected to precipitate or crystallize due to its relatively low solubility in H_2O. If the reaction product is soluble after neutralization, removal of Na_2SO_4 by filtration would decrease the burden of inorganic impurities in the product and could facilitate isolating the product. However, if the subsequent processing involves extraction into an organic solvent, neutralizing with concentrated H_2SO_4 might afford a triphasic mixture (liquid, liquid, solid) and unnecessarily complicate processing; in that case using an acid that forms by-products with greater aqueous solubilities would be preferred. Similarly, if the product crystallizes upon acidification, use of concentrated HCl would be preferable over concentrated H_2SO_4, as NaCl has greater solubility in water than Na_2SO_4, and NaCl would be less likely to contaminate the product crystals.

Additional information can be gleaned from Table 10.3. Of the organic acids listed (acetate, benzoate, citrate, and oxalate), the sodium salts on a molar basis are less soluble in H_2O than the corresponding lithium or potassium salts. Lithium salts have greater solubilities in alcohol than do the corresponding sodium or potassium salts and are more likely to be carried over into a rich organic extract than other alkali metal salts. The purification burden from residual lithium salts can be significant: lithium salts are known psychotropic agents, and they need to be controlled at low levels in an API. In the dissolving metal reduction involved in the preparation of a cimetidine intermediate, the water-soluble product **6** was isolated by extraction into *i*-PrOH; for the reduction Na(0) was preferred over Li(0), as **6** produced from the Li(0) reduction was contaminated by higher levels of inorganic salts (Figure 10.4) [4]. Enzymes that are affected by ionic strength [5] may be inhibited by dissolved Li salts carried over from a work-up (Figure 10.5). Using reagents that generate sodium or potassium salts instead of lithium salts may be preferred from the standpoint of simplifying work-up and purification.

II.B. Extraction

In the context of the fine chemicals industries, extraction is usually an operation performed by mixing two immiscible liquids in order to selectively partition a

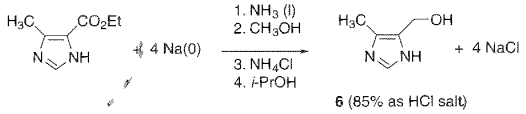


FIGURE 10.4. Dissolving metal reduction: Na(0) preferred over Li(0) due to by-product solubilities

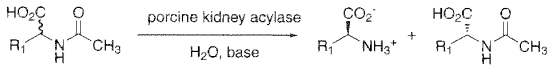


FIGURE 10.5. An enzyme inhibited by high ionic strength

solute into one of the liquid phases. Liquid-solid extraction may also be carried out, usually to remove a compound from a biomass. The removal of caffeine from coffee beans by supercritical CO_2 is an example of a liquid-solid extraction. For the purposes of this discussion, liquid-liquid extractions will be considered.

In most liquid-liquid extractions during work-ups, an impurity is extracted into an aqueous phase while the unionized product remains in the organic phase. Ionizable products may also be purified by extractive work-ups. Purification of an amine may be effected by extraction into an acidic aqueous phase to remove acidic and neutral impurities, followed by basification of the rich aqueous extract and extraction into an organic solvent. An acidic product may be purified by extraction into a basic aqueous phase to remove basic and neutral impurities, followed by acidification of the rich aqueous phase and extraction into an organic solvent. An elegant example of taking advantage of product functional groups during work-up is shown in the isolation of the imipenem intermediate **7** (Figure 10.6), which was developed as a continuous process [6].

TIP: Understand the partitioning of the desired product in each phase during every stage of the extraction process. Collect each "spent" phase, label the container, and store until it is clear that the extract can be discarded without losing yield or valuable process history that could be collected by analyzing the extract.

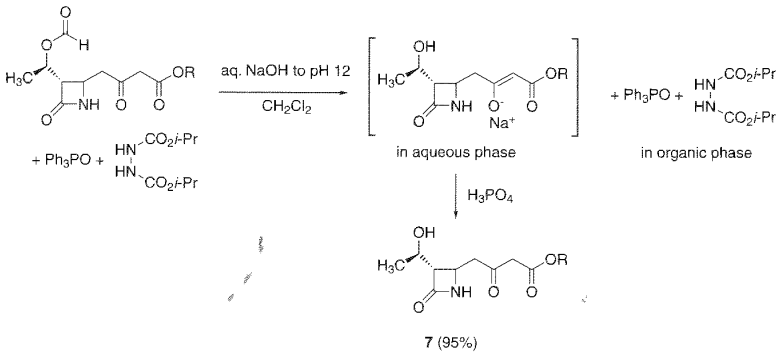


FIGURE 10.6. Isolation of a ß-keto ester by extraction as the enolate anion

Water miscibility of a solvent is important for work-up considerations. Some solvents have such low water solubility that ready phase separations occur when reactions in this solvent are washed with inorganic aqueous solutions to remove impurities. The result is minimal loss of the product to the spent aqueous phase. With water-soluble solvents, e.g., THF and acetonitrile, the presence of either highly lipophilic or ionic compounds may allow for good phase separation during aqueous extractions.

TIPS: To rapidly develop extractions of reactions run in water-soluble solvents, e.g., THF and acetonitrile, first try washing reaction aliquots on a test-tube scale. Note any phase separation, the presence of any emulsions that take a significant amount of time to separate, and any losses to the aqueous phase. If problems arise, inorganic salts may be added to the mixture in order to "salt out" the organic product into the organic phase. Effective phase splits may occur if there is less of the organic solvent present, i.e., if the reaction were run more concentrated. A cosolvent such as EtOAc or $PhCH_3$ may be added to improve the partitition coefficients of the product in the organic and aqueous phases, thus eliminating emulsions. As a last resort, replace the reaction solvent with a higher-boiling, more water-immiscible solvent, and reexamine extractions.

Buffered solutions can also be used for work-up [7], essentially as described in Figure 10.2. By using a properly buffered solution there is no need to adjust the pH, which can speed processing. Buffered solutions are used to remove NH_3 and other compounds. A drawback of using buffers is the increased amount of inorganic waste.

Minimizing the number of extractions and total extraction volume is important in streamlining processing and maintaining good productivity. If many extractions and large volumes of solvents are necessary, another solvent or solvent combination may be substituted for more efficient operations. If the extraction coefficient is known for the solute and the two solvents, the volume of the second and subsequent washes can be calculated. For instance, if 90% of the product is removed from the aqueous phase with the first organic extraction, then a second extraction with somewhat more than 10% of the original solvent volume may suffice for efficient extraction of the remaining solute. Experimentation is necessary to determine the minimal extractions that are practical.

Usually extractions are carried out at room temperature, primarily for convenience; extractions at higher temperatures may allow for smaller solvent volumes to be used, due to the increased solubility of compounds at higher temperatures. In the isolation of the phosphinyl carboxylic acid **8**, extractions were carried out

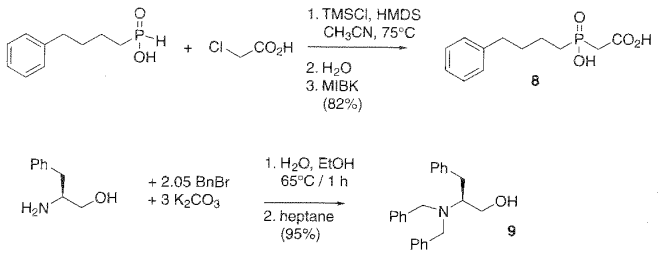


FIGURE 10.7. Reactions conveniently worked up by extractions at higher temperatures

at 30–35°C to minimize solvent usage (Figure 10.7) [8]; as expected, slightly elevated levels of H_2O were found in the warm extracts. In the isolation of the amino alcohol **9** (Figure 10.7), extractions were conducted around 65°C, and the product crystallized from the cooled extract [9].

When there is no alternative to employing multiple extractions, chemical engineering approaches may afford more efficient operations in a pilot plant or manufacturing facility [10]. Many of these extractors are countercurrent devices, such as the Karr reciprocating plate tower, in which the light phase is continually fed into the bottom of the extractor while the heavy phase is fed into the top of the extractor.

Extractions may be introduced into a work-up to provide for greater safety in operations. For instance, unreacted 1,4-dibromobutane was conveniently removed by heptane extraction of an aqueous phase containing the intermediate lithium carboxylate (Figure 10.8) [11]. Without this step, the lachrymator 1,4-dibromobutane (bp 63–65°C/6 mm) was ineffectively removed. On scale this compound would have been very irritating to personnel, especially those removing the product from a dryer.

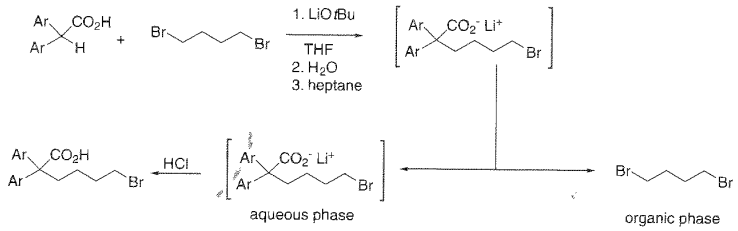


FIGURE 10.8. Extractive removal of a reactive alkylating reagent

An aqueous solvent is not necessary for liquid-liquid extractions. Many organic solvents and solvent combinations are insoluble, a property that forms the basis for countercurrent chromatography [12, 13]. Solvent pairs are drawn from lipophilic solvents (such as heptane, toluene, and CH_2Cl_2) and hydrophilic solvents (such as MeOH, EtOH, ethylene glycol, and acetonitrile) [14–17]. Water, acetone, and acetic acid may be added as cosolvents. In principle this approach may be effective in separating organic compounds of different polarity, such as Ph_3PO and a lipophilic olefin, the products from a Wittig reaction.

II.C. Activated Carbon Treatment

Trace amounts of polar impurities can contaminate crystallized products, and very small amounts of impurities can be responsible for producing intensely colored products. Polar impurities can be removed by stirring a solution of the product with 1–2 wt% of activated carbon relative to the solute, adsorbing these impurities to the finely divided solids. Impurities are trapped in the pores of the activated carbon by van der Waals attractive forces. There are three categories of pore sizes: macroporous (1000–100,000 Å), mesoporous (100–1000 Å), and microporous (<100 Å). Viscous solvents slow the penetration of molecules into the pores [18], and polar solvents are generally more effective than nonpolar solvents for treatment [19]. A filter aid (Section II.D.) is often used to avoid slow filtrations in removing activated carbon. After filtration, the filtrate is processed to the product.

TIPS:

- Adsorption of a molecule to activated carbon may change the pH of the resulting filtrate.
- Adsorption to activated carbon is based on equilibria. Short contact times decrease the efficiency of impurity adsorption.
- Performance of activated carbons can vary greatly.

Activated carbon treatment can cause difficulties in cleaning equipment, as the finely divided solid is moderately electrostatic and tends to adhere to almost every surface it contacts. No solvent effectively dissolves charcoal, although vessels may be cleaned by boiling out with aqueous NaOH. For this reason, activated carbon treatment on large scale is often limited to dedicated vessels. Solutions may also be passed through in-line filters containing granular, spherical, or pelletized activated carbon [20]; these filters retain the activated carbon and avoid many of the cleaning issues.

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II.D. Filtration

Fine particles often plug filter pores, slowing or stopping filtration ("blinding" the filter). Fine particles result from rapid crystallization or precipitation or from the presence of low-molecular polymers, dust, dirt, or other impurities. To enhance filtration rates, increase the surface area of the filter and/or the filtration medium. The latter is effected by filtration through filter aids such as diatomaceous earth (Hyflo®, Kieselguhr, Celite®), which creates more binding sites for impurities and allows more channels for filtrate to pass through. These filter aids may be applied as a bed to the surface of the filter paper or cloth or may be added to the stirred solution prior to filtration.

"Polish filtration" is filtration to remove a very small amount of insoluble impurities, usually just prior to crystallization. There are several disadvantages to leaving these impurities in a crystallization process: besides decreasing the purity of the isolated product, they may provide surfaces that encourage the co-crystallization of impurities in the product or the crystallization of an undesired crystal polymorph. On scale, polish filtration is often carried out by passing a solution through an in-line filter. Polish filtration may be considered part of "good housekeeping."

Other filtration processes may be used, primarily on scale and in manufacturing operations [21]. Ultrafiltration through membranes removes proteins and other large molecules from solution. Microfiltration through a variety of ceramic or polymeric filters is used to retain soluble proteins and bacteria, thus removing pyrogenic proteins and sterilizing solutions without heat. Effective microfiltration is critical for the formulation of drugs to be delivered by injection.

II.E. Concentrating Solutions and Solvent Displacement

Reaction mixtures may be concentrated to facilitate work-up or to prepare a solution for crystallization. Prior to extractions, a water-miscible reaction solvent may be exchanged for a solvent that dissolves less H_2O. Water and other impurities may be removed by azeotropic distillation or co-distillation (Chapter 4). Concentration is often performed under reduced pressure, as atmospheric distillations take longer and subject the product to greater heat and increase the chances for decomposition.

> **TIP:** The effects of extended heating on scale can be modeled in the lab by subjecting the reaction to the concentration temperature for the time anticipated as necessary to reach the desired volumes. Prolonged heating may lead to decomposition.

A solvent may be conveniently displaced with a higher-boiling solvent ("solvent chasing") by concentrating to a small volume of a mobile solution or suspension, then adding the higher-boiling solvent and continuing concentration. This process generates a mixed solvent condensate, and the solvents may need to be separated for recovery and reuse.

II.F. Deionization and Removing Metals

With the increasing use of metal catalysis, removing metals from an API has assumed great importance. Some syntheses have been redesigned because of the difficulty of reducing the concentration of residual metals to less than 20 ppm in the final product [22]. The metal-catalyzed transformation may be moved several steps away from the final step in anticipation that through purification of subsequent intermediates, the levels of metal ions in the API will pass specifications.

There are several direct approaches to removing metals (see Table 10.4). Solid metal salts and complexes may be removed by filtration. Pretreatment with activated carbon and/or filter aids may be necessary. Metal salts may be extracted into an aqueous phase under acidic conditions, by using chelating agents or by adding hydroxy acids. The extractive approach may not work well to remove metals such as palladium, which form complexes with unsaturated compounds [22, 23]. Ion-exchange resins and polystyrene-supported ligands can be used to absorb metal ions. Metal salts may be precipitated by adjusting aqueous solutions to basic pH, or by the addition of flocculating agents such as 2,4,6-*s*-trimercaptotriazine (TMT) [23]. Recrystallization may be key in reducing the levels of residual metals. The development of methods to remove metals will continue to be important.

II.G. Destruction of Process Streams

Reactive process streams should be neutralized in a timely manner to permit conscientious disposal and to avoid safety problems. All streams that have not been effectively neutralized should be considered potentially hazardous, and the hazard should be assessed, perhaps in a safety laboratory, before storage.

A salient example of not anticipating the reactivity of process streams occurred upon storage of a distillate containing primarily EtOAc and $SOCl_2$ [24]. This mixed distillate was stored in drums used to ship the $SOCl_2$ reagent, based on the theory that diluting the $SOCl_2$ with solvent would not make the waste streams more dangerous for storage in the commercial drums. The drums ruptured violently, due to the exothermic reaction of zinc metal, EtOAc and $SOCl_2$ together. (Any two of these components are relatively stable; cracked drum liners may have exposed the metallic zinc in the galvanized drum.)

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TABLE 10.4. Treatments to Reduce Levels of Metal Contaminants

Metal ion	Treatment	Means of removal
M(II), M(III), M(IV), . . .	Basification	Precipitation
	Activated carbon	Adsorption to carbon
	Ion-exchange chromatography[a,b] (including chelating resins)[c]	Adsorption to resin
	Polystyrene-supported ligands[d,e]	Adsorption to resin
Cu(I) and Cu(II)	Oxalic acid[f]	Extraction into aqueous phase
	Dilute aq. pyridine or aq. NH_3	Extraction into aqueous phase
Al(III)	Rochelle salt (sodium potassium tartrate)[g]	Extraction into aqueous phase
	Malic acid[h]	Extraction into aqueous phase
Cu(II), Pd(II), Mn(II), . . .	Chelation[i]	Extraction
	2,4,6-*s*-Trimercaptotriazine[j]	Precipitation
Pd(O)	$(n\text{-Bu})_3P$[k]	Stabilize Pd(O) in organic solutions for crystallization of product
Ti(IV)	Citric acid[l]	Precipitation

[a]For an excellent review, see "Guide to Ion Exchange," Bio-Rad Laboratories, Catalog Number 140-9997.

[b]Shanley, A., "Ion Exchange Charges Ahead." *Chem. Eng.* **1999**, *106(1)*, 65.

[c]Chelating resins are available from Bio-Rad Laboratories and other suppliers.

[d]Baumann, T. F.; Reynolds, J. G.; Fox, G. A., "Polymer pendant crown thioethers: synthesis and Hg(II) extraction studies of a novel thiacrown polymer." *Chem. Commun.* **1998**, 1637, and references therein.

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[i]Conway, M.; Holoman, S.; Jones, L.; Leenhouts, R.; Williamson, G., "Selecting and Using Chelating Agents." *Chem. Eng.* **1999**, *106(3)*, 86.

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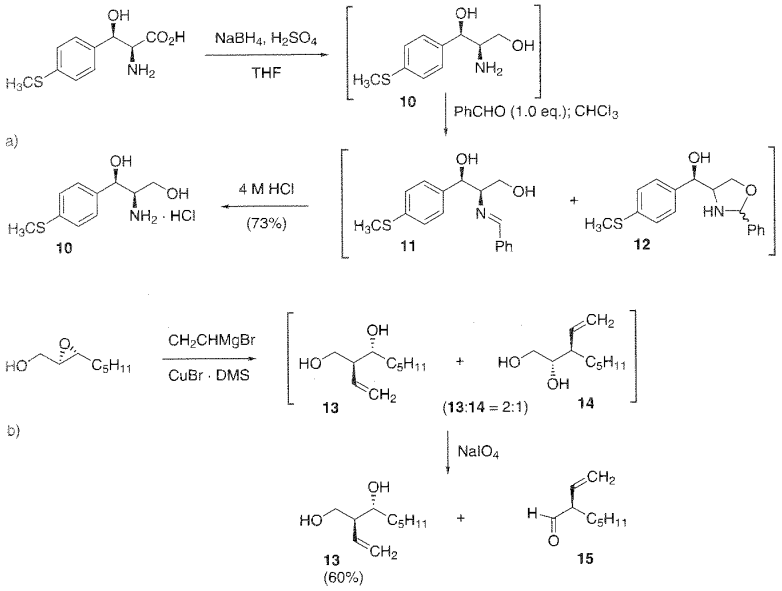


FIGURE 10.9. Work-ups eased by derivatization or further reaction

II.H. Derivatization

Intermediates may be derivatized to ease work-up. Often polar groups are derivatized and converted to less polar functionalities to facilitate extractions. The water-soluble amino diol **10** was reacted with benzaldehyde to form a mixture of the aldimine **11** and the oxazolines **12** (Figure 10.9a), which were more readily extracted into organic solvents [25]. Deprotection readily regenerated **10**. Treatment of aldehydes and ketones with $NaHSO_3$ generates water-soluble adducts that can be useful in work-ups [26]. To ease purification of the 1,3-diol **13**, the minor diol impurity **14** was oxidized to the aldehyde **15** by treatment with $NaIO_4$ (Figure 10.9b) [27]. Derivatization and deprotection require time to optimize each step, and the benefits of derivatization should be assessed before significant time is invested.

II.I. Solid-supported Reagents

The number of solid-supported reagents has grown with the growth of solid-supported chemistry. Many reagents have been developed to ease the work-up and isolation by selectively "fishing out" products and impurities [28–30].

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Increased demand for such reagents should decrease the cost. "Smart polymers," which undergo reversible changes under the influence of pH, temperature, ionic strength, and other factors are used for the isolation of biotechnology products [31]. Growth will be seen in this relatively new field.

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CHAPTER 11

Tools for Purifying the Product: Column Chromatography, Crystallization and Reslurrying

1. INTRODUCTION

The chemist has many options for purifying and isolating intermediates and final products. The operations preferred on scale differ from those routinely used in the laboratory, as discussed in Chapter 1. Deferred purification by telescoping should not be overlooked as a productivity-boosting option. Purification may include extractions and polish filtration performed as part of work-up (Chapter 10) and subsequent chromatography, crystallization, and/or reslurrying. Liquid products may be purified and isolated by distillation. Considering the drawbacks of chromatography on scale, chromatographic purifications are generally used only when reaction optimization and non-chromatographic means of purification prove inadequate to prepare high-quality product. Distillation on scale usually requires specialized equipment and is limited to relatively low molecular weight compounds that do not decompose during heating.

Isolation of solid intermediates and final product is often achieved by crystallization. Intermediates may be upgraded by crystallization, decreasing the burden on the purification of the final product. Under controlled conditions, crystallization generally provides the best purification of a product, and it may be essential

for preparing API of the desired purity and polymorphic state. As crystallization on scale can be labor-intensive and equipment-intensive, care must be taken to institute a rugged crystallization process.

The following sections discuss chromatography on scale first, as compounds are usually crystallized after chromatographic purification. The theory of crystallization is described, followed by a discussion on morphic states and salt selection. Guidelines are presented to predict how readily a crystallization and isolation process can be performed on scale. Tips on washing a filter cake and drying are followed by a description of reslurrying as an optional alternative to recrystallizing a solid.

II. PURIFICATION BY COLUMN CHROMATOGRAPHY

Column chromatography may be used for purification of compounds in the kilo lab and on larger scale. For the kilo lab, wide-diameter columns such as those described by Still for flash chromatography [1] are preferred. TLC can be used to select a preparative chromatographic eluant for flash chromatography, and chromatographic separations can also be examined on a small scale before valuable material is committed to large-scale chromatography.

TIPS:

- The key in efficiently using column chromatography is to develop a chromatographic system that maximizes the differences in elution times between the desired product and the impurities. The optimal separation occurs when the impurities do not move from the origin and the product has good mobility, e.g., moves half-way up the TLC plate. Under these conditions the solid phase is used as an absorbent, and a small amount of solvent can be used to separate the product from the impurities.
- To speed chromatographic operations, pressurize a chromatography column with an inert gas, or apply suction to the collection side of the column. Pressure from an inert gas should be applied with care, and applying suction is safer.
- Large-scale chromatography units are commercially available for preparative purifications.
- Preparative chromatography should always be carried out in well-ventilated areas. When using large amounts of electrostatic solvents, e.g., hexane, care should be taken to ground equipment and prevent fires due to electrostatic discharge. Heptane is safer than hexane (see Table 5.3).

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A simpler alternative to conventional chromatography is to treat a crude extract with a stationary phase, e.g., silica gel, in a batch mode. Solids can be removed by filtration, and the product recovered by washing the filter cake and processing the filtrates. In an early process, a solution of crude **1** (Figure 11.1) in CH_2Cl_2 was stirred with silica gel at room temperature, and the solids were removed by filtration [2]. The triol impurity **2** was adsorbed to the silica gel, and the efficiency of absorption from the solution was correlated to the grade of silica gel used. Many criteria were examined, including pore size, particle mesh size, pH of aqueous suspensions of the bulk adsorbent, surface area, and mean particle size. The larger pore size in effective batches of silica gel was suggested to be the key criterion, probably because the impurity **2** could penetrate and be adsorbed to the solids. With chromatography in a batch mode, impurities that are significantly different from the product may be removed. Selection of solvent(s) is key.

Preparative chromatography has been used for the purification of many fine chemicals and bulk chemicals [3–5]. To achieve high productivity, preparative HPLC is employed for good resolution of analytes and high flow rates. Traditional batch chromatography, with one injection and one column, is operationally simple, but capacity and productivity may be limited. Demonstrated techniques to increase the productivity of preparative chromatography include repetitive chromatography (repeated injections), recycling chromatography (recycling the eluant through the column to increase the separation between peaks), and simulated moving bed chromatography (SMB, chromatography columns in series linked in a circular manner) [6].

SMB has proved very versatile. SMB was developed for rugged use on large scale, producing up to 500,000 tons per year of *p*-xylene. Fructose and sucrose have been separated by SMB since the 1960s. For process development and manufacturing in the pharmaceutical and fine chemical industries, the productivity and separation costs of SMB can be superior to those of one-injection batch chromatography [7]. SMB has also been used at early stages of development; enantiomers were separated using a chiral stationary bed [8, 9], resolving 125 g per day [9] of a racemic mixture that was difficult to separate by crystallization. A laboratory unit for SMB has been described [10].

A sizable financial outlay may be necessary to purchase chromatography equipment for use on scale. Equipment expenses for SMB are greater than for traditional chromatography due to the need to purchase multiple pumps and control

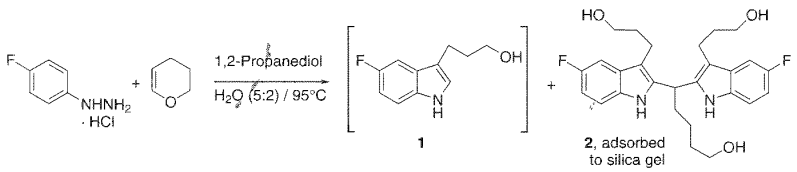


FIGURE 11.1. Purification by Silica Gel Treatment in a Batch Mode

equipment. Often a significant expense is for the columns and specifically for the solid support in the columns. Chiral stationary phases may be extremely expensive, while zeolites and resins contribute only marginally to overall cost [7]. Small particles with relatively narrow size distributions usually afford the highest loading and best chromatographic resolution. Pore volumes may be key considerations [11]. Since small particles provide high back-pressures at high flow rates (such as 1.5 liters/min), particle size, flow rate, and system pressure must all be considered for efficient operations. Reconditioning and reusing the stationary phase is necessary to minimize operating costs.

When column chromatography is used on scale in the pharmaceutical industry, it is usually for the purification of potent molecules that have high value per gram. Transferring active ingredients dissolved in solutions can be much safer than transferring solids, due to the danger of generating air-borne particulate solids. When multiple isolation and drying steps can be eliminated, chromatography may be an attractive alternative for the purification of highly potent molecules. For instance, in the preparation of pergolide mesylate, chromatographic purification increased the safety of operations and greatly increased productivity (Figure 11.2) [11–13]. First the methylthiomethyl ether impurity **3** was removed by adsorption to HP-20ss resin, using radial chromatography [11]. HP-20ss resin is a high-porosity copolymer of styrene and divinylbenzene, which adsorbs hydrophobic compounds. Reverse-phase chromatography was not practical in removing impurities **4** and **5**, as pergolide was not retained at low pH, where it displayed reasonable solubility. At higher pH values the reduced pergolide solubility would have required significantly reduced column loading. After radial chromatography through HP-20ss resin, preparative HPLC using silica gel columns was used to remove **4** and **5**, with a maximum loading of 250 g of pergolide per run [12].

II. CRYSTALLIZATION

Productivity considerations largely define a good crystallization. A good crystallization process reliably provides high-quality product with suitably low levels of impurities. The process should be optimized to provide the greatest possible yield

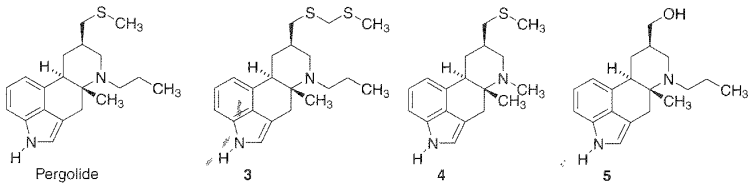


FIGURE 11.2. Impurities in Pergolide Removed by Tandem Chromatography

as a first crop, minimizing the need to devote personnel time to isolating a second crop. The process should be flexible enough to allow the use of many types of different filters and dryers. Key physical parameters should be identified to allow for ready scale-up. Extended operations, such as aging of crystal slurries, may be developed to control crystal size and quality. Knowing the amount of time needed for extended operations is important in order to optimize the use of scale-up equipment. Safety considerations are key, particularly in the selection of solvents and during the transfer of potent biologically active compounds.

In the pharmaceutical industry most solid compounds are crystallized in batch operations, i.e., the crystalline product is isolated at the end of the operating cycle. Many bulk chemicals, such as table sugar, are prepared through continuous processes, in which the product is collected throughout the crystallization cycle. Batch crystallization produces a narrower range of particle size and may afford better control for the efficient crystallization of molecules from complex mixture [14].

Suspensions are stirred during crystallizations on scale. This is in contrast to the technique taught in undergraduate chemistry labs [15]. Without stirring, crystals may form a thick crust at the surface where cooling occurs. This process, called "fouling" [14], can slow further cooling of the batch. Transferring such encrusted product to a filter may be difficult, resulting in reduced yields. Stirring evenly distributes crystals and promotes good crystal growth. Lack of agitation can lead to a problem with crystal slurries of dense solids: once the agitator has stopped and solids settle over the impeller, it may be very difficult to resume agitation.

> **TIP:** As an example of crystallization conditions to avoid, consider a crystallization from diisopropyl ether during storage in a laboratory freezer (−20°C, no agitation) over a weekend!

III.A. Crystallization Theory and Crystallization Pressures

Crystal formation occurs as molecules are regularly arranged within repeating unit cells of the crystalline solid, with compounds unlike those in the unit cell being excluded. Through this ordering and selection process, purification occurs. Excellent texts are available to provide the reader detailed discussions on crystallization [16, 17].

Controlling the crystallization pressure is essential for both purification by crystallization and for efficient operations on scale. By adjusting solution conditions to decrease the solubility of the product within the metastable zone, the desired molecules can be pressured to come out of solution and crystallize (Figure 11.3) [18]. Gradual cooling without seeding leads to one nucleation event and the

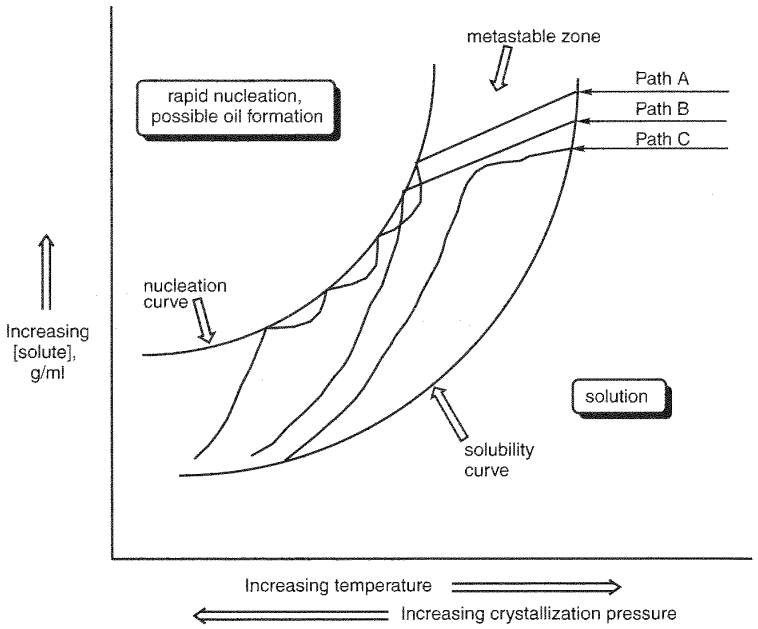
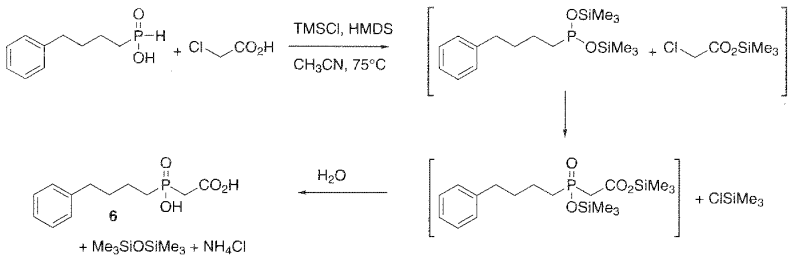


FIGURE 11.3. Effects of Crystallization Pressure

formation of relatively small crystals (Path B). Slowly applying the crystallization pressure (path C) can produce large crystals, depending on the size and number of seeds. If the crystallization pressure is too great (path A), supersaturation occurs, and molecules may be forced out of solution too quickly as small crystalline solids, noncrystalline precipitates, or oils. Sometimes a "cloud point" is noted, from the formation of oil droplets or tiny crystals. While small crystals may be of high quality, extended filtration times may result as the solids begin to plug the pores of filter media. Precipitation rarely brings about significant purification of the product; moreover, precipitates are usually ill-defined small particles that can plug the pores of filter media and halt filtration. The formation of oil droplets may be verified by light microscopy examination. Oils are difficult to displace from a filter cake by washing. Oils tend to foul filters, slowing filtration rates, and they occlude impurities in the isolated product. Conditions that produce oiling and precipitation should be avoided. Seed crystals are added to solutions of compounds adjusted to the metastable conditions in order to prompt good crystal growth.

The importance of avoiding excessive crystallization pressure is shown with the crystallization of the phosphinyl acetic acid **6** (Figure 11.4). In the initial process **6** was crystallized from an aqueous solution, which led to the formation of an oil dispersion, then a crystalline suspension [19]. This process provided high-



MIBK Work-up Crystallization
1. Distill off CH_3CN and $Me_3SiOSiMe_3$
2. Extract concentrate with MIBK (3 portions)
3. Wash combined MIBK extracts with H_2O
4. Concentrate to afford H_2O < 0.5% (by KF)
5. Adjust volume with fresh MIBK
6. Cool to 70°C, seed with **6**
7. Hold 30 min. for crystal growth
8. Cool to 0 - 5°C
9. Hold at 0 - 5°C for ~ 1 hr, filter and wash

FIGURE 11.4. Crystallization of a Phosphinyl Acetic Acid from MIBK

quality material at the beginning of the manufacturing campaign. However, over an extended campaign the process did not prove rugged enough, giving rise to colored product of lower quality that did not convert readily to the subsequent intermediate. The low-quality batches were largely caused by the inability to displace the oil from the wet cake by routine washing. The aqueous crystallization was judged too difficult to control on scale. Crystallization of **6** from MIBK, as outlined in Figure 11.4, however, gave a rugged process. In the MIBK process, crystallization pressures were applied by cooling a concentrated solution of **6**. Thus it was essential to change the solvent in order to control the crystallization pressure, which then allowed facile isolation of high-quality product.

TIP: For reliable crystallization, crystallize near, but not at the cloud point.

There are many ways to apply crystallization pressure. The most common way is to cool a warmed solution (Figure 11.3). Loewenthal's discussion on solvents for laboratory recrystallization may help guide the selection of solvents for scale-up operations [20], and a systematic approach to crystallization by cooling is available [21]. Increasing the concentration of a solution, i.e., decreasing the volume of solvent, is frequently used as a crystallization pressure; slow evaporation is often used to form crystals suitable for single-crystal X-ray analysis [22]. Another common method of applying crystallization pressure is to increase the amount of antisolvent charged (Figure 11.3).

Increasing the ionic strength of a solution also applies crystallization pressure. Figure 11.5 shows the decreasing solubility of O_2 in H_2O as NaCl is added [23]; increasing the ionic strength of a solution similarly decreases the solubility of organic compounds. Controlling the pH of a solution is another way of applying a crystallization pressure, as shown in Figure 11.6. For zwitterionic (internally neutralized) compounds such as amino acids, minimal solubility is found at the isoelectric point. These techniques and combinations of them are used on scale to crystallize products.

As crystallization begins, two processes are underway: crystal nucleation and the growth of existing crystals. With excessive nucleation, many small crystals form. Often a solution is seeded to provide surfaces on which solutes can crystallize, thus encouraging growth of the crystals present and discouraging nucleation. With crystallizations controlled by cooling, seeds may be added to a saturated solution; the solution is held at that temperature for a short time, e.g., 30 minutes, to initiate good crystal growth. (Occasionally, gradual cooling is preferred over a step-wise cooling protocol.) Then the suspension is gradually cooled to an optimal temperature and optionally aged before the product is isolated by filtration and washing. How quickly a slurry can be cooled for rugged crystallization is determined by experimentation; slow cooling was key for the crystallization in Figure 11.11, but was not essential for the example in Figure 11.4. These guidelines are used to prepare relatively large crystals of high quality, with gentle crystallization pressure being applied throughout the process to avoid the formation of small crystals. Guidelines for effecting a thermal crystallization are shown in Table 11.1. Similar considerations apply for crystallizations driven by other crystallization pressures.

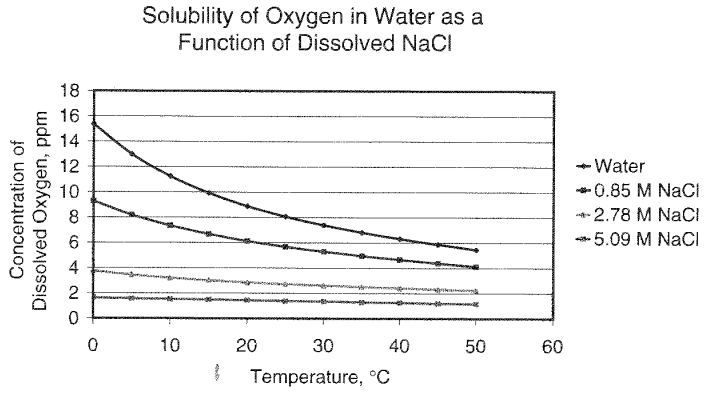


FIGURE 11.5. Solubility of Oxygen in Water as a Function of NaCl Concentration

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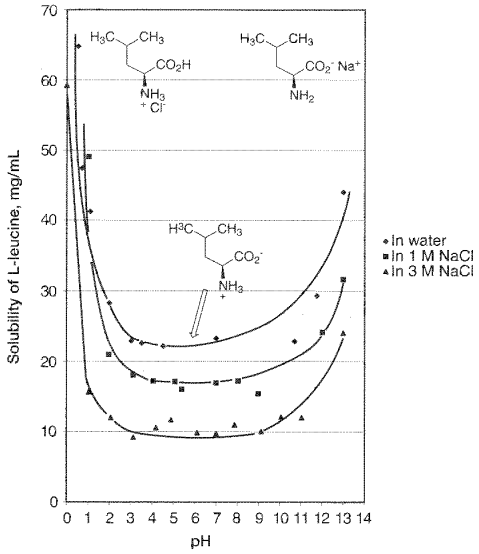


FIGURE 11.6. Solubility of Ionizable Compounds as a Function of pH

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TIPS:

- Seed crystals can be used to define a metastable zone. If seed crystals dissolve after being added to a solution, saturation conditions have not been achieved. If the addition of seeds leads to the formation of an oil dispersion, supersaturation conditions were reached.
- Monitor the aging progress by quantitating the amount of product dissolved in the supernatant. An aliquot can be quickly centrifuged or filtered and a portion of the supernatant or filtrate can be analyzed by HPLC.

Seed crystals may be added to provide a template for formation of the desired crystal form and crystal size. Typical batches of piclamilast (Figure 11.7) from uncontrolled crystallizations were needles in the size range of 50–2000 μm, which needed to be micronized for administration by inhalation. The desired crystals were 100 μm long, with a narrow size distribution. Controlled seeding with 3 wt% of seeds (3 μm long, from micronization) reproducibly gave crystals of the desired size, using the equation in Figure 11.7 [24].

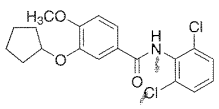
TABLE 11.1. Guidelines for Effecting a Thermally Controlled Crystallization

Ideal characteristic	Problems if ideal characteristic not achieved / Approaches to address problem on scale
Solvent: nontoxic, safe for scale-up, nonreactive with product	Yields will decrease on scale if reactive solvent is used; safety and toxicity concerns prompt additional handling considerations and testing. **Solution**: develop process with another solvent.
Product solubility in solvent: 10–25% in hot solvent, 0.05–2.5% in cold solvent[a]	With higher solubilities in cold solvent, greater losses to mother liquor and reduced isolated yields. **Solution**: add small amounts of antisolvent as cosolvent, e.g., add H_2O to EtOH recrystallization; or substitute a similar solvent, e.g., *i*PrOH for EtOH.
Seeding produces desired crystals.	Uncontrolled crystallization may produce small crystals, perhaps low quality product. **Solution**: investigate seeding in metastable zone. Examination by optical microscope may be helpful. To control crystal growth it may be necessary to remove dust from seed crystals by reslurrying.[b]
Cooling produces desired crystal form, purity, and particle size.	Rapid cooling may lead to formation of kinetic polymorph, small crystals, low-quality product. **Solution**: controlled temperature gradient could be step-wise or ramped cooling, or combination.
Consistent yield is obtained, with majority of product isolated in one crop.	Inconsistent yields may produce suboptimal results on scale. Need to isolate a second crop reduces productivity. **Solution**: examine effect of temperature on solubility profile: isolation at colder temperatures e.g., −30°C, may be practical[c]; determine if product is lost to mother liquor or wash filtrates; check for impurity formation during crystallization; change crystallization solvent.
Consistent quality of product obtained.	Inconsistent yields may produce suboptimal results on scale. **Solution**: check for impurity formation during crystallization; optimize crystallization and/or washing protocol; change crystallization solvent.

[a]For a more detailed approach to crystallization, see Thompson, M. D.; Authelin, R.-R., in *Process Chemistry in the Pharmaceutical Industry;* Gadamasetti, K. G., Ed.; Marcel Dekker: New York; 1999, pp. 371–388.

[b]Bennett, M. C.; Fentiman, Y. L., "Growth Rate of Sucrose Crystals Related to Krypton Surface of Seeds." In *Industrial Crystallization;* The Institute of Chemical Engineers: London, U.K.; 1969, pp. 217–226.

[c]For example, see Mauragis, M. A.; Veley, M. F.; Lipton, M. F., "Evaluation and Scale-Up of the Synthesis of the Pyrrolopyrimidines U-101033E and U-104067E." *Org. Process Res. Dev.* **1997**, *1*, 39–44.



Piclamilast[d]

$$\frac{\text{mass of seeds}}{\text{mass of crystals}} = \left(\frac{\text{size of seeds}}{\text{size of crystals}}\right)^{i}$$

	i
needles	1
plates	2
cubes or spheres	3

FIGURE 11.7. Piclamilast and Equation Used for Controlled Seeding

TIP: Seeding may be used at the beginning of a scale-up campaign but may not be necessary in the later stages of the campaign. Adventitious seeding may occur by crystals present in the processing equipment.

Crystallization pressure may be applied by diluting a solution of the product with an antisolvent. Antisolvents are generally selected from those solvents that are miscible with the solvent. Water may be a good antisolvent for compounds readily soluble in EtOH; heptane may be a good solvent for compounds readily soluble in EtOAc. Supersaturation can be quickly reached when an antisolvent is added to a solution, leading to the formation of oils and poor crystallization. Oil formation may be noted at the entry point of the antisolvent to the solution and can be minimized by adding antisolvents slowly.

TIPS:

- Addition of antisolvent often leads to transient oiling at the point of addition. Add slowly with good agitation to prevent localized oiling.
- Inverse addition, i.e., adding a solution of the product to the antisolvent, may be necessary in some cases for preparing acceptable crystals. Rapid crystallization in the antisolvent may eliminate the tendency to oil. Control of crystallization may be more difficult to effect with this inverse addition.

Dissolving a compound by heating a solution containing an antisolvent may not be straightforward. Warming a suspension of product in solvent/antisolvent may not lead to dissolution. If dissolution is caused by warming, it is prudent to select solvent and antisolvent with similar boiling points to avoid preferential loss of one solvent with heating and difficulties on scale.

In the isolation of water-soluble compounds, small amounts of water can dissolve significant amounts of material and have an adverse effect on processing. The pyridinyl carboxylic acid **7** was isolated after adjusting the pH to the isoelectric point, at which the zwitterion displayed minimal solubility (Figure 11.8) [25]. Water was removed by azeotropic distillation to facilitate the isolation. In the subsequent resolution of **7** by formation of the diastereomeric quinine salts, water was also found to be deleterious, as hydrated diastereomeric salts formed and gave no resolution. The selective crystallization of the desired salt **8** was driven by the formation of the *i*PrOH solvate, which crystallized faster than the undesired diastereomeric salt.

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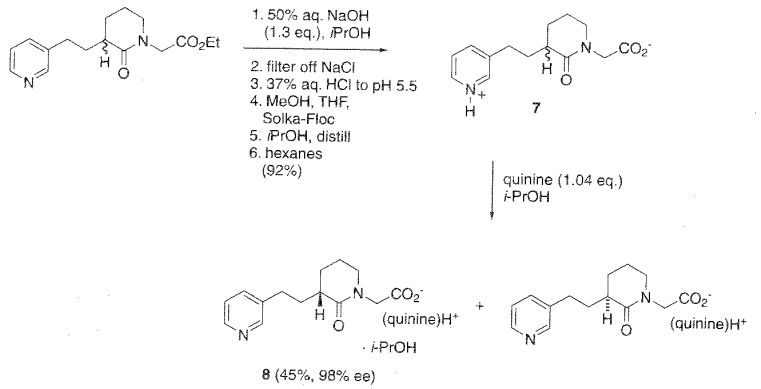


FIGURE 11.8. Isolation of a Water-Soluble Zwitterion and a Quinine Salt

Ionic strength and pH were used as crystallization pressures in the isolation of captopril, another water-soluble compound (Figure 11.9) [26]. When hydrolyses were conducted in 10*N* NaOH, the high ionic strength of the medium minimized the amount of O_2 that could dissolve, almost eliminating formation of the disulfide **9**. The subsequent addition of concentrated HCl led to a high concentration of NaCl, and rapid acidification led to oiling of the product. A process was developed to control the crystallization of captopril by gradually adding the concentrated HCl, and cooling the suspension to maximize the yield.

Particle size and particle size distribution can be controlled to a great extent by crystallization, using the techniques in Table 11.2. Small particles are filtered and washed during isolation more slowly than large crystals. Through gradual cooling, very small crystals (fines) dissolve and crystallize as part of the existing, larger crystals. This process is termed *Ostwald ripening*. By controlling cooling and other crystallization pressures, it is possible to control crystal size and quality.

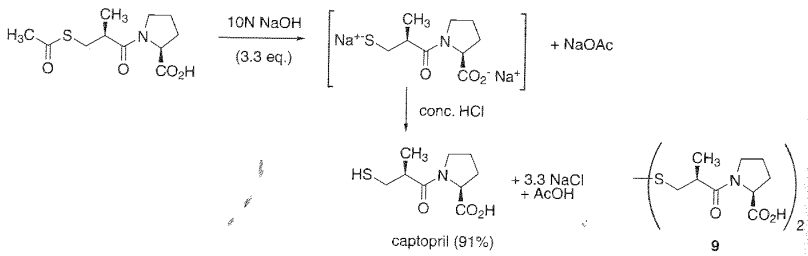


FIGURE 11.9. Isolation of Captopril from a Highly Ionic Medium

TABLE 11.2. Options for Controlling Particle Size for API

Option	Comment
Slow cooling & aging	Can lead to large crystals with relatively narrow particle size distribution[a]
Fast cooling	Can lead to small crystals
Rapid agitation	Can lead to small crystals, by dispersing nuclei during crystallization or shearing crystals
Impinging jet	Can produce small crystals with narrow range of particle size[b,c]
Spray drying	Can produce small crystals or amorphous solids

[a]Bennett, R. C., "Making Big Crystals." *Chem. Eng.* **1997**, *103*(10), 90.

[b]Midler, M., Jr.; Paul, E. L.; Whittington, E. F.; Futran, M.; Liu, P. D.; Hsu, J.; Pan S. H., "Crystallization Method to Improve Crystal Structure and Size." U.S. 5,314,506, 1994 (to Merck); Dauer, R.; DiMechele, L.; Futran, M.; Kieczykowski, G. R., "Dual Jet Crystallizer Apparatus." U.S. 5,578,279, 1996 (to Merck).

[c]Kirwan, D. J.; Orella, C. J., "Crystallization of Biological Molecules." In *Handbook of Industrial Crystallization*; Myerson, A. S., Ed.; Butterworth-Heinemann: Boston; 1993, p. 234.

Impinging jets, routinely used in the plastics industry, have been used to crystallize small particles with a narrow particle size distribution [27, 28]. The impinging jet crystallizer is a cylindrical chamber with two spray nozzles that enter from opposite sides of the chamber. A solution of the material to be crystallized is fed into one nozzle, and the agent to induce crystallization is fed into the other nozzle. The smaller the nozzle apertures, the faster the velocity of the solutions into the chamber, and the faster the two streams mix and reach a uniform environment. In this manner a stream of finasteride (Figure 11.10) in AcOH and water was fed into one nozzle, and a stream of water (the crystallizing agent) was fed into the other nozzle. Crystallized finasteride had an average particle size of 10–15 μm.

Spray dryers can produce small crystals through the rapid evaporation of solvent. This operation can lead to the formation of amorphous solids. Spray drying of solutions of abecarnil (see Figure 12.3) produced the least stable polymorph, the B-form crystals [29]. The formation of this polymorph was attributed to the high degree of supersaturation reached during drying.

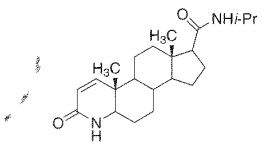


FIGURE 11.10. Finasteride

TIP: Recrystallizing a compound several times, especially from the same solvent, does not guarantee the preparation of analytically pure material. Ineffective recrystallizations may only partially reduce impurity levels. The crystallized product may also be solvated or hydrated. Analyze products by at least two independent methods, e.g., elemental analysis [30], spectroscopy, and HPLC, in order to establish purities.

III.B. Classification of Solids: Morphic States

Solid compounds can exist in four morphic states: polymorphs, psuedopolymorphs (solvates), amorphous, and desolvated solvates [31–35]. Crystals may diffract light under an optical microscope and usually exhibit narrow melting point ranges. Polymorphs are crystals of the same substance that differ only in the arrangement, not the composition, of molecules in the unit cells. Psuedopolymorphs are crystals of the desired material that include a fixed molar ratio of solvents in the unit cell; they are more appropriately termed solvates. When a molecule is solvated in the unit cell by H_2O, the crystal form is termed a hydrate. Desolvated solids may form by loss of solvents through heating under vacuum or through exposure to air [36]. Usually some of the crystal structure remains after loss of the solvent; desolvated solvates often display low bulk density. Amorphous materials have no significant order on a molecular level and do not exhibit discrete melting ranges.

Differences in morphic states can affect stability, solubility, crystal morphology, hydration, and calorimetric behavior. The ability to prepare a desired polymorph might be necessary for the formulation and pharmaceutical acceptability of a compound. The solubility and hence bioavailability of some drugs is affected by polymorphism [34, 35]. When crystal morphology is changed, ease of filtration and drying on scale might also be changed. Investigators may resort to extreme measures in order to prepare a desired polymorph [37]. The importance of understanding how to reliably prepare a desired polymorph may not be appreciated until the adverse effects of an inadvertently formed polymorph are encountered.

Methods to distinguish polymorphs are shown in Table 11.3. Byrn [31] suggests that a combination of methods be used to characterize critical solids: two for identifying the phase, or morphic state, and two for securing the composition and stoichiometry.

Polymorphs and solvates often form. In the case of multiple polymorphs, the thermodynamically least stable polymorph often forms first during a crystallization, as is the case with abecarnil [29]. Usually the final product is most thoroughly investigated, due to the processing considerations outlined earlier. Polymorphism

TABLE 11.3. Techniques to Distinguish Morphic Forms

Technique	Comments[a,b,c,d,e]
X-ray powder diffraction	More highly organized crystals afford more intense diffraction peaks. Polymorphs can be distinguished, depending on crystal lattice differences. Detection limit 5–15% for minor polymorph.[a]
DSC, melting point	DSC methods may be developed to determine crystal purities, and transformation of one polymorph to another during heating.
Thermogravimetric analysis (TGA)	Solvates, hydrates. Can be used to determine extent of solvation.
Microscopy	Polymorphs, pseudo polymorphs, and amorphous solids can be distinguished by morphology.
Infrared spectroscopy	Diffuse reflectance analysis eliminates the mechanical stress of preparing a KBr pellet, and may permit identification of more fragile crystal forms.[d,f]
Solid-State NMR	Specialized technique, and instruments not widely available[g]
Solution NMR	Can be used to determine solvents in pseudopolymorphs
Gas chromatography	Can be used to determine solvents in pseudopolymorphs
Elemental analysis	Solvates, hydrates
Karl Fischer titration	Hydrates, extent of hydration
Powder density	Desolvated solvates

[a]Byrn, S. Pfeiffer, R.; Ganey, M.; Hoiberg, C.; Poochikian, G., "Pharmaceutical Solids: A Stategic Approach to Regulatory Considerations." *Pharm. Res.* **1995,** *12,* 945.

[b]*Polymorphisim in Pharmaceutical Solids;* Brittain, H. G., Ed.; Marcel Dekker: New York; 1999.

[c]Brittain, H. G., "Spectral Methods for the Characterization of Polymorphs and Solids." *J. Pharm. Sci.* **1997**, *86,* 405.

[d]Threlfall, T. L., "Analysis of Organic Polymorphs. A Review." *Analyst* **1995**, *120,* 2435.

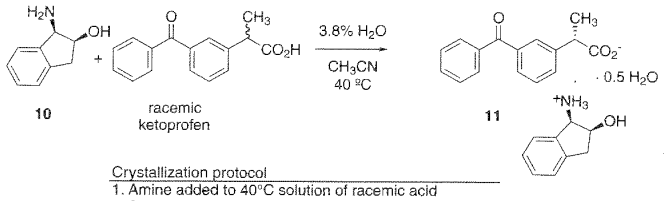
[e]Haleblian, J.; McCrone, W., "Pharmaceutical Applications of Polymorphism." *J. Pharm. Sci.* **1969**, *58,* 911.

[f]Culler, S. R., "Diffuse Reflectance Infrared Spectroscopy: Sampling Techniques for Qualitative/Quantitative Analysis of Solids." In *Polymorphism in Pharmaceutical Solids;* Brittain, H. G., Ed.; Marcel Dekker: New York; 1999, pp. 93.

[g]Bugay, D. E., "Solid-state nuclear magnetic resonance spectroscopy: Theory and pharmaceutical applications." *Pharm. Res.* **1993**, *10,* 317.

for final products is more frequently documented. Further details may be found in Chapter 12.

To control processing in the formation of hydrates it is often necessary to control the amount of water present during the crystallization. In the process to resolve ketoprofen (Figure 11.11), 3.8% of water was charged to the reactor before the resolving agent **10** was added. Without H_2O present, salt formation began as **10** was being added to the solution of racemic ketoprofen. If more than 3.8% H_2O was charged, the onset of crystallization was delayed. The desired salt **11** was found to crystallize with about 0.5 equivalents of water, and the diastereomeric salt of **10** with (*R*)-ketoprofen was found to contain no H_2O in the crystals [38].



Crystallization protocol
1. Amine added to 40°C solution of racemic acid
2. Seeded with diastereomeric salt, held at 40°C / 30 min.
3. Cooled over 4 h to 5°C.
4. Held at 5°C / 30 min., filtered and washed

FIGURE 11.11. Crystallization of an (S)-Ketoprofen Salt as the Hemihydrate

III.C. Salt Selection

Salt formation may be key for the efficient purification of ionizable compounds. Various salts can display different solubilities and tendencies to crystallize and might possess physicochemical differences that can be exploited for convenient processing on scale. Salt forms of drug candidates are selected for desired stability, bioavailability, and formulation characteristics (Chapter 12). A few trends for salt selection are shown in Table 11.4.

Some examples of the practical solubilities of salts of acidic compounds are shown in Figure 11.12. In the development of a COX-II inhibitor, Fujisawa workers took advantage of the different solubilities of the potassium and sodium

TABLE 11.4. Some Counterion Selections for Salt Formation

	Comments
Cations, for crystallizing acidic compounds	
Na^+	may crystallize from H_2O
K^+	may be water-soluble
$(n\text{Bu})_4N^+$	may extract into and crystallize from organic solvents
Ca(II)	crystallize from H_2O. Usually low solubility, small particles
Ba(II), Mg(II)	crystallize from H_2O. Very low solubility, small particles, may be hard to filter.
Acids, for crystallizing amines	
CH_3CO_2H	nontoxic
Oxalic	toxic, inappropriate for API
Succinic	nontoxic
Maleic	beware of impurities from Michael addition
Fumaric	beware of impurities from Michael addition
Citric	nontoxic; relatively high molecular weight may increase processing burden relative to smaller acids
Methanesulfonic	pharmaceutically acceptable for API

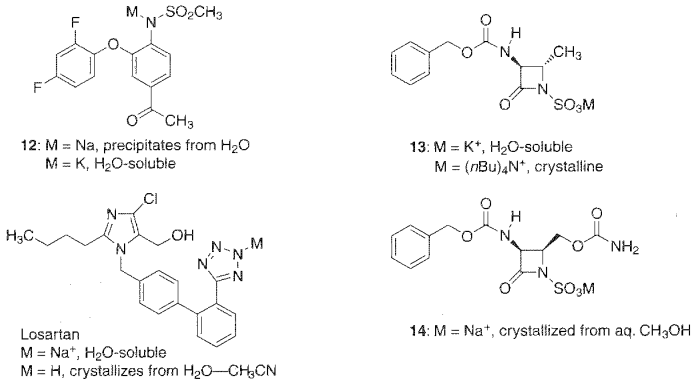


FIGURE 11.12. Practical Solubility of Selected Salts

salts of an aryl sulfonamide **12** [39]. The crude sulfonamide was precipitated as the sodium salt from water (for good recovery, five equivalents of NaOH were used to salt out this intermediate), and after acidification the unionized sulfonamide was extracted into CH_2Cl_2. Impurities were removed by an aqueous $NaHCO_3$ wash, and the product was extracted into aqueous KOH for charcoal treatment. Under these conditions the potassium salt does not precipitate. After acidification the product was isolated from *i*-PrOH/H_2O. The substituted sulfamic acid **13** was found to be water-soluble as the potassium salt, and the tetrabutylammonium salt could be extracted into and crystallized from organic solvents [40]. The similar sodium sulfamate **14** was crystallized from aqueous methanol [41]. Losartan was soluble in water as the sodium salt and after acidification was crystallized from H_2O-CH_3CN [42]. These examples show that the different solubilities of acidic compounds and the corresponding salts can be exploited for convenient isolation.

Fumaric acid (**15**) and maleic acid (**16**) have been used extensively to prepare salts of drug substances, but chemists should be aware of the reactivity of these compounds toward amines. Michael reactions are expected on α,β-unsaturated esters, but not generally expected for α,β-unsaturated acids such as **15** and **16**. L-Aspartic acid is prepared commercially by the enzyme-mediated addition of ammonia to **15** (Figure 11.13a) [43]. During an accelerated stress study of the drug product from BMS-180048 fumarate salt (**17**), the major impurity was identified as the fumarate adduct **18** (Figure 11.13b) [44]. Maleic acid was isomerized to **15** upon heating 4,4′-bipyridine in DMF or DMSO (Figure 11.13c) [45]. These data suggest that an equilibrium may exist for **15** and **16** in the presence of amines, especially in the presence of polar solvents like water (Figure 11.13d). Equilibrium of drug substance as salts with **15** or **16** might lead to instability of

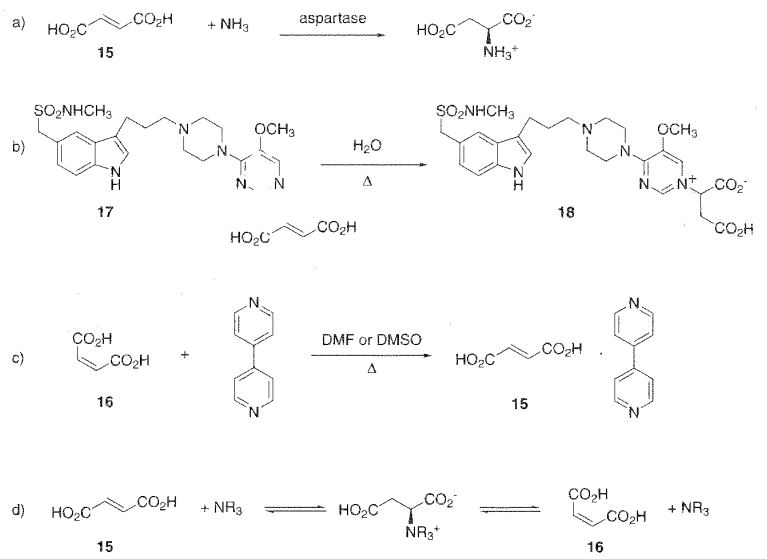


FIGURE 11.13. Reactions of Fumaric and Maleic Acids with Amines

the drug substance. Other acids, such as succinic acid, might prove more useful in the preparation of stable drug products.

The crystallinity of compounds often is not as expected, and there is no substitute for actually crystallizing a compound. In the generation of the glycine derivative **19** (Figure 11.14), the secondary amine salt **20** crystallizes and is removed from processing by a simple filtration [46]. The more basic tertiary amine **19** might be expected to bind the HBr and crystallize as the salt, but under these conditions the excess secondary amine crystallizes preferentially as the HBr salt. Predictions of crystallizing ability should always defer to experimental data.

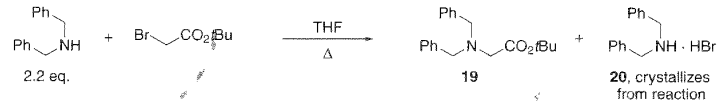


FIGURE 11.14. Crystallization of a Secondary Amine Hydrobromide in the Presence of a Tertiary Amine

III.D. Predicting the Ability to Scale Up a Crystallization Process by Lab Examination

For ease of operations, desirable physical characteristics of crystals can be identified by considering the steps necessary for transferring the crystallized product. Slurries must readily flow from the crystallizer to the filter. Relatively sturdy crystals can be recovered by filtration, using a broad selection of filters. Fragile crystals, which may collapse upon the compression of filtration and blind the filter, can be readily isolated from a more limited selection of filters. Small, electrostatic crystals may be difficult to transfer from the filter to the dryer and from the dryer to the storage containers. Guidelines to assess crystal characteristics and possible actions for the less-than-ideal cases are shown in Table 11.5. Scale-up operations may need to be discussed with others in order to select the optimal equipment for filtration and isolation.

III.E. Washing and Drying Solid Products

Washing a wet cake and drying it are operations that apply to solid products from both crystallization and reslurry operations. There are two purposes in applying a wash to a product wet cake. The most common is to displace impurities adsorbed as mother liquor to the surfaces of solids. The composition of the wash solvent(s) is often similar to that of the solvent used for crystallization in order to avoid precipitating impurities onto the solvent-wet cake or dissolving the product. If air or inert gases such as N_2 are drawn through the wet cake extensively, evaporation of the solvent may deposit impurities formerly dissolved in the mother liquor onto the product crystals. Removing such adsorbed impurities requires extended contact of the wash with the crystals in order to first dissolve and then displace the impurities. Hence cakes should not be allowed to dry out before the wash is applied. A slow, even wash application is important in displacing mother liquor. The ideal wash volume is 1–2 volumes of wet cake. Usually the temperature of the wash is that of the slurry as it was being applied to the filter, although a wash of another temperature can also be applied. The efficiency of the washing operation should be monitored by IPC (Chapter 7). Guidelines for washing a product are shown in Table 11.6.

The second reason for applying a wash to a wet cake is to displace the solvent with another solvent, usually a lower-boiling solvent to ease drying of the product. In this case it is essential that the solvent applied dissolve as little product as possible. Temperature selection may be important.

The product is usually removed from the filter when the exit rate of wash is judged to be sufficiently slow, or when the amount of residual solvents in the solvent-wet product has decreased to the desired level. The filter cake is

Sun Ex. 1022

TABLE 11.5. Laboratory Considerations to Assess the Ability to Scale Up a Crystallization Process

Ideal characteristic	Problems if ideal characteristic is not achieved / Approaches to address problem on scale
Slurry can be readily suspended by agitation.	Dense solids may be difficult to remove completely from the bottom of crystallizer, complicating transfer to filter. Thixotropic slurries are very difficult to transfer. **Solution**: increase agitation to suspend solids, or add filtrates to suspend solids left in dish of crystallizer. Dilute slurry with additional solvent. Or redevelop process.
No oil seen in slurry (microscopic analysis).	Oil may plug filters, slow operations, and afford impure product. **Solution**: develop process using gentler crystallization pressure.
Slurry transfers readily from the flask. When poured, very little cakes to wall.	On scale, difficult to dislodge solids by mechanical means. **Solution**: spray with wash or filtrates to dislodge.
Mother liquor or wash readily suspends remaining material for transfer to the filter.	Difficult to mechanically remove solids from the dish of a vessel. **Solution**: spray with wash or filtrates to dislodge.
Good filtration rate: almost complete removal of mother liquor from cake in Buchner funnel after no more than ca. 5 min. (For a 500 ml slurry, producing a filter cake about 4 cm high.)	Filtrations that are slow in the lab will be much slower on scale. **Solution**: grow larger crystals through better crystallization control. Or use filters with larger surface area, e.g., centrifuge or filter press.
Little or no compression of solids as the solvent is removed by filtration.	If appreciable compression is seen, filtrations may slow as cake thickness increases. **Solution**: use filters with large surface areas, e.g., filter press. Load centrifuge to small cake thickness.
Filter cake does not crack or pull away from the wall of the funnel.	Washing will be less effective for cakes that crack and pull away from the filter **Solution**: load filter gradually and evenly.
Mother liquor can be recirculated through cake.	Fines that pass filter reduce yields. **Solution**: recycle filtrate through filter cake, collect fines on a second filter, or use filtrates in subsequent batch.
Washing the cake with solvent removes impurities, and does not disrupt surface or edges of cake.	Excess solvents may be needed to displace impurities. **Solution**: redevelop wash protocol. Monitor by IPC.
Cake is readily transferred from funnel to dryer.	Powdery, electrostatic, or solvent-wet cakes problematic. **Solution**: use special handling, or redevelop process if necessary.
Product does not melt down in dryer or cause fires due to residual flammable solvent on wet cake.	Liquified products are difficult to handle, may decompose. **Solution**: correlate residual solvent content ("wetness") and dryer temperature to avoid melt-down.
Product is not hygroscopic.	Hygroscopic solids will gain weight and may be difficult to transfer and store. **Solution**: transfer quickly to storage containers; monitor H_2O uptake, perhaps re-equilibrate; redevelop process.

TABLE 11.6. Guidelines for Washing a Wet Cake on the Filter

Ideal characteristic	Problems if ideal characteristic is not achieved / Approaches to address problem on scale
Wash is applied while crystals are still wet with mother liquor.	If air or gases are drawn through filter cake, evaporation of solvent may precipitate impurities onto crystals. **Solution**: do not allow filtration to dry filter cake before applying wash.
Wash solvent(s) dissolves impurities.	If wash does not dissolve impurities, wash may precipitate impurities onto crystals. **Solution**: select another wash solvent(s). Monitor wash progress with IPC.
Wash solvent(s) dissolves no product on filter.	Isolated yields decrease if wash dissolves product; with partial dissolution, good crystallinity and ability to wash cake thoroughly are lost. **Solution**: select another wash solvent(s); add small amount of antisolvent to wash; lower wash temperature
Wash volume is 1–2 cake volumes, applied in one or two portions.	Decreased productivity with larger volumes of cake wash. **Solution**: wash with increased volumes as needed to remove impurities.
Apply washes evenly.	Uneven wash application will result in decreased efficiency for removing impurities from batch. **Solution**: slow filtration rate to allow wash to evenly spread over cake; smooth filter cake to remove any cracks and depressions from applying wash.

transferred to the dryer for removal of residual solvent, often under heat. Knowing the interaction of residual solvent content and dryer temperature is essential to prevent melt-down in the dryer.

> **TIP:** To determine the melt-down temperature for a wet cake, place a small amount of the wet cake in a melting point tube and heat gradually.

IV. PURIFICATION BY RESLURRYING

Reslurrying a solid can sometimes be an attractive alternative to recrystallization. Reslurrying is analogous to trituration. Since attention does not need to be paid to dissolving and recrystallizing the product, reslurrying is less labor-intensive than recrystallization. Reslurrying can remove impurities adsorbed to the surface of crystals, and after suitable contact with solvent the product is isolated by filtration. For example, excess *p*-nitrobenzyl bromide was removed from **21** by

Sun Ex. 1022

reslurrying a residue product at room temperature (Figure 11.15) [47]. A crystal polymorph can change through reslurrying, as was found by reslurrying dirithromycin at 70°C in water (Figure 11.15) [36]. The solids from reslurrying are washed and dried as described in Section III.E.

TIPS:

- Reslurrying can sometimes be avoided by simply changing the work-up or crystallization procedures. If reslurrying removes water-soluble impurities, including an aqueous wash during the work-up may eliminate the need to reslurry the product. Alternatively, the product may be crystallized from solvents that dissolve impurities that would otherwise be removed by reslurrying.
- Recrystallization from biphasic solvent combinations may be effective.

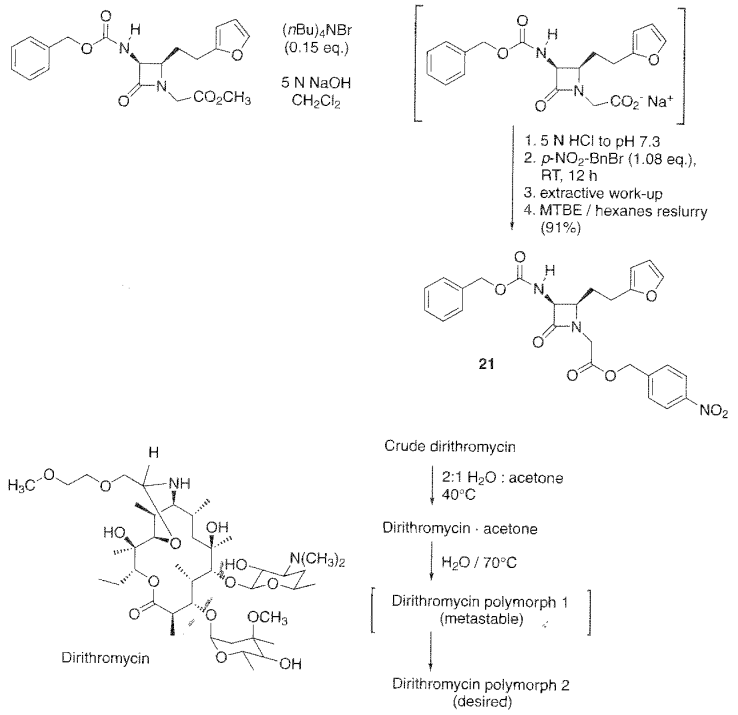


FIGURE 11.15. Purification by Reslurrying

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CHAPTER 12

Final Product Form and Impurity Considerations

I. INTRODUCTION

The greatest financial impact on the cost of a drug substance is often found in the final process of preparing it. Product yield, physical characteristics, and chemical purity and impurities are very important for those who manufacture and formulate the active ingredient into the drug product, or dosage form. Processes to control the preparation of the drug substance and drug product must be disclosed to the FDA as part of the NDA. If production batches do not meet the purity and impurity specifications filed, the manufacturer will attempt to upgrade material by rework procedures. All rework procedures are costly because as they consume drug substance and resources and prevent the preparation of other batches of drug substance. The formulation of a drug substance is keyed to critical physical characteristics, and significant changes in these characteristics may delay formulation and hence distribution of drug product to customers. Impurities that impart unacceptable taste or smell to the formulated product may lead to loss of sales

revenues. Extra attention must be paid to develop reliable processes to prepare the final product.

The majority of medicines today are formulated as tablets [1]. Tablets are formulated rapidly and economically, and they have high patience compliance. Also, many compounds, such as aspirin, degrade rapidly in solution and are formulated in solid dosages to increase stability [2]. Drug substances that are oils, liquids, and solids may be formulated into capsules, tablets, lyophiles, creams, or microsuspensions. Administration may be through ingestion, injection, topical application, inhalation, and other routes. The reader may consult other texts for discussion of formulation options [1, 3]. Formulations are selected for stability and the ability to best deliver the active agent to the affected area of the patient or consumer.

To understand important physicochemical considerations for drug substances, a brief description of the tabletting process follows. The drug substance is mixed with various excipients (nontherapeutic ingredients) to prepare a powder blend that is compressed into tablets. Often the drug substance is mixed with fillers, which are added to provide tablets of acceptable size and weight, and tablet disintegrating agents. Then liquid binders are added, and the blended, wet mass is granulated and dried. This process of "wet granulation" produces granules that flow readily and are readily compressed into tablets. After a sieving or screening process to produce the desired size, the granules are mixed with lubricants and any remaining tablet disintegrants. Then the granules are allowed to flow from hoppers into tabletting dyes. There the mixture is compressed by two punches and ejected from the dye by the bottom punch [1].

For efficient manufacturing of a dosage form, consistent distribution of the drug substance at the required concentration is essential. To ensure drug potency there must be tightly controlled distribution within an individual dosage unit, within portions of a pharmaceutical batch to prepare a dosage form, and from batch to batch. Thorough mixing of solids is necessary for even distribution of drug substance within tablets and within other dosage forms.

With final products, special handling considerations are necessary to ensure that the impurity profiles and impurity levels are consistent. Nonclinical supplies, such as material prepared for toxicological studies, are usually made under conditions of good laboratory practice (GLP). GLP is established by federal regulations to control the quality of product based on established protocols. Good manufacturing practice (GMP) and current good manufacturing practice (cGMP) are guidelines to ensure consistent quality and integrity of pharmaceutical products. Though sometimes dreaded, in the final analysis cGMP is simply good science. Regulations for GLP and cGMP are published in the Code of Federal Regulations and may also be found through the FDA web page [4]. Developments for GLP and cGMP change rapidly and will not be discussed here; the reader is referred to the excellent text by Repic for discussion on the approach to GLP and cGMP [5]. The FDA is the best source of details.

II. THE IMPORTANCE OF SOLID STATE CHARACTERISTICS

The extended stability of a dosage form is a key consideration in formulating a drug substance. Studies have shown that for analogous compounds with similar solution stability, the rate of decomposition in the solid state increased as the melting point decreased [6]. Molecules that are part of a strong crystalline lattice (and which display a high melting point) are effectively immobile, minimizing interactions with reactive molecules and functional groups. The degradation of solid materials is faster for impure crystals and those with mechanical defects [7].

Not all drug substances are prepared as crystalline solids. Amorphous solids, such as nelfinavir mesylate [8], often display increased solubility and bioavailability [7]. Lyophilized powders, which are prepared by freeze-drying solutions of the drug substance, may be crystalline or amorphous before they are reconstituted by adding water [7]. Whether the form is crystalline or amorphous, the goal is to prepare medicines that offer the most benefit to the consumer.

Most of the drug substances marketed in solid dosage forms display melting points above 150°C [9]. Compounds melting below 100°C may cause tabletting difficulties, as the compression required typically produces localized temperature increases of 3–30°C [10]. If the formulation mixture sticks to the punches and dyes of the tabletting presses, formulations will be slowed. Low-melting compounds may be formulated in capsules to avoid difficulties in formulating as tablets. In large-dosage formulation of tablets, abrasive compounds with high melting points may not compact readily during tabletting, and plasiticizers, e.g., avicel, may be added [11]. If the crystalline lattice is too strong, poor solubility and hence poor bioavailability may result. (The latter consideration may not apply to salts, which would be expected to have better solubility in aqueous systems than would high-melting non-ionic compounds.) Formulating a physiologically active compound that melts below 60°C may be viewed as a challenge. Any compound that melts below 60°C has limited options for formulation and may demonstrate less-than-desired stability. For rapid development, drug candidates should display melting points above 60°C. The melting point of a potential drug candidate should be one of the first physicochemical characteristics considered.

To provide material of consistent quality for formulation, it is necessary to study the solid state properties of the drug substance. Solid state properties can affect the performance of the dosage form, which includes bioavailability and stability [12]. The FDA requires definitive characterization of drug substance as part of an NDA to ensure continued the substance's potency and purity. Detailed requirements for such characterization have not been established: The FDA's approach is that general guidelines may not be appropriate to characterize each unique, individual drug. Every pharmaceutical company filing a new drug entity must convince the FDA of having made the best effort possible.

The physical characteristics of a solid drug substance can have profound effects on the reproducibility of formulation. Crystal morphology can affect the flowability and mixability of the drug substance (and all excipients). For instance, needle-like crystals would be expected to display radically different behavior than cube-like crystals. Consistent crystal habit (the external shape of the crystal), particle size, and particle size distribution are essential for reproducible formulation. Water may be added during the granulation of solids as part of "wet granulation," and the presence of water and any heat derived from mixing may lead to a change in hydration state or crystal morphology. Such changes may not cause formulation problems if the changes in hydration state or crystal morphology occur consistently throughout the formulation. If the drug substance tends to hydrate during formulation, the hydrated active ingredient may be the preferred form.

Crystal morphology can be controlled during crystallization. For example, single-crystal X-ray studies showed that acetanilide molecules were arranged in a linear chain of hydrogen-bonded units that were aligned with the crystal needle axis (Figure 12.1). This hydrogen bonding is typical of secondary amides. Crystallization of acetanilide from non-hydrogen-bonding solvents, e.g., CCl_4 or benzene, produced long needles of acetanilide. Crystallization of acetanilide from solvents that are proton acceptors or proton donors was expected to disrupt intermolecular hydrogen bonding and limit the crystal growth along the long axis; crystallization from either acetone or MeOH produced short, rod-like crystals [13]. Impurities present with the product may lead to selective formation of polymorphs [14]. Crystal engineering may be used to design crystals [15].

Drug products are frequently isolated as polymorphs or solvates. One solvent-free crystalline form and three solvates were noted for aztreonam [16]. Dirithromycin has been crystallized as two anhydrous polymorphs, nine solvates [17], and "forms solvates with nearly all of the pharmaceutically acceptable solvents" [18]. Lorazepam forms multiple polymorphs and solvates [19]. At least 14 polymorphs and solvates were found for an organic dye complex, and the more effort put into preferentially growing a crystal form, the more polymorphs and psuedopolymorphs were uncovered [13]. A second polymorph of natamycin was observed 35 years after the discovery of this natural product [20]. As more batches of an intermediate or final product are prepared, the greater the chances that a new polymorph or solvate will be formed. Crystallization conditions must be

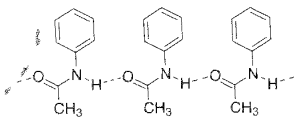


FIGURE 12.1. Hydrogen-Bonding Along the Long Axis of Acetanilide Crystals

thoroughly understood to ensure the continued preparation of a desired polymorph or solvate (see Chapter 11).

A polymorphic form with a higher melting point may display poor bioavailability [21], due to the difficulty in overcoming the high lattice energy for the process of dissolution in the body; however, relatively few marketed drugs display major differences in bioavailability due to polymorphs [22]. With regard to selecting a polymorph, stability, ease of chemical preparation, ease of formulation, and bioavailability are primary concerns. Usually these factors lead to the selection of the thermodynamic polymorph as the preferred form of the drug substance.

After formulation, changes in the morphic state of an active ingredient can have a profound effect on the dosage form. The gradual formation of a thermodynamically favored polymorph led to tablet disintegration [23]; gradual hydration could also induce transition to another polymorph and create similar difficulties with the dosage form.

To address these important solid-state issues, many pharmaceutical companies have an experienced group of "crystal engineers" to develop suitable forms of drug candidates and to develop reliable processes to prepare these materials. This "final form team" usually is involved once a potential drug candidate has been selected and before the preparation of the first batches needed for toxicological studies.

II.A. Stability Testing

Stability testing is required by the FDA as part of the NDA for bulk drug substance and drug product. The purpose of stability testing is to establish a shelf life for the drug product, the period during which it is therapeutically useful. The decrease in potency must not exceed 10% over the shelf life [24]. A preferred shelf life is two years [24, 25].

Stability testing establishes how the quality of the drug substance varies with time, as influenced by temperature, humidity, and light. The duration and conditions of the studies should cover the time expected for storage, shipment, and use of the drug substance and drug product. Decomposition may be slow at room temperature, so samples may be subjected to higher temperatures in order to predict long-term stability [25]. Stability studies also generate degradents, which may be identified as impurities in the drug substance. Suggested FDA conditions for stability testing are shown in Table 12.1.

Bulk stability testing can be performed early in the development of a potential drug substance in order to foresee any stability difficulties. However, the interaction of the formulated drug substance with excipients may also affect the stability of the drug product. Therefore, good stability of bulk drug substance does not guarantee good stability of the drug product.

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TABLE 12.1. Stability Conditions for Testing Bulk Drug Substance

	Conditions	Minimum time period at submission
Long-term testing	25 ± 2°C/60 ± 5% RH	12 months
Accelerated testing	40 ± 2°C/75 ± 5% RH	6 months
Photostability testing (temperature must be controlled)	Exposure to an artificial daylight fluorescent lamp *or* to both cool white fluorescent and a near-UV fluorescent lamp	Overall illumination of ≥1.2 million lux hours and integrated near-UV energy of ≥200 watt-h/m^2

Sources: "Guidance for Industry. Q1B Photostability Testing of New Drug Substances and Products." http://www.fda.gov/cder/guidance/1318.htm (*Federal Register* May 16, 1995); *Federal Register* September 22, 1994.

The primary routes of degradation of drug substance and drug product are through oxidation and hydrolysis [26], along with dehydration, photolytic reactions, rearrangements, and loss of volatile components such as HCl [7]. The stability and instability of compounds must be considered relative to the test conditions employed, which may be harsher than those outlined in Table 1. For instance, cimetidine was found to be stable for five years when stored at room temperature in a closed container [27]. At pH 5.4 and 50°C there was no decomposition over 30 days; hydrolysis to the urea occurred when cimetidine was held in 1 N HCl at 45°C for 36 hours (Figure 12.2). By heating in concentrated HCl at 100°C for two hours, the guanidine was formed. Degradation products of some other drugs are also shown in Figure 12.2 [16, 28–30].

To predict the stability of molecules, the interaction of functional groups within the drug substance and with excipients, solvents, and oxygen must be considered. Intermolecular and intramolecular reactions of electrophilic and nucleophilic functional groups may occur, with neighboring group participation. Interactions with excipients [31] must also be considered. For instance, it would be unwise to formulate a drug product containing an amine group with a sugar such as mannose because a Schiff base may form [24]. The reactivity of functional groups within molecules can also be used to anticipate the stability of compounds.

II.B. The Importance of Controlling Particle Size of a Drug Substance

Particle size and distribution can be very important, especially in the early phases of formulation development, when investigations are underway to establish optimal dosage forms. Rapid dissolution is favored by small particles, but small

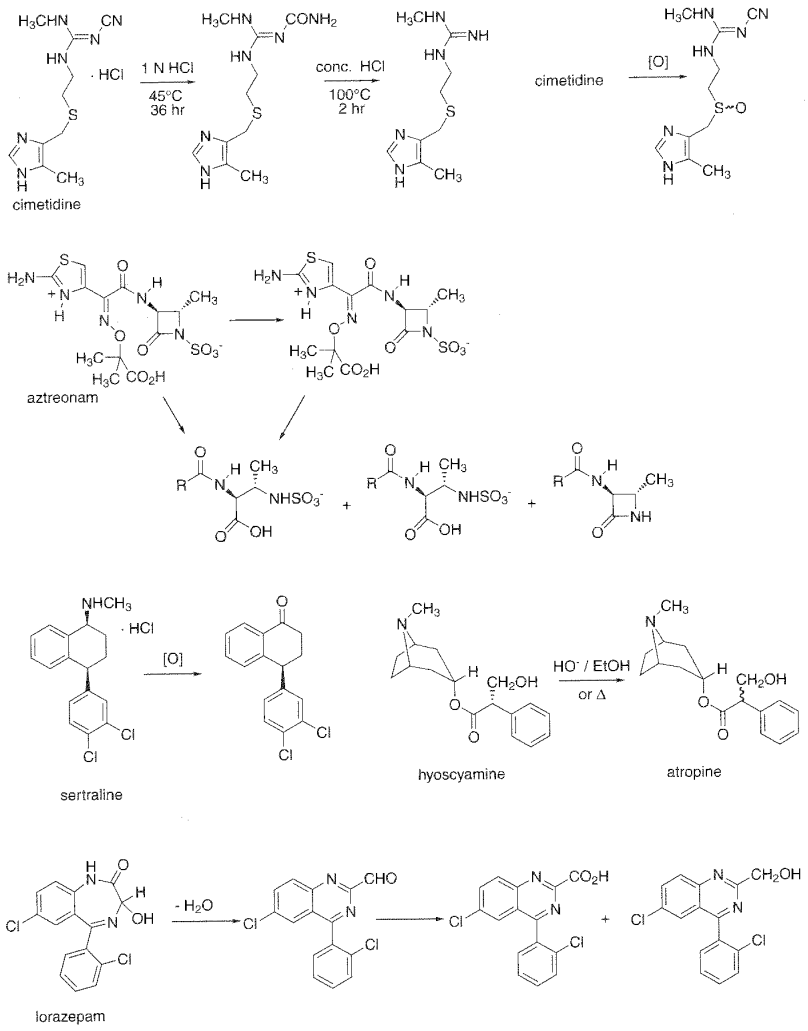


FIGURE 12.2. Degradation of Some Active Pharmaceutical Ingredients

particles are more prone to decomposition due to the increased surface area [32]. Small particles may also tend to agglomerate, accumulate static charge, and consequently flow poorly [33]. Comparative bioavailability studies may be needed to justify the time and resources to develop means to tightly control particle size and distribution.

Particle sizes can be controlled by crystallization (Chapter 11) or by size reduction through milling or grinding. Milling or grinding always reduces drug substance yields by retaining some product in the equipment. (The small amount of hard-to-remove solids left in dryers, mills, and grinders is called a "heel.") Heat generated during milling may melt the drug substance, leading to difficulties in formulation. Size reduction can create dusts of bioactive compounds, increasing the personnel exposure hazard. Crystallizing the product as small crystals avoids size reduction, but small particles are filtered and washed more slowly during isolation. It may be necessary to select equipment and develop a process for optimal isolation of small crystals. The choice between size reduction and forming small crystals should be examined as needed.

III. PREPARING AND SELECTING THE POLYMORPH

Early in the characterization and development of processes to prepare a final product, crystallization conditions should be screened on small scale to identify the desired salt form (if appropriate) and to investigate the possibility of forming multiple polymorphs, solvates, and hydrates. The benefits in attempting to prepare new polymorphs can be substantial. First, a new polymorph or solvate with superior formulation or stability characteristics may be isolated. Second, if an undesirable crystalline form is prepared, conditions can be designed to avoid its formation on scale. Third, it may be essential to define conditions to reliably prepare a metastable polymorph if the most stable polymorph has not been chosen for development.

Criteria for selecting polymorphs and solvates are shown in Table 12.2. For drug substances, hydrates are preferred over solvates of organic solvents, due to toxicity considerations. The structural solvent in marketed crystalline drugs is almost invariably water [12] or a nontoxic substance such as EtOH that is generally regarded as safe (GRAS).

The thermodynamically favored form of a final product is usually the most desirable crystalline form, and screening studies should define the stability of the polymorphs. A less stable form may be preferred if it displays markedly improved dissolution and bioavailability. In this case it would be necessary to ensure that the less stable form can be reliably prepared on scale before committing to preparing this polymorph exclusively.

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TABLE 12.2. Criteria for Polymorph / Solvate Selection

Ideal characteristic	Problems if ideal characteristic is not achieved / Approaches to address problem
Optimal bulk stability	Special handling and storage conditions needed. **Solution**: choose more stable form if possible.
Desired bioavailability	Reduced particle size may be necessary. **Solution**: choose more stable form if possible, or prepare drug substance with reduced particle size. Alternative dosage form may be necessary.
Presence of desirable solvates, if any	Many organic solvents are unacceptable as solvates due to toxicological reasons. **Solution**: H_2O is the solvent most often present in solvates.[a] Prepare hydrate.[b]
Ease of formulation	Quality of dosage form may be unreliable. **Solution**: redevelop formulation or find alternative polymorph or solvate.
Ease and effectiveness of crystallization and isolation on scale	Uncontrollable processing may lead to unacceptably large variations in drug substance quality and particle size; hence unreliable formulations. **Solution**: develop reliable crystallization and isolation procedure that can be effected readily on scale.
Ease and effectiveness of rework on scale	Lack of an effective rework means low-quality batches may be discarded. **Solution**: rely on IPC to control processing to drug substance; better approach is to develop reliable rework procedure.

[a]Byrn, S. Pfeiffer, R.; Ganey, M.; Hoiberg, C.; Poochikian, G., "Pharmaceutical Solids: A Stategic Approach to Regulatory Considerations." *Pharm. Res.* **1995,** *12,* 945–954.

[b]For a case study in preparing hydrates instead of solvates, see Mauragis, M. A.; Veley, M. F; Lipton, M. F, "Evaluation and Rapid Scale-Up of the Synthesis of the Pyrrolopyrimidines U-101033E and U-104067F" *Org. Process Res. Dev.* **1997**, *1,* 39–44.

The importance of selecting the most stable polymorph can be seen in the considerations necessary to isolate a metastable form of abecarnil (Figure 12.3) [34]. Polymorph characterization had identified three forms: B, the least stable; A, which was very similar to B; and C, the most stable. Early studies showed that B

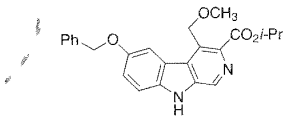


FIGURE 12.3. Structure of Abecarnil

and A could be reliably crystallized from *i*-PrOAc or CH_3OH, respectively. The B form was readily crystallized and stable both as a dry powder and when held as a suspension in *i*-PrOAc for a day. Transformation of B into A occurred slowly, and transformation into the most stable C form was observed after periods of days. (It is unclear whether bioavailability or other considerations led to the selection of the B form.) When the process was transferred from development to production, process optimization provided a somewhat purer product containing less $Et_3N \cdot HCl$, and the initially formed B form was rapidly converted to the A form during isolation from *i*-PrOAc on scale. The B form could no longer be reliably prepared on scale. Since the physical characteristics of the A form were nearly identical with those of the B form, a process was developed to selectively crystallize the A form for use as the drug substance.

A seeding strategy with a tightly controlled cooling profile was necessary to isolate the A form of abecarnil and avoid the formation of the C form. The solubilities of each form in *i*-PrOAc were determined as a function of temperature. A-form crystals with no C-form solids were necessary for seeding: if seeds contained only 5% of the C-form solids, the isolated product contained 50% of the C form. The A-form seed crystals were activated by slurrying in *i*-PrOAc (10 volumes per weight) immediately prior to charging to the reactor; slurrying activated the seeds presumably by dissolving impurities on the surface of the crystals and cleaning the surfaces for crystal growth. On scale the solutions were seeded at a temperature below that which caused formation of the C-form crystals. The warm solution was inoculated with a slurry containing 3 wt% of activated, pure A-form seeds, and the slurry was cooled at 0.5–1.0°C/min to prevent formation of the C-form crystals. When the slurry reached 30°C, the product was immediately isolated by centrifugation. The slurry was loaded to a cake thickness of 1 cm for rapid drying to prevent the liquid-mediated transformation of the A form to the C form. Although this protocol was reliable on scale, the authors acknowledged that isolation of the most stable C form would have afforded a simpler process [34].

> **TIP:** Considerable time should be spent *EARLY* in the development of a drug to determine the optimal final form of the drug substance.

III.A Varying Crystallization Conditions in Order to Prepare Polymorphs

Many approaches can be taken to screen for polymorphs, and the goal of this search is to isolate a new crystalline form, not to optimize the isolated yield. New solvents and solvent combinations may give rise to new forms when the final

product is heated to dissolution and cooled. By varying polarity, crystallization from new solvent-antisolvent combinations may lead to new forms. When a crystallization pressure is rapidly increased, as by rapidly cooling a solution, a kinetically favored form may crystallize. The thermodynamically favored polymorph may form with more gradual cooling. An extended pH adjustment may result in the formation of metastable crystals that were overlooked in processes that use rapid pH adjustment. With extended aging of solutions or crystalline suspensions, a thermodynamically favored form may crystallize. In order to screen for the presence of hydrates, recrystallizations should be attempted in the presence of varying amounts of H_2O, as crystallization of a substance from water-immiscible solvents in the presence of varying amounts of H_2O has produced different hydrates [12].

Trace amounts of impurities can lead to the formation of a new crystalline form or the preferential formation of another polymorph, as discussed for crystallization of abecarnil. For this reason it is wise to screen for polymorph formation using both highly purified final product and material of routine purity. The solids resulting from the removal of solvents from a final product extract may be appropriate for polymorph screening.

> **TIP:** Screen for polymorphs using crystallizations in the presence of water and trace amounts of all solvents used to prepare and formulate the drug substance.

IV. PURITY AND IMPURITY CONSIDERATIONS: FREEZING THE FINAL PROCESS

Impurities in a final product must be known and controlled. Without sufficient control of the quality of the drug substance, the safety of drug product is not assured. The FDA was formed to ensure that companies manufacturing and selling food and drugs control quality in order to protect consumers. Inadequate control of product purity and impurities also indicates that processing is not fully productive, as batches will be destroyed or reworked to improve the quality. With frequent need to rework batches, additional time is justified to optimize conditions.

Poor quality of an intermediate or a product can require significant troubleshooting in order to resolve difficulties (see Chapter 15). Poor quality implies unacceptable levels of impurities, which may include the presence of an impurity exceeding the specifications. The presence of a new impurity at a significant level, particularly in the final product, may also prompt troubleshooting. Problematic impurities may adversely affect processing in a subsequent step, be toxic or irritating, or have an undesirable odor or taste.

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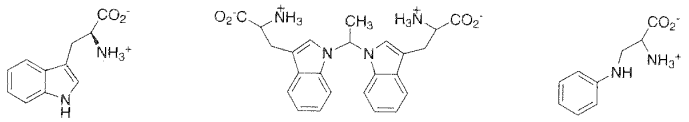


FIGURE 12.4. Possible Causative Agents for EMS Syndrome in Tryptophan Dietary Supplements

Low levels of impurities can be particularly problematic. In the late 1980s and into the early 1990s, outbreaks of eosinophilia myalgia syndrome (EMS) were associated with low levels of a fermentation-derived impurity found in tryptophan dietary supplements. As one researcher at the Center for Disease Control reported, "98.5% purity doesn't mean very much when we are talking about biologically active contaminants that, in varying minuscule amounts, can create powerful effects" [35]. Possible causative agents were identified as the unusual amino acids **1** and **2** (Figure 12.4) [36, 37]. To halt EMS-related problems, the manufacturer used another microbial strain for the manufacture of tryptophan by fermentation.

Another highly potent contaminant that may be formed in a routine chemical processing step is dimethylcarbamoyl chloride (DMCC), a known animal carcinogen (Figure 12.5) [38]. This impurity, formed during the use of DMF as a catalyst for acid chloride formation, is probably destroyed by subsequent reaction of the acid chlorides. Since DMCC is a carcinogen, it was proposed that assays be developed to detect DMCC even at ppb concentrations and that appropriate measures be taken to contain this impurity.

Impurities detected by odor and taste may also be present at the ppb levels and failing to control the levels of these impurities can have a significant financial impact if patient compliance is negatively affected. Finding a way to eliminate these impurity-related problems is usually easy once the causative agent has been identified. However, identifying the causative agent may be difficult when the impurities are present in very low amounts.

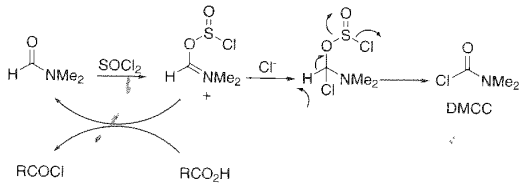


FIGURE 12.5. Formation of Dimethylcarbamoyl Chloride

TIP: Troublesome impurities can form by what may be considered a poor reaction from a synthetic organic chemistry standpoint. Even poor-yielding reactions can generate significant amounts of impurities and cause products to be reworked and routes redesigned.

IV.A. Considerations for Preparing the Toxicology Batch and Subsequent Batches

Material prepared for toxicological screening is generally the first batch of drug candidate prepared on scale, often in the kilo lab or scale-up laboratory. (For economy of operations, one batch of drug candidate may be prepared for both toxicological screening and Phase I.) The purity of this batch must be compared to a purified standard, and both the impurity profile and relative amounts of each impurity must be established. According to FDA guidelines, every impurity must be identified when detected in a drug substance at the level of 0.1% (or 0.05% if the drug product is administered in high doses) [39]. Once the toxicological studies have been completed, and the material displays acceptably low levels of toxicity, the impurities in the toxicological batch are said to be qualified, i.e., judged safe at the described level.

Subsequent batches of drug candidate will be compared to the material used for toxicological studies. If the level of each impurity is less than that detected in the toxicological batch, and if no new impurities are detected, no action is needed. If an impurity is found at a level greater than that observed in the toxicological batch, or if a new impurity greater than or equal to 0.1% is identified, the FDA does not consider that such material can be safely administered to humans. Such material must be reworked in order to reduce the levels of qualified impurities to no more than those detected in the qualifying toxicological batch and to remove any new impurity found at a level of 0.1% or more [39]. Alternatively, additional toxicological studies, which may be costly, can be done to qualify batches containing such outstanding impurities.

To avoid reworking batches in the future, it is important to establish reasonable criteria for routine quality and impurity levels of the drug candidate batch to be used for toxicologic screening. This batch should then be prepared to set the standard for routine quality. Crystallization to raise quality may be appropriate, but no attempts should be made to generate ultra-pure drug substance unless it is certain that this quality material can be routinely prepared. It would be inappropriate to prepare high purity material on small scale using chromatography or solid-phase synthesis unless these means would be used for routine manufacture of the drug substance; otherwise, the impurity profiles and impurity contents could differ from those batches purified by conventional recrystallization or solution phase

synthesis. The opportunities to change physical characteristics and impurity profiles usually are limited to the first years of drug development, so thorough analytical investigations should take place early in the development of a drug candidate and throughout the preparation of clinical and manufacturing batches [40].

Purity specifications should be set reasonably high for filing purposes. If high levels of impurities are included, identification is required, which demands commitment of personnel. A delicate balance may be required between committing to prepare unreasonably pure drug substance and preparing drug substance with unacceptably high levels of impurities. Significantly, the FDA and other regulatory agencies will readily allow upgrading, but not downgrading of purity specifications.

In order to establish routine impurity profiles and levels, ideally the final isolation of drug substance should be optimized, and this process should be used for the preparation of material destined for toxicological studies and later Phase I studies. The types of impurities found in drug substance will be largely determined by the starting materials and reagents used in the final step to prepare the drug substance. Thus the ideal penultimate compound should be identified early in investigations, and parallel development work should converge on this penultimate compound. To save development time and costs, it is important to "freeze the final process" early, that is, to identify early the most desirable final chemical transformation to prepare the drug substance [40]. Nonetheless, in the sprint to prepare a potential drug candidate for Phase I studies, it may be difficult to develop the ideal last step, the ideal final purification procedure, and at the same time prepare the drug substance by the timelines.

IV.B. Minimizing Impurities in the Drug Substance

Rework procedures are usually employed to upgrade final products and key intermediates, even if the identity of the troublesome impurity has not been secured. Resubjecting the product to the original crystallization and isolation conditions may not sufficiently remove the key impurity. Rework procedures may need to be developed based on chemical information and intuition.

Once the structures of the impurities are known, developing procedures to minimize key impurities in a drug substance is generally straightforward. Two basic choices are available: to minimize the formation of an impurity, or to minimize the presence of this impurity in the drug substance. Complete analyses may be necessary for all intermediates and reagents. By setting specifications at acceptable levels of impurities in intermediates and reagents, the burden of purifying the final product can be greatly reduced or eliminated. A generalized scheme to minimize the presence of impurities in the drug substance is shown in Figure 12.6.

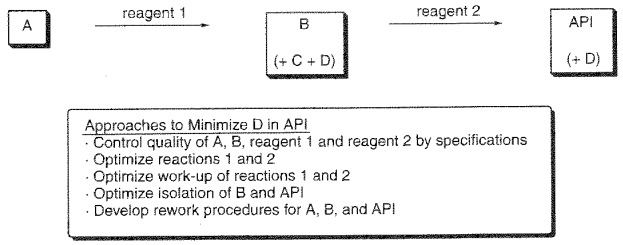


FIGURE 12.6. Approaches to Minimize the Presence of Impurities in a Final Product

An example of this approach is shown in Figure 12.7. During the preparation of the fosinopril sodium intermediate **3** about 2% of the regioisomeric impurity **6** was formed [41]. Compounds **3** and **6** are too similar to be readily separated based on their chemical properties, and it was hoped that through purification of the subsequently derived intermediates, no regioisomer-derived impurities would be carried along to the final product. Since **3** is a low-melting solid and was isolated as a solid residue, no purification by crystallization was readily available.

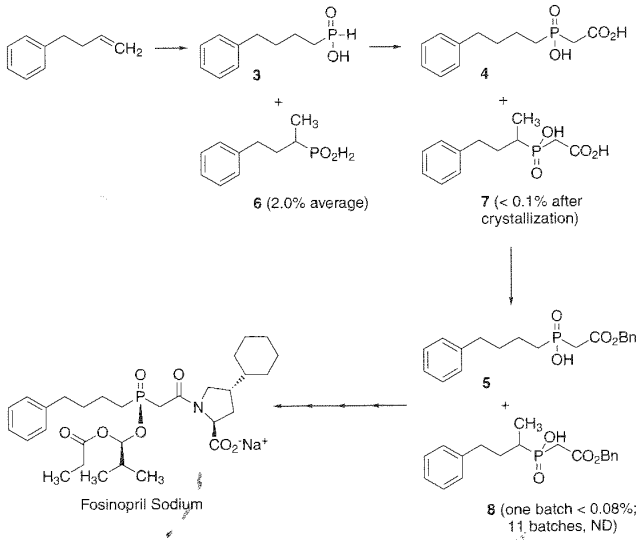


FIGURE 12.7. Removal of Regioisomer-Derived Impurities by Crystallization

(Purification of **3** could be effected by crystallizing the dicyclohexylamine salt, but preparing and splitting the salt would have entailed development of two additional steps.) With the conversion of **3** to **4**, the presence of **7** was also detected; the crystallization of **4** reduced the levels of **7** to an average of <0.1%. Subsequent preparation and crystallization of **5** effectively purged the regioisomer **8** (**8** was detected in only one of 11 batches). Since there are four crystallizations in converting **5** to fosinopril sodium, any contamination of fosinopril sodium with regioisomer-derived impurities would be far below the 0.1% level.

If the formation or presence of impurities cannot be eliminated, experiments can be run to determine the tolerance of the final step or overall process for various levels of the impurity and impurity precursors. An optimized process was devised to manufacture betamethasone, **11**, which raised the yield by 30% and increased the purity of **11** to over 99% (Figure 12.8) [40]. The chlorinated by-product **10**, formed in the first step, was converted to the corresponding betamethasone impurity **12**. The latter impurity was new and found at levels approaching 0.1% in batches of **11** prepared by the PCl_5 route. Running a qualifying toxicological study was not viewed as a favorable option. It was found that the processing steps to betamethasone could tolerate the presence of up to 1% of **10** in batches of **9**; if levels of **10** were greater than 1%, the batch of **9** was treated in DMSO at 100 °C to convert residual **10** into **9**. This early rework procedure allowed the preparation of betamethasone with an impurity profile comparable to or better than batches prepared by the original route.

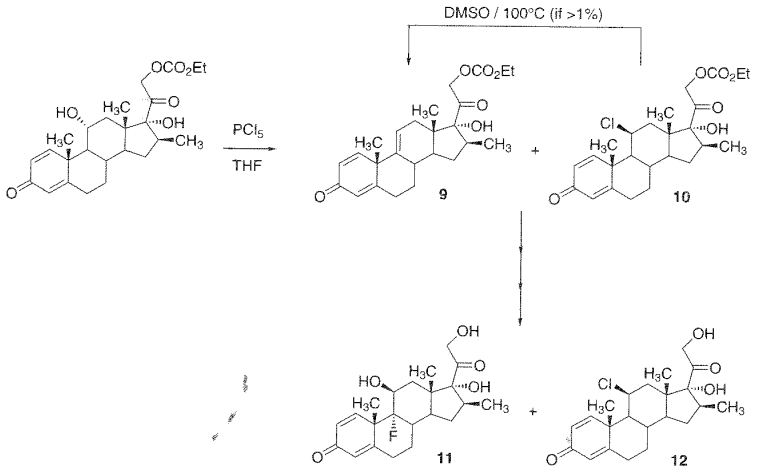


FIGURE 12.8. Reworking an Intermediate to Decrease the Impurity Burden in a Final Product

TIP: Control the impurities in the penultimate intermediates to control the impurities in the drug substance.

Colored impurities can pose great difficulties in a drug substance. Since low levels of impurities can cause intense colors, identifying and removing the troublesome agent may be very difficult [16]. Colored impurities are generally formed by metal salts or by polyunsaturated compounds. The drug substance may be analyzed by atomic absorption or other means to determine whether metal contaminants are present. If metal complexes do not give rise to the colored species, perhaps the colored impurities can be absorbed to charcoal or solid phases (solid phase extraction, SPE [42]) and eluted for identification.

An empirical approach may be necessary to avoid generating unidentified colored impurities. For instance, the formation of colored products may be reduced by conducting reactions at lower temperatures.

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CHAPTER 13

Vessels and Mixing

I. INTRODUCTION

This chapter focuses on how mixing influences scale-up. It also presents some alternative reactors that may help scale-up operations and touches on a few concepts regarding mixing and the types and properties of reactors. For detailed discussions of these concepts the reader is referred to chemical engineering texts [1–5].

The selection of processing equipment is largely determined by two financial considerations. One is the actual capital costs for equipment, and the other is the cost of building a new plant. For the high-volume production of chemical intermediates, where productivity is essential, reactors may be designed or purchased specifically for the dedicated preparation of one product. These expenditures often are approved specifically for the manufacture of products with demonstrated success in the market place or for those with a high chance of success. Most of the reactors used in the pharmaceutical industry are selected for flexibility—they can run several different processes—and most processes are adapted to use existing equipment. This is particularly true for scale-up operations in pilot plants. Purchasing equipment that is flexible enough to be used for many processes avoids the cost of building new plants. Designing and building a production facility and installing and commissioning equipment represent a considerable commitment of time, resources, and finances.

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Reactors must provide efficient mixing of the contents and good heat transfer from or to the contents. These features allow for safe, reproducible operations. Applications of mixing processes are shown in Table 13.1, and standard reactors (see Figure 1.3) are used for most of these processes. Specialized considerations may be necessary for heterogeneous reactions. Hydrogenations and fermentations, which are often heterogeneous gas-liquid-solid reactions, are often conducted in specialized reactors, designed to maximize the contact of different phases.

Heat transfer in reactors can be carried out in several ways. For the standard reactor shown in Figure 1.3, heat transfer fluid is circulated through the external jacket. Heat may also be transferred by circulating the vessel contents around coils or tubes within the vessel, by recirculating the vessel contents through an external heat exchanger, or by cooling vapors through an external reflux condenser. Directly injected liquid nitrogen can also be used to cool a reaction. The rate of heat transfer is directly proportional to the surface area [6], and for vessels cooled externally the rate of heat transfer decreases as the volume increases, indicative of the fact that surface area:volume ratio reduces as vessels increase in size (Table 13.2). The cooling rates attainable in scale-up vessels will be considerably slower than those of small laboratory vessels.

TIP: Mimic scale-up operations in the laboratory by gradually heating and cooling reactions.

The motion of the vessel contents is influenced by the agitator and any baffles. The agitator, or impeller, provides the power to move the vessel contents. There are two types of impellers: radial-flow impellers, which move the liquids along the radius of the impeller, and axial-flow impellers, which move the liquids parallel to the axis of the agitator shaft. Without baffles, low-viscosity fluids tend to create

TABLE 13.1. Applications of Mixing Processes[a]

Physical processing	Application classes	Chemical processing use
Suspensions	Liquid-solid	Dissolving and crystallizing
Dispersions	Liquid-gas	Absorption (e.g., reduction with H_2 and oxidation with O_2)
		Desorption (e.g., loss of CO_2 from a decarboxylation)
Emulsions (unstable[b])	Liquid-liquid	Extractions
Blending	Miscible liquids	Reactions
Pumping	Fluid motion	Heat transfer

[a]Oldshue, J.Y. *Fluid Mixing Technology*; McGraw-Hill: New York; 1983, pp 4–6.

[b]Stable emulsions are used to formulate drugs as creams and ointments and to prepare products such as shampoos that are used in the consumer product industries.

TABLE 13.2. Reactor Dimensions and Surface Area:Volume Ratios

Reactor	Internal radius[a]	External height[a]	Surface area for heat transfer[a,b]	Surface area:Volume[d] (cm^2/cm^3)
100 mL flask[b]	2.9 cm	[b]	104 cm^2	1.042
1 L flask[b]	6.2 cm	[b]	483 cm^2	0.483
5 L flask[b]	10.6 cm	[b]	1412 cm^2	0.282
20 L flask[b]	16.8 cm	[b]	3564 cm^2	0.178
50 L flask[b]	22.9 cm	[b]	6561 cm^2	0.131
100 L flask[b]	28.8 cm	[b]	10416 cm^2	0.104
50 gallon reactor	14 in.	88 in.[c]	17.2 ft^2	0.084
300 gallon reactor	23 in.	123 in.[c]	70.4 ft^2	0.058
500 gallon reactor	23 in.	148 in.[c]	97.4 ft^2	0.048
750 gallon reactor	27 in.	147 in.[c]	123.1 ft^2	0.040
1000 gallon reactor	27 in.	176 in.[c]	149.1 ft^2	0.037

[a]Data for reactors provided by Pfaudler, Inc.

[b]Round-bottomed flasks were considered as simple spheres. The radius was calculated from the formula $v = 4/3\pi r^3$, and the surface area was calculated by the formula $A = 4\pi r^2$. No compensation was made for the thickness of the glass vessels.

[c]As measured from the bottom of the legs to the top of the mechanical drive for the agitator.

[d]Calculated using the nominal volume of the flasks and reactors.

vortices and swirl with poor mixing; baffles disrupt vortices and promote flow patterns that lead to good mixing. With baffles in place either radial-flow or axial-flow agitators can provide good mixing for most chemical operations used in the chemical processing industry [7].

TIPS:

- Generally there is no choice in agitators for the available multipurpose equipment because considerable time is required to change an agitator in a vessel. In some vessels the agitator can be removed through the manhole, and replacing an agitator might require as little time as one shift. For other vessels it may be necessary to first pull the head off the reactor, in which case more than one shift would be required to replace the agitator and ensure the reactor was leakproof.
- Anchor agitators are the only agitators that stir extremely close to the surface of the vessel, analogous to a teflon half-moon paddle on an agitator shaft stirring on or just above the bottom of a round-bottomed flask. Anchor agitators are used for pseudoplastic fluids [8], which are rarely encountered in manufacturing fine chemicals.
- To model agitation that may be encountered on scale, use a baffled resin flask or a Morton flask. Agitate the mixture by overhead stirring with the agitator blade positioned above the bottom of the vessel.

The Reynolds number, a dimensionless parameter, is useful in describing fluid flow and has implications for the scale-up of chemical processes. The Reynolds number (N_{Re}) is defined in Equation 1. Agitation produces three regimes of mixing: laminar, transitional, and turbulent [9]. Laminar flow, or flow around the edge of the vessel, occurs at values of N_{Re} less than 20; this type of flow is usually not encountered with the low-viscosity solvents routinely used in the chemical processing industry. Transitional flow takes place at values of N_{Re} between 20–10,000 and combines features of both laminar and turbulent flow. Fully turbulent flow begins with values of N_{Re} above 10,000. One significant aspect of N_{Re} is that turbulence is proportional to the square of the agitator diameter; hence, to achieve turbulence in a large reactor that is similar to that in a small reactor, the agitation speed in the larger reactor must be slower.

$$N_{Re} = \frac{D^2 \rho N}{\mu} \qquad \text{Eq. 1}$$

N = agitator speed (revolutions/s);
D = diameter of agitator (cm);
ρ = density of solution (g/cm^3);
μ = viscosity of solution (g s/cm)

On a qualitative basis the Reynolds number can be appreciated by considering the speed of the impeller tips. At a constant stirring rate, the turbulence of a mixture increases greatly as the radius of the impeller increases. A quantitative approach to scaling down agitation has been described [9].

Rapid distribution of reaction components does not take place on scale in conventional stirred reactors. For instance, based on pH measurement it may take 3–5 minutes for a reagent added at the top of a 500-gallon vessel to be evenly distributed throughout the solution. Mixing can be described as macromolecular mixing, which relates to the average composition of the vessel contents, and as micromolecular mixing, which considers the contacts of molecules on a molecular basis and any gradients that may result [10]. Suitable micromolecular mixing can be difficult to perform on scale.

Micromolecular mixing (micromixing) is important in many processes, including crystal nucleation and growth [10]. Micromixing is also important for reactions that are sensitive to the stoichiometry of reagents (see Figure 14.2) and for reactions in which rapid heat transfer is critical. Sometimes micromixing difficulties can be circumvented by an extended addition or inverse quenches. Such alternatives are not effective when scaling up reactions that demand good control of localized effects.

II. BATCH VS. CONTINUOUS PROCESSING

There are three approaches to processing operations: batch, continuous, and semibatch or semicontinuous (Figures 13.1. 13.2, 13.3). Batch processing is used to

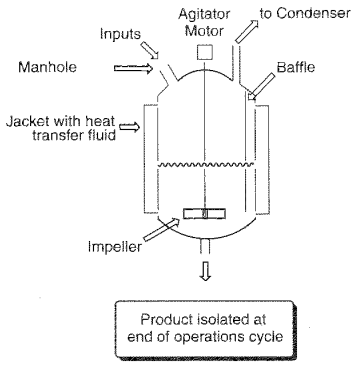


FIGURE 13.1. Batch operations

make most drug substances and intermediates. Continuous and semicontinuous operations are most often used on large scale for the manufacture of bulk chemicals and agricultural chemicals. Each option has its own scale-up advantages, as discussed in the sections following and summarized in Table 13.3.

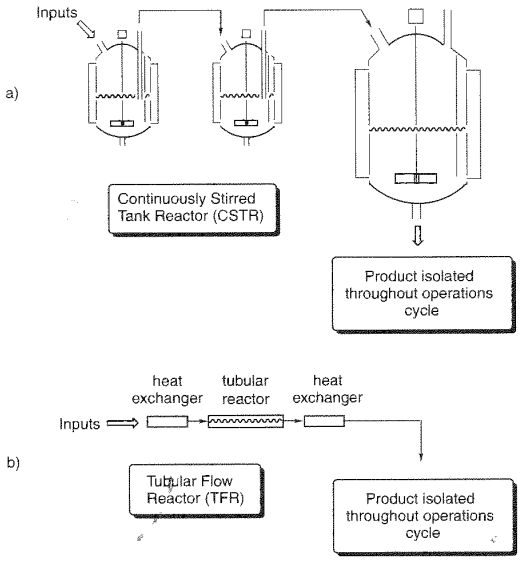


FIGURE 13.2. Continuous operations

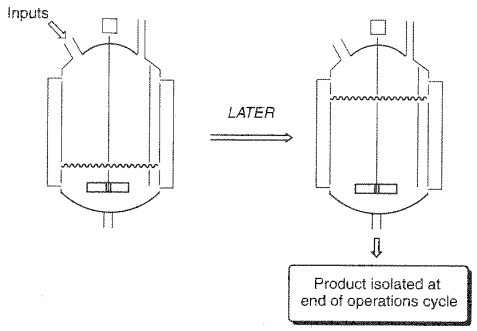


FIGURE 13.3. Semicontinuous operations

II.A. Batch Processing

Batch operations are run for reactions requiring hours for completion, with relatively small product outputs [4]. Unit operations, such as crystallization, can be finely controlled on scale for the entire batch. The product from a batch is isolated at the end of an operations cycle and can always be readily correlated with input materials. For these reasons batch processing is used to make most drug substances and intermediates.

As one progresses to larger and larger reactors, micromixing becomes a greater concern, and tight temperature control becomes more difficult. Other issues may arise, such as the optimal placement of agitators, pH probes, thermocouples, and other reaction monitoring devices. These parameters can be readily controlled by using a small reactor, but running many small reactions is a tedious way to accumulate large amounts of material.

II.B. Continuous Operations

Continuous operations are generally used for large-volume products in which reaction conditions are closely monitored to achieve maximal productivity. Such operations are carried out on scale by allowing a reaction to pass through a small reactor. The products are usually made by reactions completed in minutes, which allows for fine control of process conditions. Reactions requiring longer reaction times may be used in continuous operations if the reaction products are stable enough to permit recycling a reaction stream through the reactor. Product is isolated throughout the operations cycle. Continuous operations are used by the bulk chemical and agricultural chemical industries.

TABLE 13.3. Characteristics of Batch and Continuous Operations

Feature	General-purpose reactor	Continuous-flow reactor
Typical industrial use:		
Laboratory	General approach for scale-up	Rarely used
Pilot plant	Most often used	Rarely used
Manufacturing	Often used for pharmaceutical & fine chemicals; rarely used for bulk chemicals	Often used for bulk chemicals & agricultural chemicals; rarely used for pharmaceutical & fine chemicals
Temperature response rate for reactor contents	Slower in larger vessels	Response can be very rapid
Localization of physical effects	Macromixing and micromixing always considerations	Equipment can be selected for excellent micromixing and localized physical effects
Reaction times for reactions typically used in these vessels	Reactions with relatively long reaction times or short reaction times generating products stable under the reaction conditions	Reactions with a short residence time or those with products stable while recycling through reactor; also unstable products
Useful for	Most reactions	Reactions where relative stoichiometry of reactants and products is critical; reverse quenches; tight temperature controls; efficient mixing of heterogeneous streams; localization of catalysts and physical effects
Cost for reactor	$50,000 (50-gal reactor) and more	Under $1000 for static mixer for pilot plant; specialized reactors more costly
Additional equipment needed	Equipment traditionally available in most pilot plants and manufacturing plants	Pumps and heat exchangers in addition to receiving vessels and traditional vessels
Relative operating safety	Good	Very good, as only a small portion of batch is subjected to processing at any moment
Utility demands	Must transfer heat from entire batch and large reactor	Transfer heat from part of batch and small reactor
Additional development time	Some time may be needed to optimize processing if labile compounds are produced	Need to determine reaction time for suitable residence time in reactor, or recycle stream through reactor

One type of continuous operation is the continuously stirred tank reactor (CSTR, Figure 13.2a), in which the reactants are continuously fed to the first vessel, and the vessel contents overflow into the successive vessels. This principle allows for good mixing and isolates the contents in the second and subsequent vessels from contact with reagents entering the first vessel. In principle the

composition of each vessel is homogeneous, but there is a stepped gradient throughout the process. The total volume of the reactors is held constant, because product is withdrawn from the last reactor at the same rate that inputs are added to the first reactor.

One use of CSTR operations is for crystallization. As a crystalline slurry passes from one vessel to another, aging occurs, but aging in the presence of like crystals. Coupling a CSTR with continuous isolation allows for large amounts of material to be prepared in a very productive fashion using small vessels. Another use of CSTR is to control conditions in which the product from a reaction might be sensitive to the reagents added to the first reactor.

A variation of continuous processing is the tubular flow reactor (TFR, Figure 13.2b), in which the reactants are continuously charged at one end of a tube and the products are continuously removed at the other end. Within a TFR the reaction components are mixed both radially and axially, depending on the viscosity of the mixture, the tube diameter, and any mixing elements inside the tube. Stationary mixing elements are employed to provide good mixing by dispersing the reaction streams inside the tube. (The importance of static mixing elements can be visualized by filling a vertical tube with honey. As the honey is poured from the tube, the fluid in the middle of the tube exits first, leaving behind residual honey adhering to the wall of the cylinder. For most fluids that are less viscous than honey, the material in the center of the tube exits the cylinder much faster than does fluid near the wall of the cylinder.) One type of a TFR is a plug flow TFR, in which the reaction components in principle are mixed only radially. In

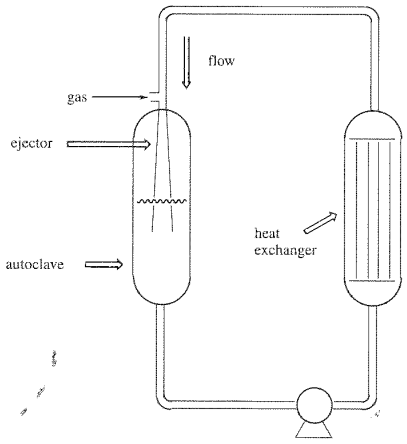


FIGURE 13.4. Schematic of a Buss loop reactor

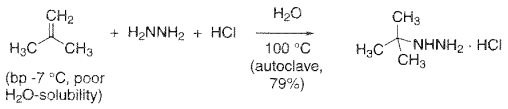


FIGURE 13.5. A reaction that could be run in a Buss loop reactor

essence the TFR is an extension of a CSTR operation, using many small vessels in sequence.

Continuous processing is useful for reactions that need rapid heat transfer [4], for preparing unstable compounds, and for reactions in which physical effects are localized. When safety or stability is a major concern, continuous processing has advantages over batch processing in that only a small portion of the batch is subjected to reaction conditions at any moment. Following is a discussion of some large-scale and small-scale applications.

Heterogeneous reactions, particularly gas-liquid or gas-liquid-solid reactions, often create scale-up challenges due to the difficulties posed by mixing and intimate contact of components on scale. Loop reactors have been used to disperse reaction components efficiently, and with a heat exchanger exothermic reactions can be controlled. A schematic of a Buss loop reactor is shown in Figure 13.4 [11]. Hydrogenations are a classic example of heterogeneous reactions, and such loop reactors were developed for the hydrogenation of fats and oils. The same approach could be applied to reactions of immiscible components or reactions that need to be conducted under pressure. One possible application is the preparation of *t*-butyl hydrazine hydrochloride [12] (Figure 13.5).

A continuous catalytic distillation process was described for the preparation of MTBE (Figure 13.6) [13]. In this process a stream containing isobutylene and *n*-butene was fed into the bottom of a distillation column packed with a cationic ion exchange resin, while MeOH (bp 65°C) was fed into the top of the column. In the zone packed with the ion exchange resin catalyst, MTBE (bp 55°C) was formed by a reversible reaction. By fractionating below the catalytic zone, the product was removed as it formed, while unreacted *n*-butene was recovered above the catalytic zone. Considerable optimization was undoubtedly necessary to optimize this countercurrent continuous process, but the goal was justified for designing a process to prepare this high-volume chemical.

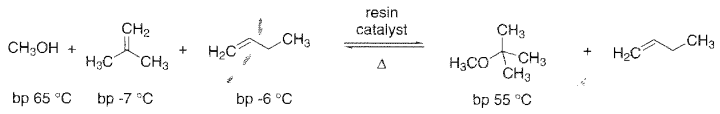


FIGURE 13.6. Preparation of MTBE by a continuous catalytic distillation process

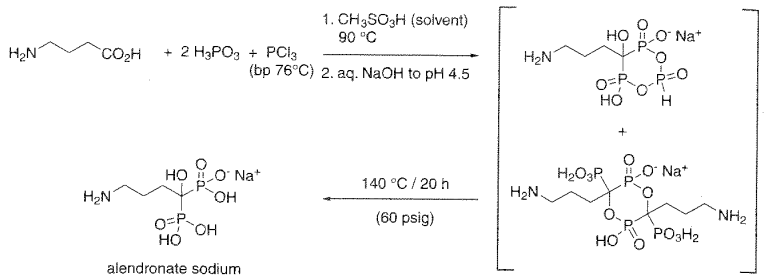


FIGURE 13.7. Preparation of alendronate sodium

In the preparation of alendronate sodium, a continuous process afforded a better opportunity to control processing than did batch operations (Figure 13.7) [14]. The phosphonation was best conducted at 90°C, and in batch operations PCl_3 (bp 76°C) was difficult to charge and contain. With the loss of PCl_3, by-products were formed. At 90°C the reaction was known to be very exothermic, and this condition posed safety concerns for large-scale reactions. By continuously charging the starting materials and PCl_3 in a 1:2:1 ratio to a small vessel, both the stoichiometry and the reaction temperature could be readily controlled. At steady-state conditions the overflow from the reactor flowed into a quench vessel. Subsequent hydrolysis produced alendronate sodium.

A continuous operation in a laboratory was described to generate and use an unstable intermediate, the unstable chloride **2** (Figure 13.8) [15]. The half-life of **2** was determined to be 20 minutes (in $CDCl_3$), and unacceptable yields of **2** were

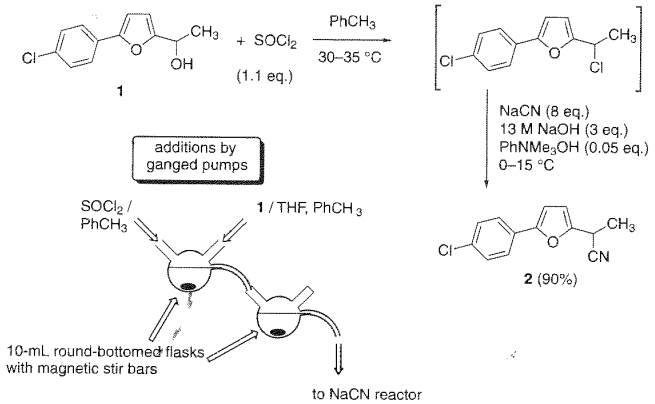


FIGURE 13.8. Generation and use of an unstable intermediate by continuous processing

produced when reactions were run on scales of more than 100 g **1** in a batch mode. $SOCl_2$ and **1** were continuously charged to a 10-mL round-bottomed flask. The reaction mixture was allowed to overflow into a second 10-mL round-bottomed flask and into a larger vessel for a PTC-mediated reaction with NaCN. The second vessel was used to increase the residence time and allow for more complete conversion. At steady state, the residence time was about one minute, and the reaction temperature was 30–35°C. *Through continuous operations over one week, about 10 kg of* ***2*** *was produced using two 10-mL reactors.* This approach has obvious scale-up potential.

II.C. Semicontinuous Operations

In a semicontinuous or batch flow process, one or more ingredient is charged to the reactor, and the remaining components are added gradually. None of the reaction mixture is displaced through overflow. The total volume of a vessel usually increases as the reaction progresses, and the product is isolated at the end of the operation cycle. This type of operation is useful for exothermic reactions in vessels with limited heat transfer capacity.

A variation of continuous processing is sometimes called semicontinuous processing if the product from a continuous flow reactor is collected in a vessel and isolated at the end of the operation cycle.

The preparation of ethyl 4-pentenoate (**3**, Figure 13.9) is an example of semicontinuous processing [16]. Over a period of 9 hours, allyl alcohol was fed

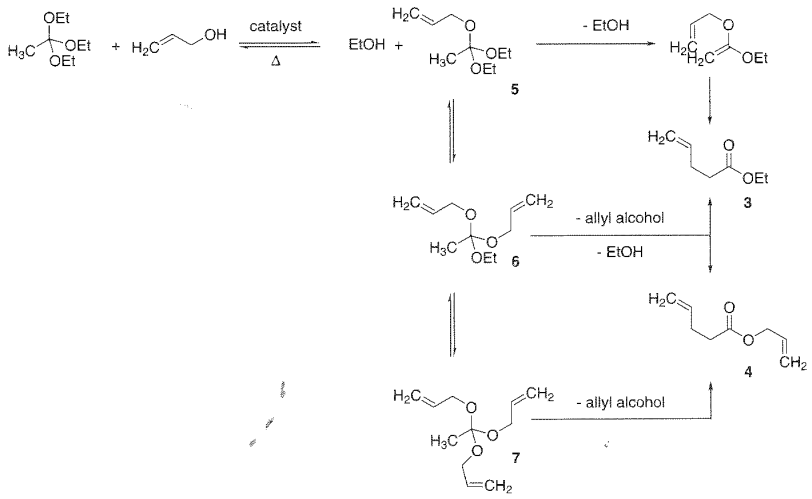


FIGURE 13.9. Preparation of ethyl 4-pentenoate by semicontinuous operations

subsurface to a reactor charged with triethyl orthoacetate, and the by-product EtOH (with some allyl alcohol) was continuously removed by distillation. If allyl alcohol and triethyl orthoacetate were combined in a batch-wise operation, the products were about a 1:1 mixture of **3** and the unwanted allyl ester **4**. The key was to operate the batch so that formation of the mixed orthoacetates **6** and **7** would be avoided. By decreasing the charging rate, allyl alcohol was not allowed to accumulate, and intermediate **5** was converted to the product **3**. Computer modeling was used to simulate conditions and optimize the processing on scale.

A semicontinuous process was developed to crystallize captopril (Figure 13.10). Captopril is highly water-soluble, and to minimize losses to the filtrates, concentrated reagents were used. The large amount of NaCl by-product (3.3 equivalents) "salted out" the product, and captopril was isolated in 92% yield. But due to the high concentration of salts, the product tended to oil. This problem was avoided by slow acidification of the hydrolysate, or by performing a semicontinuous crystallization [17]. To prepare for the semicontinuous process, a crystallizer was charged with a suspension of captopril in water containing NaCl and acetic acid. Into this artificial mother liquor the basic hydrolysate was gradually added, and concentrated HCl was added to maintain the slurry under acidic conditions. In this manner the hydrolysate immediately encountered many seed crystals under conditions that encouraged crystal growth of the product. Captopril was conveniently crystallized without oiling.

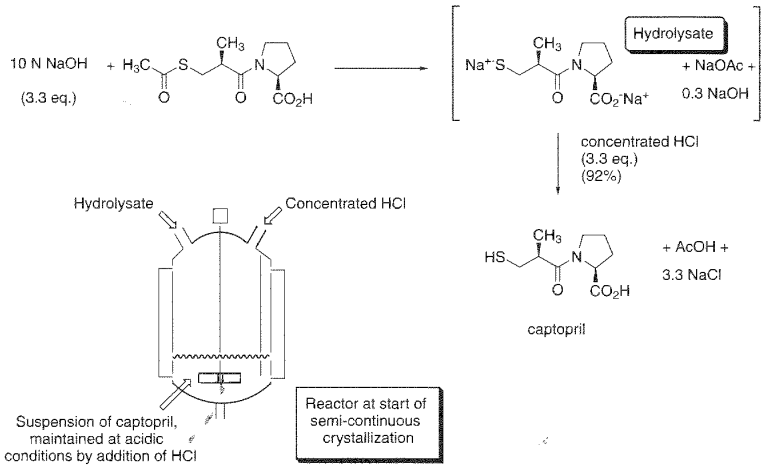


FIGURE 13.10. Crystallization of captopril through semicontinuous processing

II.D. Drawbacks of Continuous Processes

There are a number of drawbacks to using continuous processes. Resources are needed to develop the process: the appropriate residence time to reach a level of suitable reaction completion must be determined under the desired conditions of temperature, flow rate, and any other critical parameters. The reaction system may have limited flexibility for running other reactions. Pressure drops occur when using tubular flow reactors, and these can be calculated [18]. Once the conditions have been developed, time is necessary to reach steady-state conditions. What happens to material produced while the conditions are approaching steady state? Such material is not produced under the desired conditions and hence is atypical of the majority of the batch. Effective control equipment is mandatory for large-scale operations; otherwise expensive material is at risk and may need to be reworked.

Associating batch inputs with product output can be difficult for continuous operations. The FDA frowns on blending batches. One approach is to operate as semicontinuous processes: the material from continuous processing may be collected in a holding vessel for subsequent isolation and drying as a discrete batch.

Despite the drawbacks, for some processes continuous operations may be preferred over conventional batch operations.

III. USE OF CONTINUOUS FLOW REACTORS TO SCALE UP PROCESSES

Continuous flow reactors (flow cell reactors) allow physical effects to be localized and tightly controlled. Focusing physical effects permits scaling up of reactions that may be difficult to accomplish in good yield under other conditions. Many of the examples below can be run on small scale or in a pilot plant with a small amount of time investment.

III.A. Static Mixers

Static in-line mixers were developed for the intimate mixing of many mixtures, from solutions to heterogeneous mixtures (such as two immiscible liquids or gases in liquids) to viscous fluids, such as peanut butter [19]. Commercial in-line mixers are tubes as small as 0.8 in. outside diameter by 6 in. long. Inside the tubes stationary elements are positioned to blend the components of the mixture in primarily a radial manner. By providing a reactor with a high surface-area-to-volume ratio, efficient heat transfer is allowed. Static mixers are used for reactions where good

micromixing is necessary to minimize by-products due to localized excesses of reagents. A static mixer was used in the Kowalski reaction (see Figure 8.17) to minimize by-products that arose from inadequate temperature control and micromixing. "Instant" quenching or pH adjustment can also be achieved by static mixers.

Continuous processes have recently been described in two patents for the preparation of cyclopropylamine, **10**, (Figure 13.11), an intermediate for both the pharmaceutical and agricultural industries. In the earlier patent a two-reactor train was used in a CSTR approach [20]. To the first flask were charged simultaneously a solution of **8** in H_2O and an aqueous solution of NaOCl. The overflow from this reactor was collected in a second reactor which was charged with 45% aqueous NaOH at temperatures below 30 °C. The extended addition allowed for temperature control of the very exothermic hydrolysis and decarboxylation. Subsequently the basic mixture was transferred to a distillation apparatus, and **10** was isolated by distillation in yields as high as 96%.

The later patent described the use of a tubular reactor in a more continuous process [21]. A suspension of **8** and two equivalents of NaOH in H_2O was treated with one equivalent of aqueous NaOCl at temperatures no higher than 15°C. After about 20 minutes the resulting solution was passed through a tubular reactor heated to 80°C, with a residence time of about 1.5 minutes. The output from the tubular reactor was metered into a distillation column that contained refluxing H_2O. The product **10** was recovered by distillation in 93% total yield for two fractions. The modifications offered in the second patent were claimed to increase productivity.

In the two processes to make **10** described above, no mention is made of the urea **11** (Figure 13.10). Hydrolysis of the isocyanate **9** under the conditions stated is probably rapid enough to minimize the formation of **11**.

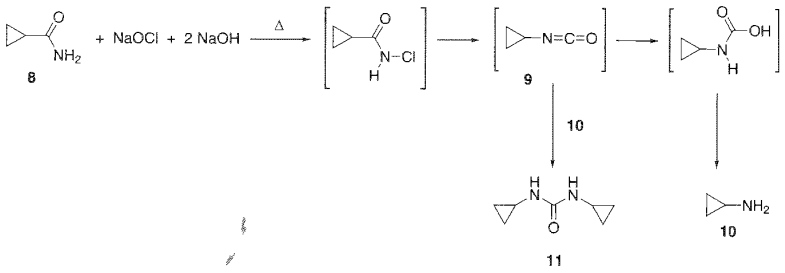


FIGURE 13.11. Preparation of cyclopropylamine by Hofmann degradation

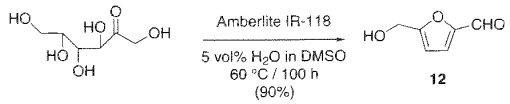


FIGURE 13.12. Continuous dehydration of fructose by recirculating through a bed of ion-exchange resin

III.B. Immobilized Catalysts

The immobilization of catalysts has provided very powerful ways to contain them for convenient work-up and to extend their lifetime. Some examples mentioned earlier included polymeric TADDOLates (see Figure 3.24), using a third phase in phase-transfer-mediated reactions (see Figure 9.6b), and the preparation of MTBE using an ion exchange resin (Figure 13.6). The continuous dehydration of fructose on a laboratory scale has been described (Figure 13.12) [22]. A 0.5 M solution of fructose in DMSO containing 5 vol% H_2O was recirculated through a glass column at 60°C packed with an ion-exchange resin. The eluent was continuously applied to the top of the column by a peristaltic pump. The concentration of 5-hydroxymethyl-2-furaldehyde (**12**) plateaued some time after 50 hours. Recirculating a solution through a column containing a reagent [23] or catalyst can be readily used in the laboratory and scaled up.

Immobilized enzymes have been used for years in the preparation of fine chemicals. Racemic amines were resolved by enzyme-mediated acylation (Figure 13.13) [24]. Solutions of the racemic amine **13** and the ester **14** were combined just before being pumped onto the top of a column packed with the enzyme immobilized on glass beads. The nonenzymatic acylation was slowed down by decreasing the contact time of **13** and **14**, and by conducting the reaction in 3-methyl-3-pentanol. The eluant was drained directly into concentrated HCl in order to convert the unreacted amine into the hydrochloride salt **15** and prevent any further nonenzymatic acylation.

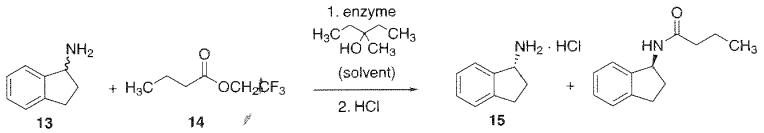


FIGURE 13.13. Resolution of an amine by enzyme-mediated acylation

III.C. Photochemical Reactors

Continuous-flow reactors permit a practical scale-up of photochemical reactions. Direct scale-up from conventional laboratory photochemical reactors would be difficult: Since few large-scale reactors allow light to be transmitted through the sides of the vessel, a light source would have to be immersed in the reaction. Good circulation around any light source is necessary because the power of transmitted light drops off as the square of the distance from the light source [25]. Factors for the scale-up of photochemical processes have been discussed [26].

A practical photochemical bromination has been described (Figure 13.14) [27] for both laboratory and pilot plant operations. Initial investigations by irradiating a solution of **16** and NBS showed that after a lag time the reaction became extremely exothermic, with potential for a runaway reaction. 1,3-Dibromo-5,5-dimethylhydantoin (DBH) proved to be a milder brominating agent and was used in the presence of catalytic Perkadox-16N to initiate the free-radical reaction. The reaction was pumped through a tube irradiated by a sunlamp. The reaction solution was recirculated through the tube reactor until the reaction was complete. This process was successful with inputs of 4.25 kg. For further scale-up a specially designed reactor was employed (Figure 13.14). The reaction was pumped through a Teflon tube coiled around the light source in a cylindrical well, and the residence time was chosen so that the reaction was 97% complete as the solution left the photochemical chamber. Using this equipment the yield of **17** was 90% on a 20 kg scale.

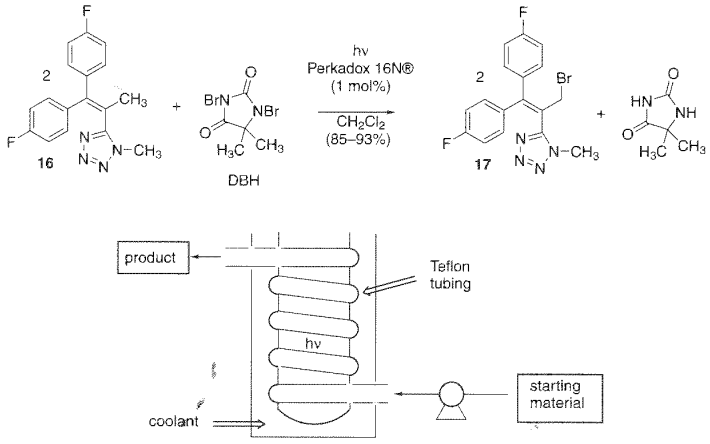


FIGURE 13.14. Practical photochemical bromination on scale

III.D. Microwave Reactors

Microwave irradiation has been used to accelerate many reactions through flash heating [28–30]. The potential of this approach was recently shown in the asymmetric allylic alkylation in Figure 13.15 [31]. BINAP and the other ligand used in this work were chosen because they afford relatively slow conversions under conditions without microwave irradiation.

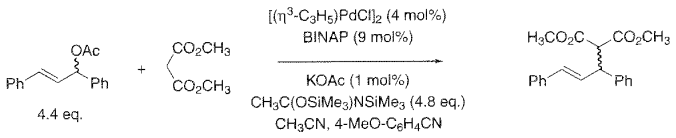
Microwave irradiation generates high temperatures and corresponding high pressures, and reactors should be equipped with pressure relief valves. This concern has limited the use and scale-up of microwave-enhanced reactions. A continuous microwave reactor has been described [32], and continuous flow reactors are available commercially for laboratory use [33].

III.E. Sonochemical Reactors

In the process of sonication, electrical energy is converted into mechanical energy. The sound waves produce cavitation (the process of formation and collapse of microscopic bubbles) which leads to great mechanical shear forces. Particles are "hammered" to form smaller particles, and the increased energy of the system can promote chemical reactions. Ultrasonic chemistry has recently been reviewed [34]. Most research in sonichemistry has been carried out in ultrasonic cleaning baths. Operations on scale can be carried out by using commercial flow cells [35].

III.F. Plug Flow Reactors

Plug flow reactors can provide safe operations for exothermic reactions, as shown in Figure 13.16 [36]. Rearrangement of the acetylene **18** readily took place in hot *N,N*-diethyl aniline or *o*-dichlorobenzene, but several uncontrolled reactions were



Temperature or microwave power	Time (min)	Product yield	Product ee
23 °C	4300	99%	77% (*R*)
35 W	15	99%	65% (*R*)

FIGURE 13.15. Microwave acceleration of an asymmetric palladium-catalyzed alkylation

Sun Ex. 1022

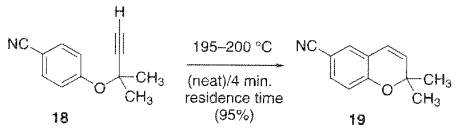


FIGURE 13.16. An exothermic reaction conducted in a plug flow tubular reactor

seen when the reaction was conducted in batch operations. A hazard evaluation showed a strong exothermic reaction at temperatures above 105°C. The reaction could be performed by slowly adding **18** to hot *N,N*-diethyl aniline, but work-up was laborious. The rearrangement could be conducted neat, avoiding all toxic solvents. By passing neat **18** through a narrow hot tube, the heat generated was readily dissipated and the exothermic reaction was controlled. Melted **18** was pumped through a stainless steel tube (0.125 in internal diameter × 25 ft, 20 mL/min.) at 195–200°C, converting 52.3 kg of **18** to **19** in 95% yield. This approach was easily used in both the laboratory and on scale.

TIP: A plug TFR reaction can be carried out using a GC oven as the heat source.

III.G. Electrochemical Reactors

Electrochemical processes are often touted as being "green chemistry" because electricity is considered inexpensive, and toxic metal reagents are usually avoided. Electrochemical processes have produced tons of bulk chemicals [37], the best-known of which may be adiponitrile from reductive dimerization of acrylonitrile (Figure 13.17) [38]. An electrochemical synthesis to manufacture fenoprofen is shown in Figure 13.18, with the magnesium provided as a sacrificial electrode [39]. Flow cell technology has been used for these operations on a commercial basis.

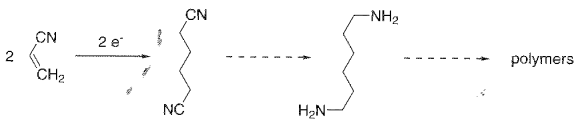


FIGURE 13.17. Electrochemical preparation of adiponitrile

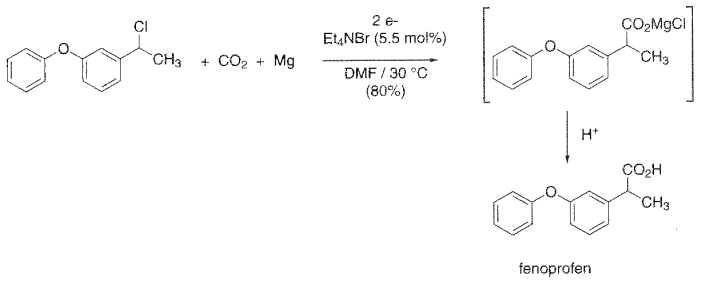


FIGURE 13.18. Electrochemical preparation of fenoprofen

Electrochemical reactions can be readily carried out in the laboratory [40, 41]. Oxidations are a little easier to perform because there is no need to exclude atmospheric oxygen; in fact, many electrochemical oxidations can be simply performed in a beaker. The deprotection of the ß-lactam **20** was carried out in good yield (Figure 13.19) [42], replacing $Ce(NH_4)_2(NO_3)_6$ (CAN). An electrochemical epoxidation was carried out to prepare indinavir sulfate intermediate **21** in good yield (Figure 13.20) [43]. While the stereoselecitvity of this reaction is less than that of the NCS-mediated epoxidation, the product was prepared in only one step. Commercial equipment is available for scaling up electrochemical reactions [44].

TIP: Continuous flow reactors allow practical approaches for processing operations that would otherwise be difficult to carry out on scale. The time invested to set up a continuous process may pay off with significant rewards later.

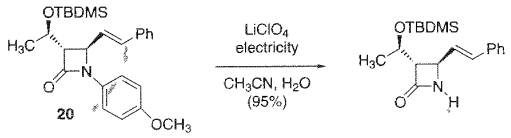


FIGURE 13.19. Deprotection of an amide by electrochemical oxidation

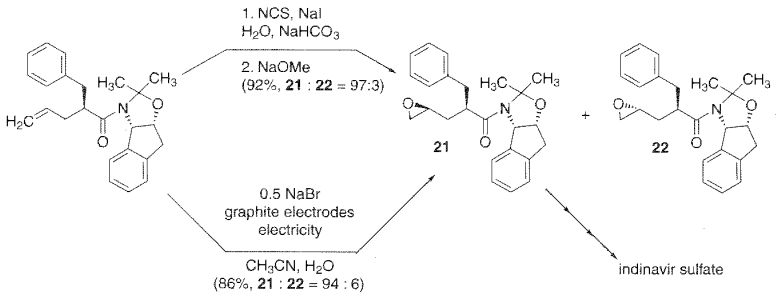


FIGURE 13.20. Epoxidation through electrochemical oxidation

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CHAPTER 14

Preparing for and Implementing the Scale-up Run

I. INTRODUCTION

There are two key objectives for effectively scaling up a process: to anticipate and solve processing problems in the laboratory and to thoroughly execute the scale-up operation.

The detailed method for developing a process and carrying it out on scale varies according to the phase of development of the final product, time pressures to prepare the final product, and the protocols favored by both the group who developed the process and the group carrying out the scale-up run. Considering the variability of these situations, people tend to dismiss discussions on implementing scale-up runs as being not entirely relevant to their own situation. Nonetheless, given the risk and expense involved in scaling up, everyone involved in a project should follow these guidelines to prepare for and implement the scale-up run:

- Thoroughly understand the process.
- Ensure that the process is safe to scale-up.
- Discuss potential process pitfalls on scale with those who will run the process. These discussions should include key control points and potential problems from extended operations, mixing, and out-of-range processing.

- Have reliable in-process controls ready.
- Ensure that the materials on hand are of suitable quality to prepare product of desired quantity and quality.
- Ensure that equipment is available and is able to perform the desired processing.
- Carry out the process thoroughly, relying on the information gained during laboratory process development. Monitor the process closely, using in-process assays. Observe processing at the critical steps, especially for the initial runs.
- After the run, follow up with analyses. Ensure that high-quality material was prepared. Critique processing to identify areas for future optimization.

II. ANTICIPATING SCALE-UP PROBLEMS

For optimal use of personnel and equipment, it is key to anticipate and solve potential scale-up problems in the laboratory. The pressure to solve a processing problem is much less in the laboratory than it is on large scale.

> **TIP:** According to Murphy's Law, whatever can go wrong, will. Plan scale-up operations as though Murphy's law is true.

There are several categories of processing problems encountered on scale. Most arise from nonhomogeneous operating conditions (physically derived impurities), extended processing (chemically derived impurities), and processing outside normal ranges (physically or chemically derived impurities). Operations outside the desired ranges often happen because of difficulties in exerting fine control over processes. Temperature and pH excursions may occur if reagents are added too quickly; metering pumps and control valves may be used to control such additions. Due to the large mass of most reactors used for batch processing, the temperature of the vessel contents may lag behind any operations designed to add or remove heat. Hence it is easy to overheat or overcool vessel contents. The development person is very familiar with processing outside normal ranges and may have purposely conducted runs beyond the optimal limits in order to determine the effects of errors during processing.

Extended processing occurs on scale, relative to the times for routine operations in the laboratory. Transferring large amounts of solvents and solid material requires time. Concentrating off 500 liters of solvent may require well over two hours, depending on the boiling point of the solvent, the equipment used, and the partial pressure during concentration. Draining water from a 500-gallon vessel by

gravity may require one hour; less time would be required if a 3-in. diameter hose were used instead of a 1-in. hose or if the water were transferred by pump or pressure. The rate of heat transfer is proportional to the ratio of surface area to volume; therefore more time is required to reach operating temperatures in larger vessels. It is important to remember that most reactors for scale-up operations are cylindrical; for cylinders, the surface area increases proportionally to the radius, while the volume increases proportionally to the square of the radius (see Table 13.2). Such increases necessitate longer operating times for scale-up that often are not appreciated by those who have no experience with processing on a larger scale or by those who no longer work on scale-up operations.

Extended operating times can allow by-products to accumulate from low-yielding or slow reactions. For instance, heating during extended concentrations can decompose more product than was encountered during laboratory runs. An example is the formation of esters when removing an alcoholic solvent from a solution of a carboxylic acid product (Figure 14.1). The esterification is catalyzed by the carboxylic acid and may be driven by azeotropic removal of H_2O. The rate of esterification will be accelerated by increased acidity of the medium, decreased steric hindrance of R, and use of a primary alcohol [1]. Similar considerations apply for predicting transesterification when removing an alcoholic solvent from a solution of an ester (Figure 14.1). When crystal suspensions are aged for extended times, the product may be contaminated with higher levels of impurities that crystallize more slowly than the desired product (see Figure 11.8). Transformation of one polymorph to an undesired, thermodynamically stable polymorph may also occur when product suspensions are aged excessively (see discussion for Figure 12.3).

The third cause of processing problems on scale is due to difficulties in mixing. Thorough mixing on scale is not instantaneous, as mentioned in Chapter 13. Mesomixing, or radial dispersion of a feed stream as it enters a reactor [2], can be important. Localized pockets of reagents forming during additions can lead to by-products if the reactions are rapid and sensitive to heat or stoichiometry. By applying the snapshot principle many problems due to mixing can be recognized.

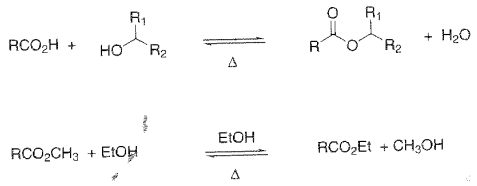


FIGURE 14.1. Esterification of carboxylic acids and transesterification of esters with extended processing

Mesomixing was found to play a significant role in the reaction of α-naphthol with diazotized sulfanilic acid (Figure 14.2) [2]. The formation of the desired product **1** and the minor byproduct **2** are rapid. Even under dilute conditions **1** and **2** can react with diazotized sulfanilic acid to form the bis-azoadduct. Long addition times promoted thorough micromixing and minimized the formation of the bis-azo dye. When the reaction mixture was made more viscous by the addition of hydroxyethylcellulose, levels of the bis-azo dye rose due to less efficient dispersion during addition. Smaller amounts of this impurity were formed when the reagents were added directly into the turbulent area within the radius of the agitator [2]. Further dispersal on scale can sometimes be implemented by spraying the feed solution into the reaction mixture.

Close attention must be paid to heterogeneous conditions that occur during work-up and isolation. Thorough extraction of by-products from rich phase into a second phase may not occur if agitation is poor. Residues left in a kettle from a prior extraction, e.g., saturated brine drained away from a rich extract, may contaminate the product. An insufficient settling time may lead to an incomplete phase split, and impurities carried over in the emulsion may contaminate the product. An aqueous wash could be hung up in an invisible spot (e.g., a dip leg or a hose that was not flushed properly) and contaminate the rich extract. Uneven application of cake washes can lead to inhomogeneous product. Uneven heating during drying can lead to localized decomposition.

III. SCALE-UP CONSIDERATIONS

Many scale-up considerations have already been identified in earlier sections, such as solvent selections, the importance of detecting water in process streams, and

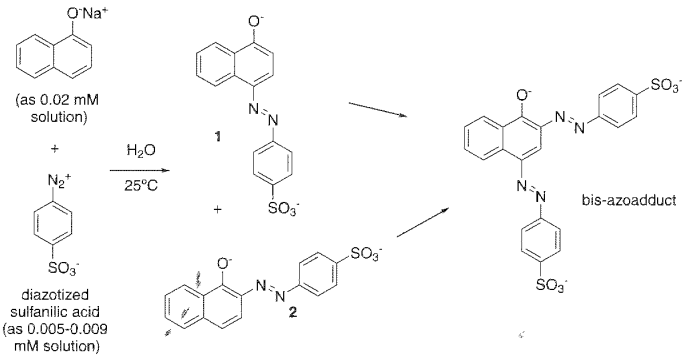


FIGURE 14.2. Diazotization affected by mesomixing

others. This section focuses on areas for implementing efficient, cost-effective scale-up of processes.

III.A. Identify the Goals of Scale-up

The first step in preparing to scale up a process is to identify the goals. It is important to know the required quality and quantity of product to be produced and especially whether quality is more important than quantity or vice-versa. Who is the customer? If the customer is the one who owns of the next process step within the synthetic sequence, some collaboration may occur to satisfy the processing needs of both steps. If the customer is the company that will purchase the final product, rigid specifications may be in place to ensure its quality. The deadlines for preparing material may need to be clarified: There may be a difference between when the customer *wants* material, and when the customer *needs* the material. The deadline will influence the amount of process optimization.

During the development of the process to prepare **6** (Figure 14.3), material prepared from ethyl chloroacetate sometimes converted slowly to the ester **7** [3]. To facilitate the preparation of fosinopril sodium intermediates, the preparation of **6** was investigated, and it was found that the slow conversion to **7** was caused by low levels of nitrilotriacetic acid (**5**) in **6**. The origin of **5** was excess ethyl chloroacetate, which reacted with NH_3 liberated during the hydrolysis of intermediate **4**. By substituting chloroacetic acid for ethyl chloroacetate, basic conditions were not needed to prepare **6**, and the NH_3 generated during the modified Arbuzov reaction was always neutralized through formation of NH_4Cl. Batches of **6** prepared from chloroacetic acid did not generate **5**, and conversion of **6** to **7** was facilitated.

III.B. Safety Considerations

To ensure safety during lab development and scale-up, a complete chemical hazard assessment must be done. Not all reactions need to be thoroughly subjected to analysis: For instance, the basic hydrolysis of an ester in water under relatively dilute conditions would not be expected to pose an extreme safety hazard. Safety testing can determine how exothermic a reaction is and whether the reaction can be conducted safely on scale [4, 5]. For instance, by knowing the amount of heat evolved in a reaction and having assessed the system's ability to remove heat from a reactor, it is possible to calculate the amount of time needed on scale to add a reagent that produces an exothermic reaction.

The safety of operators can also be a key factor, particularly through exposure during reagent additions and isolations of final product. In the nitration of the

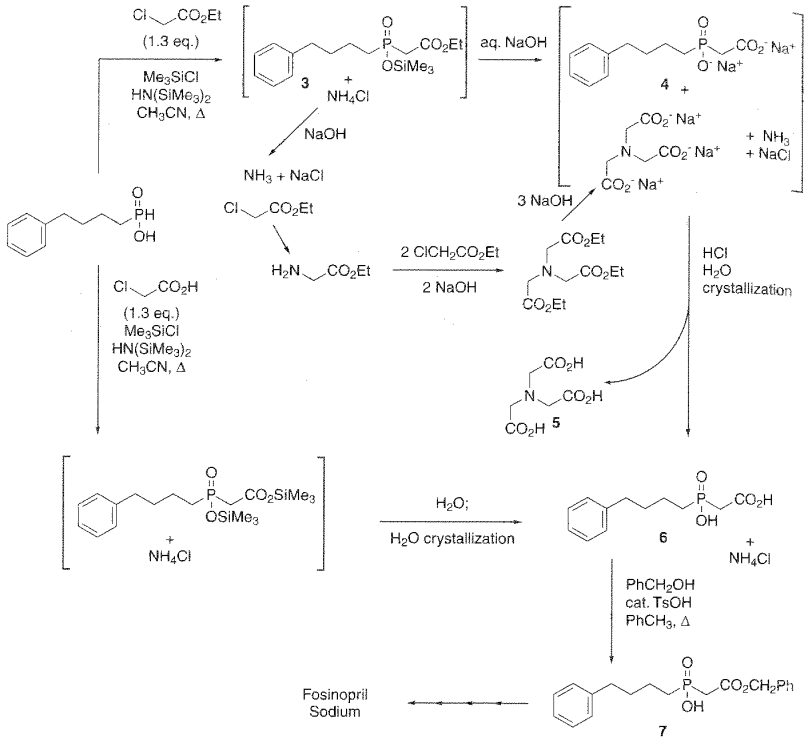


FIGURE 14.3. Reagent substitution to facilitate subsequent conversion of an intermediate

ketone **8** (Figure 14.4), the concern was how to minimize operator exposure while adding the solid **8** to 70% HNO_3 [6]. In this particular process, yields were increased by using 90% HNO_3. Adding the solid **8** to 90% HNO_3 permitted good temperature control of the reaction, but when only about two-thirds of **8** had been added, the reaction became a heavy suspension due to crystallization of

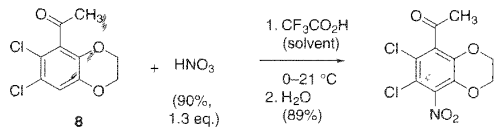


FIGURE 14.4. Nitration of an aromatic ketone using trifluoroacetic acid as solvent

the product. Potential operating difficulties and operator exposure were minimized by an alternative sequence, in which 8 was first charged to the reactor, followed by trifluoroacetic acid as solvent, and then 1.3 equivalents of 90% HNO_3. Safety testing, including CHETAH calculations, RSST, ARC, and DSC, indicated that these conditions were also less exothermic than the initial route. Reaction calorimetry and reactor simulation can also be useful tools for minimizing the time needed for effective scale-up [7].

III.C. Identify Critical Processing Steps

The written process history should be reviewed and discussed with those who have experience with the process. All aspects of the processing need to be considered. If the addition rate of reagents is critical, what is the deciding factor to control the addition rate? Should the reagents be added above or below the surface of the reaction? Will the reagent freeze upon addition to a low-temperature reaction? What is the acceptable temperature range, permissible H_2O content, and endpoint for the reaction? What are the acceptable conditions (e.g., temperature and pH) for the work-up? If the rich extract is to be concentrated, what are the acceptable ranges of temperature, concentration, and H_2O content? Is the crystallization forgiving, or must extreme care be taken? Is specific equipment needed to isolate and dry the final product? These are some of the questions that may be asked.

III.D. Define Equipment Limitations

In most scale-up operations multipurpose equipment is used so one has little choice of specialized equipment. In fact, in many companies it is the equipment available for scale-up operations that defines the processing conditions. For instance, a reduction may be carried out by transfer hydrogenation if a pressurizable vessel is not available for hydrogenation using H_2 from cylinders.

It is important to assess the compatibility of equipment for the intended purposes. However, specialized equipment, e. g., a hydrogenator, may be needed for a reaction. Corrosivity can limit equipment choice: for instance, special equipment is needed for reactions that generate HF, and some metal reactors will corrode if aqueous HCl is used at conditions more acidic than pH 2. Corrosion testing has been discussed in depth [8]. Reactions conducted at −70°C will require specialized equipment, and cooling and maintaining reactions to this temperature may require extended operations. Reactions conducted at −50°C may be more easily carried out. Using steam heat, high-temperature reactions may be conducted as high as 140°C, and other heat media may be necessary to conduct reactions at higher temperatures. These are only some of the considerations; equipment limitations and possibilities should be discussed thoroughly with those who have experience using that equipment.

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TIP: Make sure that hoses, seals, and probes will stand up to operating conditions. CH_2Cl_2 will dissolve some seals and pH probes; unsupported pH probes may be broken inside a reactor. Metal sampling lines may corrode within a reactor, contaminating the batch with metal salts.

The equipment set-up must be designed for safe operations. For decarboxylation of the pyridinone **9** (Figure 14.5), it was necessary to heat the reaction to 230°C; the product **10** (mp 124–126°C) sublimes under these conditions [9]. Condensation of the product on the surface of the vent system could have impeded the exit of CO_2, which would lead to very hazardous conditions under the high reaction temperatures. The vent system was designed to accommodate the maximum rate of CO_2 evolution, and all parts of the vent system were heated to over 135°C to prevent condensation of **10**. Vaporized **10** was trapped in a scrubber charged with 6% NaOH.

III.E. Use a Rugged IPC for the Scale-up Operation

As discussed in Chapter 7, rugged in-process controls are essential for efficient scale-up operations. Obtaining a representative sample from the reactor may be difficult due to concerns about limiting exposure of the operators and the environment to reactor contents, avoiding contamination of the reaction product, and working within constraints that are imposed by the design of vessel in accessing a reaction. Also, if the reaction is heterogeneous, more care must be taken to obtain a representative sample.

When the samples have been withdrawn from the vessels, suitable analytical separations must be available to analyze the reaction. This would include starting materials, products, impurities, and solvents, as appropriate. Quantitations may need to be developed for key components. Karl Fischer titrations may be needed

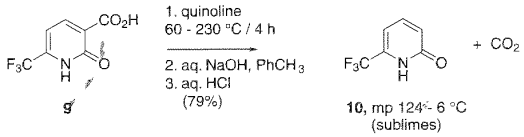


FIGURE 14.5. Scale-up concerns during a decarboxylation

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at various points in the processing. Other key tests may include GC to follow solvent displacements and LOD to determine completed drying of the product.

III.F. Develop Contingency Plans for Incomplete and Runaway Reactions

As part of process development, contingency plans must be developed in case processing is not completed within the expected time period. The most common approach is to extend processing until a suitable endpoint has been reached. It may be necessary to add additional reagents, so a safe way to carry out such additions on scale must be discussed.

For safety purposes, contingency plans may be needed for runaway reactions, assuming that safer conditions have not been developed in a timely manner or the required operations are highly exothermic. In such cases it may be suitable to organize a surge tank, so that any reaction that surges from a vessel can be safely contained by a receiving vessel.

III.G. Know Effects of Extended and Interrupted Processing

One of the two key objectives of scaling up a process effectively is to anticipate and solve processing problems in the laboratory. The effects of extended processing on scale can be examined readily in the laboratory, near the end of the process development cycle. For instance, a small reaction aliquot (perhaps 2% v/v) of a reaction may be kept in the reaction vessel at the reaction temperature for twice the normal time for reaction, and then analyzed by the in-process method used to determine the reaction endpoint. To mimic an extended concentration time, an aliquot of a rich extract may be concentrated to the desired volume and moisture content, then held at the concentration temperature anticipated for scale-up operations. Determining whether impurities will co-crystallize in a product slurry can be accomplished by storing an aliquot at the isolation temperature, then assaying the product. The effects of interrupted processing can similarly be examined in the laboratory. In this manner convenient process holding points may also be identified.

> **TIP:** To anticipate the results of extended processing on scale, subject reaction aliquots to extended or interrupted processing in the laboratory.

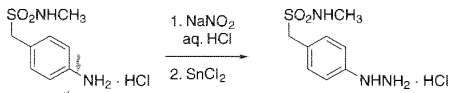
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III.H. Develop Methods to Qualify Components

Before committing resources and expensive chemicals to scale-up operations, examine the components of the reaction to ensure that processing proceeds as expected and affords the product in the expected yield and quality. Reaction components include all chemicals to be used in processing: starting materials, reagents, solvents, and the chemicals, water, and adsorbents used in work-ups. Different grades of reagents and solvents, different lots of commercial materials, and different batches of intermediates may all need to be qualified. There are basically two approaches: to analyze the materials and to perform a use-test.

Analyses are performed to determine the identity and quality of a reaction component. Simple tests are preferred as identity tests, such as pH measurement, titration, suitable comparison of IR spectra to standard spectra, boiling point, refractive index, and others. The quality of components can be assessed by many methods and compared to a standard. Often a standard is set to require that material be no less than a minimum purity, such as $\geq$ 96%. Specifications may also be set to require that a component contain no more than a given level of a specific impurity. By correlating the processing characteristics with product yield and quality, data can be gathered to establish suitable specifications for all components of a process.

The danger in relying on analyses to qualify process components is that analytical tests may not detect a component that had not been identified as critical. Use-tests, laboratory experiments in which batches of process components are used in the manner intended for scale-up operations, can be employed to qualify batches. If the use-test is not satisfactory, the cause can be traced to the batch or batches of materials that were used, and scale-up operations can be modified or postponed until substitute batches are available. Use-test of a batch of amine **11** (Figure 14.6) gave rise to the hydrazine **12** in yields 15–20% below the expected yield; the cause was determined to be the presence of about 50 ppm of iron salts in **11** [10]. As another example, technical-grade $KHCO_3$ contains more K_2CO_3 than does reagent-grade $KHCO_3$, and the pH of a solution of technical-grade $KHCO_3$ may be too high for suitable processing. Use-tests do have disadvantages: The procedure can be time-consuming, and close attention must be paid to



11 12

FIGURE 14.6. Amination of an aniline affected by trace amounts of Fe salts

processing to ensure that batch performance is not influenced by small deviations from the desired procedure.

> **TIP:** Intuition helps, but it is not definitive or quantitative. If in doubt, run the experiment and generate the data. Better to let data speak for itself than to conjecture.

III.I Examine Process Tolerances for Scale-up

If time allows, process parameters should be examined to determine the ranges that will be tolerated and still afford acceptable operations, yield, and product quality. On pilot plant and manufacturing scale, the accuracy for delivery of solvents and reagents is expected to be ±5 vol% and ±1–2 wt%, respectively. All laboratory processes should be expected to tolerate such ranges. If suitable processing cannot be accommodated using such ranges of solvents and reagents, considerations must be made to deliver these reaction components more accurately.

Abuse tests can also be run in the laboratory if time is available. In these experiments reagents are purposely overcharged and undercharged to determine processing fate should errors be made. Experiments may also be carried out to determine the fate of similar excursions in pH, temperature, and other parameters. With suitable in-process monitoring, many of these modifications can be carried out during one or two experiments.

III.J. Ensure That Thorough Product Analyses Are in Place

After the run has been completed, the product should be subjected to thorough analyses: purity, impurity levels, residual solvents, and other appropriate tests. The product may also be examined for suitable conversion to the next intermediate. Yield, product purity, and the amount of product in various streams (e.g., aqueous extracts, mother liquors, and washes) can be used to calculate the mass balance for the processing. Monitoring the mass balance is an excellent way to determine how well a process is understood: A low mass balance may be due to the formation of an impurity that could decrease product yield if not controlled in subsequent runs.

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TIP: Coordinate IPC and final product assays with analysts prior to scale-up run.

III.K. Identify Cleaning Procedures and Waste Disposal Procedures

Cleaning procedures are becoming increasingly important to decrease the contamination of product from batch to batch, particularly when various products are prepared in multipurpose equipment. Cleaning procedures often are directed at the best means to dissolve and remove the reaction product. The solubility of all process components, organic and inorganic, should be appreciated for thorough cleaning. A thorough discussion of cleaning and decontamination has appeared [11].

All reaction streams should be treated responsibly prior to disposal. Keep in mind that it may be necessary to neutralize reactive chemicals prior to disposal (see guidelines in Chapter 10).

III.L. Guidelines for Documentation: Efficient Process Transfer

The actually scale-up of a process is not always the primary goal of process research and development. Instead, the focus is sometimes to describe the process thoroughly so someone else can duplicate the process and prepare the final product on scale. Such technology transfer can occur between the development laboratory, the kilo lab, pilot plant operations, and manufacturing; from the development laboratory to a custom manufacturer; or from colleague to colleague. The goal of technology transfer is the efficient, effective transfer of process information. The recipient should be able to repeat the process readily. Any further development of the process should proceed with minimal duplication of the efforts invested to develop the process in the first place. The process should be thoroughly described in a process transfer document. Guidelines for the process transfer document are shown in Table 14.1.

IV. IMPLEMENTING THE SCALE-UP RUN

The focus of the scale-up run determines how the operations are approached during the run. If the focus is to corroborate process details worked out in lab, then data should be collected, and the process may be optimized during the run.

TABLE 14.1 Guidelines to Document a Process for Technology Transfer

- Provide a reaction scheme, including balanced equations for the reactions and work-ups.
- Provide a reaction flow scheme.
- Describe process thoroughly.
- Include critical process details, e.g., strictly anhydrous conditions.
- Describe in-process controls and in-process assays in detail.
- Include a suitable rework procedure.
- Summarize data using tables of yields, quality, impurities, mass balance.
- Describe procedures to neutralize by-product & waste streams.
- Describe process completely with minimal references to other documents.
- Provide history that led to development of current process.
- Explain what is known and not known in current process.
- Describe what worked and what did not work.
- Ensure that document is reviewed and approved by management.
- Provide a safety assessment.
- Propose safety considerations for scale-up.
- Describe processing concerns relevant for scale-up.

If the goal is to produce larger amounts of material, then only enough optimization is done to allow for the preparation of the required amount, and data may be collected to avoid similar problems in subsequent batches that are part of the current campaign. If the goal of operations is to optimize the use of the facilities, then extensive experimentation may be justified in order to optimize the process before it is scaled up. If the product is to be made under cGMP conditions, then all required data must be collected, and great attention must be paid to avoid contaminating the batch. Under cGMP conditions all processing changes must be documented, with justifications.

Since raw materials and personnel resources are extremely valuable, one must consider how to conduct scale-up operations with maximal efficiency. With attention continuously focused on extended process operations, people begin to work less efficiently. Back-up personnel should be available in case they are needed for efficient coverage of critical processing.

The optimal amount of time for a process is difficult to gauge but may be assessed based on the goals of the scale-up operations. For critical processing, such as the period from charging reagents through carrying out the reaction to the quench, the optimal time for a pilot plant or manufacturing run is ideally less than 8 hours, certainly no more than 12 hours. Often a reaction requiring 8 hours in the laboratory is prolonged to 16 hours due to longer periods needed for weighing and charging components, heating and cooling, and unexpected events such as equipment and chemicals that cannot be quickly located, equipment breakage, and coffee breaks. Nonetheless, the optimal time for a process is the amount of time required to reach the processing goals, and people must be flexible enough to work toward these goals.

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Good teamwork is essential for efficient operations on scale. The team may be composed of chemists, engineers, operators, analysts, and others. It is important to appreciate the experience of other team members, especially the operators, who are most familiar with the scale-up equipment. Roles of team members must be clarified; for instance, direct, hands-on involvement with operations may vary depending on whether the operations must be conducted by union members. In order to make efficient use of equipment and people, goals, critical timing, and personnel involvement must be organized before the scale-up run.

To prepare for a run, it is essential to review a process and examine the details of exactly *how* the operations will be carried out. Vessels must be selected so that reactions can be stirred at the minimum volume of the reaction (V_{min}) and so that the reaction can be contained (and usually stirred) at the maximum batch volume (V_{max}). Gases evolved during processing, for instance during decarboxylation or neutralization of an acidic stream with $NaHCO_3$, may form foams; such reaction mixtures take up a larger portion of the vessel volume. A defoaming agent was added to a Lossen rearrangement to address these problems (Figure 14.7) [12]; however, assays may be needed to detect the presence of any defoaming agent in the product. For the safety of operators and to minimize risk of contamination, any key volumes should be measured without opening the vessels. If the addition of key reagents is to be controlled by temperature, a sensitive temperature probe must be positioned so that the temperature can be monitored at the start and the end of the addition.

Identifying the primary means to control a reaction is key for reliable processing. In many cases, addition rates are not a factor, and a reaction is stirred at a given temperature range until the in-process assay indicates that the reaction is complete. For other reactions the addition rate may be essential to minimize

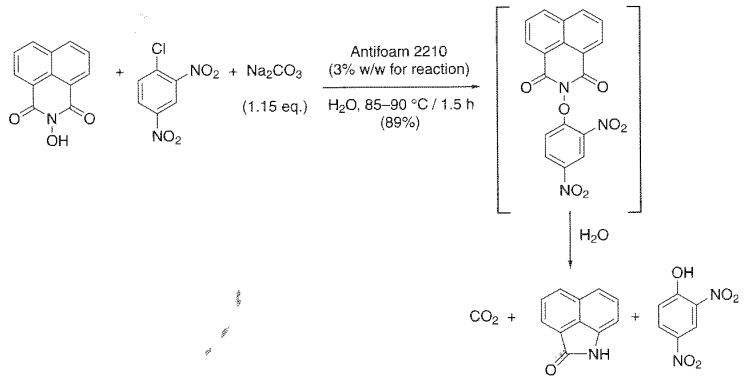


FIGURE 14.7. Defoaming agent used during a decarboxylation

impurity formation. Some reactions, usually heterogeneous ones, are affected greatly by agitation rate; these would include hydrogenations and some PTC reactions that are affected by mass transfer, e.g., the N-alkylation of pyrrolidinone in Figure 14.8 [13, 14]. Many hydrogenations are driven by maintaining a given pressure of hydrogen. Key operating conditions must be accurately monitored and controlled for ready scale-up.

Removing a reaction by-product efficiently can be necessary for good product yields and purities. In the semibatch method of preparing pentenoic acid ethyl ester (see Figure 13.9), efficient reaction of allyl alcohol and removal of the by-product EtOH were necessary [15]. The allyl alcohol was introduced subsurface, to prevent loss by flash volatilization in the head space over the reaction surface. EtOH was displaced from the reaction by operating at a temperature significantly above EtOH's boiling point. A low reflux ratio of about 4:1 (moles of liquid returned to the system:moles of EtOH collected as distillate [16]) was used to ensure that the EtOH was not returned to the reaction.

To avoid difficulties in adding reagents and transferring reaction streams, it is essential to examine *how* these operations will be carried out. In general, adding liquids is more trouble-free than adding solids, and granular free-flowing solids are much easier to add than small particles that are electrostatic or have a tendency to cake upon contact with the reaction solvent. It may be necessary to manually scoop solids into a reactor, and if the solids are irritating or toxic, special personnel protective equipment will be needed. Liquids are easier to transfer to a reaction at a slow, continuous rate; metering pumps or valves may be used to control the additions. There are five means to transfer a liquid: by gravity, siphoning, pumping, pressurizing, or suctioning. The rate of transfer by gravity and siphoning is limited by the height of the liquid above the receiving vessel. Siphoning may be used conveniently on scale to remove a supernatant if dense solids separate from a suspension. Pumping is a faster means to transfer a liquid, and one of the fastest methods is to pressurize a liquid into the vessel using an inert gas. Transfers may also be carried out by applying suction ("partial vacuum") on the receiving vessel and by allowing a liquid to be drawn into the vessel. Transferring reactive materials by suction may be inherently safer than transferring by pressure; care must be taken to ensure that volatile solvents in the receiver are not lost when suction is applied.

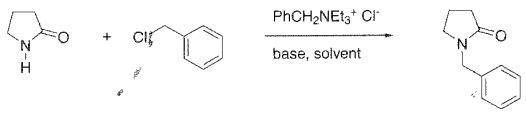


FIGURE 14.8. PTC reaction affected by agitation rate

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How a reagent is introduced into the reactor can determine the selectivity of a reaction. The simplest means is to add a liquid as a steady stream into the reactor headspace above the reaction. If better dispersion is required, a liquid may be added more slowly, added as a dilute solution, or sprayed into the reactor. It may be advantageous to introduce a liquid below the surface of the reaction, particularly if the reagent is volatile. Subsurface additions and spraying operations may tend to plug lines and halt additions. If a neat reagent tends to crystallize under low temperatures, it may be necessary to dilute the reagent with solvent to ensure smooth additions. For instance, neat oxalyl chloride (mp −10 to −8°C) may freeze and plug addition lines upon charging to a Swern oxidation at −70°C. Reliable additions are key to smooth operations.

How a reaction is monitored may determine the assessment of the reaction contents at the time of monitoring. Opening a vessel to withdraw a sample poses concerns for operator safety and contamination of the batch. Directly sampling a reaction is difficult if the reaction is conducted under pressure, at high or low temperature, or in the absence of oxygen. Suitable probes may be fitted into reactors for in-process monitoring, e.g., FTIR. Any samples withdrawn from a reactor must be representative of the reactor contents at the moment of sampling. Reaction aliquots may be withdrawn by suction through sampling tubes inserted into a reactor; such tubes should be purged with N_2 before a reaction aliquot is withdrawn. Considerable thought is justified to ensure that a reaction can be safely and accurately monitored.

When actually implementing the scale-up run, it is crucial to be sure that operations are carried out completely and thoroughly. It is often wise to obtain an additional sample to confirm that the endpoint has been reached for key steps, e.g., reaction completion. Care must be taken that material is not contaminated during transfers and that physical losses are minimal. For instance, it is advisable to clear all transfer hoses by draining or displacing liquids with nitrogen before using such equipment to transfer a different liquid phase. To complete the operations efficiently and safely, it is necessary to be alert for any suboptimal conditions. On-the-job training is necessary for confidently and efficiently operating in any scale-up environment.

TIP: Optimizing a process during a scale-up run is always tempting and occasionally may be necessary. Considerable resources are at stake with a scale-up run, however. When in doubt, perform the operations you know will work. Examine any proposed processing changes later in the laboratory.

Scale-up operations in the kilo lab are often more similar to process research than to pilot plant operations. With kilo lab operations the key is to prepare the desired material by the deadline, using whatever means are appropriate. For instance, Na_2SO_4 or $MgSO_4$ may be used for drying product-rich extracts. (It should be noted that ionizable and polar compounds will adsorb to such dessicants.) Reaction streams may be transferred by pouring or concentrated by rotary evaporation. Compounds may be purified by column chromatography or even triturating. Timely preparation of the desired material is the key for kilo lab work.

Process considerations to prepare for and execute a scale-up run can be broken down into seven areas: safety, documentation, personnel, equipment ability, analytical support, chemicals, and operations. The following checklists will help prepare for a scale-up run and provide guidelines for implementing the run in the pilot plant or the kilo laboratory. Section IV.B reviews the salient points of the checklists, and IV.C provides special reminders about kilo lab procedures.

IV.A. Checklists to Prepare for the Scale-up Run

Safety

Assess the reaction for possible chemical hazards.
Determine if any exothermic reaction can be safely controlled on scale.
Conduct safety review before entering scale-up facility:
- Determine how to handle spills,
- Identify any special personnel protection equipment needed,
- Assess safety results from operating at the extreme conditions, e.g.,
  - Agitation: too much/too little (none at all),
  - Temperature: too high/too low,
  - pH: pH too high, pH too low,
  - Concentration: too concentrated, too dilute.
- Identify any gas evolution and possible pressure build-up. Organize surge tanks if necessary.
- Assess any potential reaction from contact of reaction with heat transfer fluid, and change heat transfer fluid if necessary.

Documentation

Laboratory process description written and approved.
Prepare log sheet (batching record sheet).

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Personnel

Operators chosen.
Operators alerted for possible overtime work.
Analysts alerted for timing and need of critical IPC and final product assays.

Equipment Ability

Confirm suitability of equipment: leak test, pressure test.
Confirm appropriateness of equipment.
Confirm that equipment can be readily and thoroughly cleaned.
Perform solvent test to confirm all lines and manifolds operate satisfactorily. (Especially important for new facility.)
Confirm that back-up equipment is available, e.g., pumps, transfer hoses, portable vessels.
Confirm that the desired operations can be performed within any time constraints.
Confirm that equipment can safely operate and contain all product streams, e.g., off-gassing and sublimed products.
Ensure that anticipated reaction can be stirred at V_{min}.
Ensure that anticipated reaction can be contained at V_{max}.
Determine if agitation rate is variable speed or fixed.
Determine how to measure key reaction volumes without opening the reactor.
Confirm that scrubber can neutralize off-gases if necessary.

Analytical Support

Develop rugged IPC assays.
Order backup analytical equipment, e.g., HPLC columns.
Organize analysts to run crucial assays if tests will not be run by operations team.

Chemicals (Including Solvents and Reagents)

Assay chemicals or submit for assays.
Perform appropriate use-tests.
Any preshipment samples from bulk suppliers used to qualify bulk material.
All chemicals to be used in scale-up operations.

Operations

Complete any appropriate abuse tests (overcharge/undercharge, pH, and temperature excursions) determined after laboratory process description was issued.
Order additional materials as contingency if called for by IPC.

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Discuss the sequence of events and critical processing points in advance with head of operations.
Determine how to obtain representative samples SAFELY during run.
Determine how to transfer liquids: by pressure, gravity, suction, pump.
Determine optimal means to add reagents:
  Above-surface or below-surface.
  Dispersed or as a stream.
  By gravity, pump, pressure, or suction.
  In portions, or continuously.
  Determine if viscous fluid will require extended times for complete transfer; dissolving fluid in a low-viscosity solvent may speed transfer.
Clarify if addition rate is determined by another parameter, e.g., temperature.
Anticipate if poor heat transfer into and out of reactor will extend reaction times.
Discuss use of automated control for fine control of conditions, e.g., addition rate, temperature, pH, pressure.
Develop action plans for any incomplete processing, as determined by IPC.
Consider where any interfacial phase should go when performing phase splits.
Discuss use of vacuum to reduce distillation/concentration times.
Discuss key procedure for isolation of product, e.g., crystallization conditions.
Discuss equipment compatibility, e.g., will vessels, pumps, fittings, and gaskets be decomposed by contact with solvents, reagents, or reaction streams.
Discuss physical properties of isolated product, e.g., compressibility of crystals, melt-down in dryer.
Discuss equipment choices for isolation and drying, e.g., how to ensure even application of wash, whether to mix during drying.
Discuss results of extended processing and out-of-range processing.
Identify critical points where processing must be completed.
Identify suitable process hold points.
Discuss how operations may be overlapped to decrease the time that key equipment is occupied.

IV.B. Guidelines for Executing the Run in a Pilot Plant or Manufacturing Operation

Safety

- Everyone has a responsibility for safety.
- Know where emergency equipment is located.
- Show your concern for safety by setting an example.
- Watch out for obstacles that may get in the way.
- Speak out about dangerous operations.
- Help out in emergencies, but use your judgment before being a hero.

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Documentation

- Use completed log sheet and approved procedure.

Personnel

- Prior to a run, discuss operations with operators, engineers, and those handling the materials and equipment.

Equipment

- Confirm that all equipment is clean and ready.
- Confirm that there are no unsafe conditions, e.g., that sampling devices can safely contain a hot reaction mixture, exit paths are not obstructed in the event of an emergency, etc.

Analytical Support

- Confirm that IPC assays and reagents are ready.
- Confirm that analytical equipment is equilibrated.
- Confirm that standards have been run, with satisfactory chromatographic separations.

Chemicals

- Confirm that all components are cleared for use, including approval from QA (Quality Analysis) or QC (Quality Control).
- Confirm that all components have been located.

Operations

- Be present at all critical operations.
- Make sure that all transfers are carried out completely, and minimize opportunities for contamination.
- Conduct all IPCs in a timely fashion, and report them promptly.
- If there is doubt about the results of an IPC, address this quickly. It may be advisable to obtain another sample and reassay.
- When not carrying out operations, help out by being present but not by getting in the way.
- Be observant to foresee problems for the current and subsequent runs.

IV.C. Guidelines for Executing the Run in a Kilo Lab Operation

- Make sure all equipment is ready and fits in fume hood.
- Make sure all valves and equipment work, with no leaks.
- Position catch basins in case a vessel breaks.
- Measure key volumes in glassware before (hot) solutions are charged.
- Remove small amounts of H_2O by filtration through paper.
- Use polish filtration to remove insoluble impurities (good housekeeping).
- Optimize chromatographic separations on a small scale before committing resources to large-scale chromatographic purifications.
- Recognize that operations will take longer than they did in the lab.

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CHAPTER 15

Troubleshooting

I. INTRODUCTION

Financial considerations, such as product quality, yields, productivity, and costs of goods, are the driving forces behind problem solving and troubleshooting. Impurities can cause rejected batches, thus impacting negativly on productivity even if the batches can be reworked and ultimately produce product of acceptable quality. Decreased yields may require running additional batches, thus increasing cost and decreasing productivity. Productivity concerns may be addressed by "debottlenecking" a process, that is, by eliminating or minimizing the accumulation of process intermediates so that equipment can be used optimally. The costs of goods may be decreased by raising yields, recovering solvents, and substituting less expensive reaction components. On a manufacturing scale the impact of problem solving can be much greater than it is in the laboratory, which is why many companies have staff dedicated to overseeing manufacturing operations and resolving technical difficulties.

Troubleshooting is focused problem solving on an accelerated basis, due to the increased pressure to solve the problem quickly. (The person doing the troubleshooting is usually "under the gun.") With troubleshooting, the financial impact of the problem is readily apparent.

Troubleshooting is often necessary even for established processes that have been run routinely for years. The critical qualities of products and intermediates can change over time, which can necessitate redefining the processes to prepare them. With established processes, operations may become more lax due to

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familiarity, leading to suboptimal processing. Under such circumstances it may be difficult to discern the significant deviations from the desired processing. Often established processes are subjected to evaluation and optimization because even a small yield enhancement can lead to a significant financial benefit. In an attempt to reduce operating costs, less expensive grades of reagents and solvents may be employed, and the impurities in these reaction components can have an adverse effect on processing. These are typical examples.

Problem solving applies the scientific method. First the hypothesis is formed; then an experiment is run to test the hypothesis. Data resulting from the experiment is analyzed to determine if the hypothesis is correct. Then either the beneficial change is implemented, or the process is repeated until satisfactory conditions are found.

When a troubleshooting problem has been identified, the first measures are often to apply a patch to the process. Patches are temporary measures that may be instituted to raise the quality of a product or intermediate. A patch may involve a recrystallization to eliminate or reduce the levels of impurities generated in the isolated material; it may involve recrystallizing the intermediate producing this material. Often measures to develop patches are begun immediately after a problem has been identified, particularly when the problem arises in a manufacturing operation.

TIP: Develop a patch as insurance. Such development can be investigated in parallel with troubleshooting.

Quantitative (or at least semiquantitative) assays for the intermediates and product are useful for following the impact of reactions and operations throughout the processing. Often in-process assays can be used.

TIP: The best time to initiate troubleshooting is before a problem has occurred on scale.

II. PHYSICAL AND CHEMICAL CAUSES OF PROCESSING PROBLEMS

Most processing difficulties on scale arise from extended processing, inhomogeneous operating conditions, and operating processes outside the optimal ranges, as discussed in Chapter 14. Reviewing the batch sheet or any other history of a batch can identify extended processing and any operations outside the optimal

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ranges as possible causes of processing aberrations. Viewing process operations where the problem occurs may help identify a physical cause of the problem. For instance, impurities in a product cake may not be removed if the wash liquid was not evenly applied to the wet cake, and such uneven application of the wash may be detected during a site visit.

TIP: To troubleshoot a process efficiently, try to view the operations first-hand.

When processing problems occur on scale, they are due to the actions required to carry out the processing, to the chemical nature of the reaction components used, or to a combination of both. When difficulties arise, those responsible for the operations usually suspect the process inputs, and those who developed the process in the laboratory tend to suspect the physical manipulations of the processing. A more objective analysis often reveals that if a successful use-test was run on all components of the reaction prior to the scale-up run, difficulties on scale are probably due to the processing. Thus the processing must be optimized to achieve the desired results. The role of chemical inputs in processing difficulties on scale can be determined by laboratory use-tests. The rationale is shown in Figure 15.1.

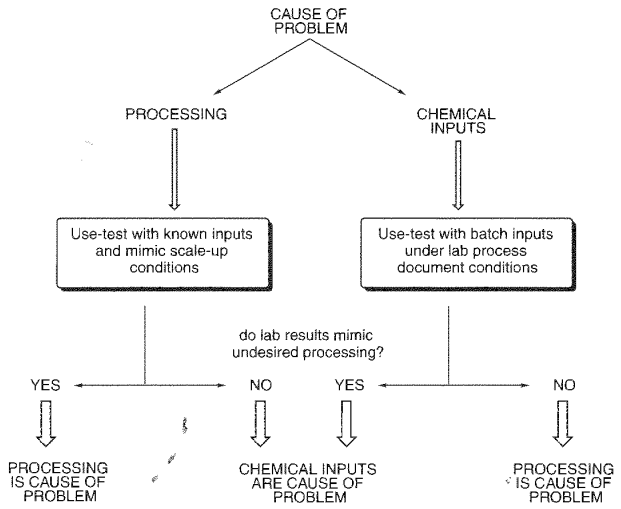


FIGURE 15.1. Use-tests to identify cause of processing problems

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To identify the cause of processing difficulties by use-testing, the most direct approach is to use batches of chemicals that have given suitable results in laboratory runs and sequentially substitute a single input from each of the components used in the scale-up run. If suitable results are obtained with this run, the substituted component is acceptable; if processing is not satisfactory, and no significant process deviations occurred, the substituted component was responsible for the undesired result.

Extensive use-testing was conducted for the reaction sequence shown in Figure 15.2. The supplier of almost every starting material and reagent was different from the suppliers of the materials used while the process was developed in the laboratory. In anticipation of scaling up an early process for a pilot plant run, an initial use-test returned the tosylate **3** with a yield appreciably below the expected range of 42–50% [1]. The cause for the decreased yield of **3** was not apparent, and repeated use-tests gave erratic yields. Each step—and an assessment of the potential impact of that step on decreased yield—was considered, starting from the end and working toward the beginning of the process (Table 15.1). Analysis of the combined mother liquor and washes indicated an acceptable mass balance, with higher-than-normal levels of the product **3** and an unknown impurity. The isolation protocol had been conducted according to the laboratory procedure, so it was not believed that the product had dissolved while the wet cake was washed on the filter. The next suspect was the efficiency of the crystallization, but when the crystallization protocol was rigorously followed in a use-test, the isolated yield of **3** did not improve. Nor did the yield improve to the earlier yield range when laboratory EtOH was substituted for the EtOH to be used on scale-up. The

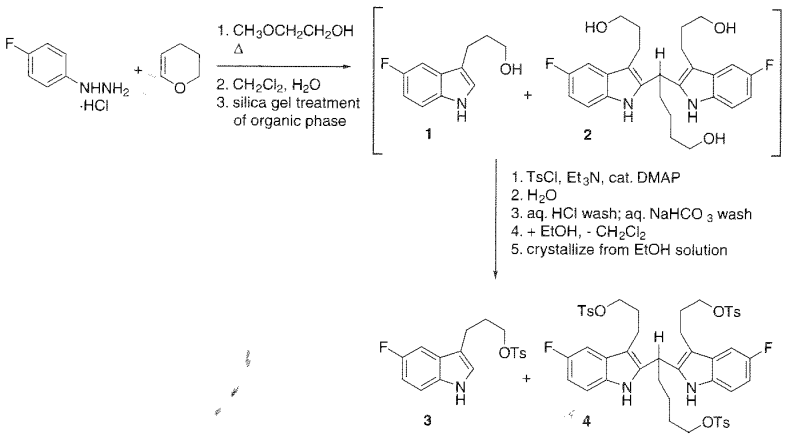


FIGURE 15.2. The process to prepare a tosylate, analyzed by use-tests

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TABLE 15.1. Troubleshooting the Reason for the Low Yield in the Isolation of Tosylate 3

	Anticipated impact on yield	Action	Results found, as compared to acceptable runs
Processing Step			
Drying	Low	Check temperature of drying oven.	No change
Isolation	Medium	Check mother liquor and wash streams for desired product.	High levels of both product and impurity
		Confirm wash applied at appropriate amount and temp.	No change in wash protocol
Crystallization	High	Confirm crystallization carried out at appropriate concentration and temperature.	No change
Extractions and work-up	Low	Confirm extractions according to protocol.	No change
Quench	Low	Confirm quenching according to protocol.	No change
Reactions	Medium	Confirm charging, temperature, and additions according to protocol.	No change
		Confirm appropriate endpoint reached.	No change
Quality of ingredients			
Hydrazine	High	Analyze quality; conduct use-test.	High quality by HPLC and NMR; satisfactory use-test
Dihydropyran	Medium	Analyze quality; conduct use-test.	High quality by GC and NMR; satisfactory use-test
$H_3COCH_2CH_2OH$	Low	Analyze quality; conduct use-test.	High quality by GC and NMR; satisfactory use-test
Silica gel	Low	Conduct use-test.	Unsatisfactory use-test; high level of impurity in filtrate
CH_2Cl_2	Low	Conduct use-test.	Satisfactory use-test
TsCl	Medium	Analyze quality; conduct use-test.	High quality by GC and NMR; satisfactory use-test
Et_3N	Low	Conduct use-test.	Satisfactory use-test
DMAP (catalytic)	Low	Conduct use-test.	Satisfactory use-test
EtOH	Medium	Conduct use-test.	Satisfactory use-test

extraction and quench operations were dismissed as having little impact on the overall yield. Analysis of the in-process data showed that the indolization had proceeded to the expected endpoints. The raw materials were analyzed, and no significant impurities were present. Except for the hydrazine starting material, all the components were available in bulk quantities, and no significant impurities were expected. Use-tests of the hydrazine gave an acceptable yield of the tosylate **3**. The other reaction components were use-tested. Finally, when flash chromatography-grade silica gel was substituted for the silica gel purchased for the scale-up run, the yield rose to the range seen with the laboratory development. This result indicated that the low isolated yield of **3** was due to characteristics of the silica gel purchased in bulk.

In order to identify a batch of silica gel for suitable scale-up of the process, it was necessary to understand its role. Treatment with silica gel in a batch mode had been instituted to absorb some "polymeric impurities" formed during the Fischer indolization. The combined mother liquor and washes from reactions treated with flash chromatography-grade silica gel were analyzed by HPLC as consisting of primarily the desired alcohol **1** along with one main impurity. The level of this impurity was increased when a reaction was treated with silica gel purchased for the scale-up runs. The impurity was isolated by preparative chromatography and identified as the triol **2**. In the combined mother liquor and washes from isolation of the product **3** there was primarily one impurity, different from **2**, and this impurity was significantly greater in the streams that had been treated by silica gel purchased for scale-up. The latter impurity was identified as the tritosylate **4**. Thus it was concluded that treatment with the silica gel purchased for scale-up did not remove enough of the triol impurity **2**, which was subsequently tosylated to give **4**. The presence of increased levels of **4** (and perhaps other impurities not detected by the HPLC method) decreased the isolated yield of **3**. The key factor that permitted the adsorption of **2** was probably the increased pore size of the flash chromatography–grade silica gel. The solution for ready scale-up was to use flash chromatography–grade silica gel, and acceptable yields for this process were obtained.

Researchers are rewarded for rapidly solving processing problems, and thus it is key to minimize the number of investigations and use-tests needed to identify the cause of processing problems. Experience and intuition did not lead to the rapid selection of silica gel as being the cause of reduced yields in the preparation of **3**. As in this case, a more organized approach may be helpful in troubleshooting, especially when the chemist is confronted with a large number of variables that have roughly equal probability of causing the processing problem. For example, suppose that eight reaction components that may effect a particular process negatively. By use-testing one variable at a time (the OVAT approach) the total number of use-tests would range from one to eight. To substantially reduce the number of use-tests, more than one variable can be changed in any run; by examining half of the variables in a use-test may also reduce number of tests. The first

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experiment would use-test four of the eight components, using for the other reaction components inputs that had been qualified by acceptable performance in laboratory runs. If the outcome of this use-test was a reduced yield, then additional use-tests would concentrate on learning which one of the four suspect components was the cause of the reduced yield. In this way the total number of use-tests is reduced from eight to three or four runs (see Figure 15.3). This approach may also help to identify problems arising from the interaction of more than one variable.

III. STEPS FOR TROUBLESHOOTING A PROCESS

The pressure to find a successful resolution to a processing problem can be intense. Once a processing glitch has been determined to be suitably serious to warrant investigation, one must compare the conditions of the wayward batches with those of successful batches. The troubleshooting approach outlined in Table 15.2 can be used to solve problems quickly.

TIPS: To save time in troubleshooting a process,

- Examine first the processing steps that occurred immediately prior to the point where the problem was noted. Then examine earlier steps, working backward to the beginning of the process.
- Address operations that are simplest to change first.

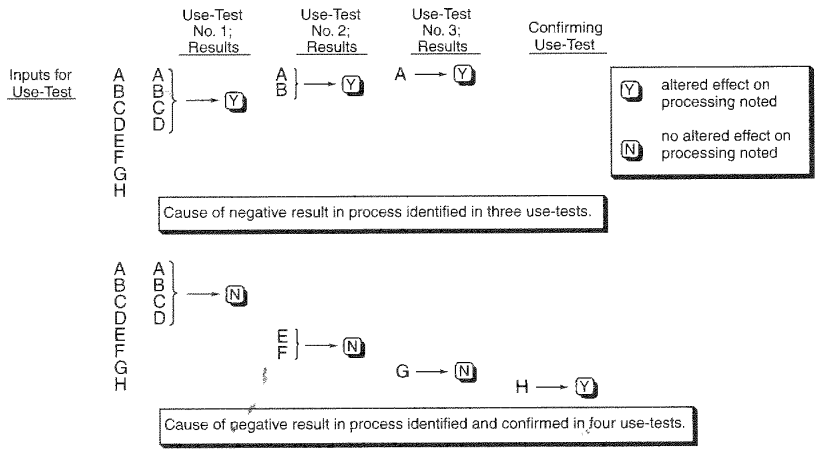


FIGURE 15.3. A systematic approach to troubleshooting a problem with multiple variables

TABLE 15.2. Steps for Troubleshooting

1. Confirm that there is a problem.
2. Determine whether the problem is serious enough to warrant spending time to investigate and resolve it.
3. Compare processing steps to those used in successful batches to determine where differences occur.
4. Use processing intuition to sort out which changes are most likely to have a negative impact.
5. Propose the probable cause of the problem.
6. Identify an assay to monitor key processing.
7. Examine processing to determine if the problem has been identified.
8. Confirm that the cause of the problem has been identified.
9. Propose alternative treatments to eliminate the problem, and institute these steps.
10. Monitor the results of the changed processing to confirm whether the changes are effective.

1. Confirm that there is a problem.

To allocate personnel resources most efficiently, first confirm that the problem exists. It is often wise to check any calculations, especially those used for purity or mass balance determinations. Check the reproducibility and reliability of the assay method and calculations. Inconsistent sampling can produce anomalous results. When monitoring scale-up batches, it may be wise to obtain another sample from the reaction; then prepare another sample for IPC analysis and reassay. Repeating the assay can either corroborate the problem or indicate that the analytical method needs additional attention. Perhaps the problem had nothing to do with the assay and was caused by sample preparation, e.g., dirty laboratory glassware. Measured process volumes may not be exact: the accuracy for laboratory glassware that is not intended for volumetric measurement may be $\pm 15\%$, and for pilot plant equipment $\pm 10\%$. Weighing samples generally permits more accurate quantitations. Some examples of actions to confirm the existence of a problem are shown in Table 15.3.

TIP: Do not place too much importance on the results of just one assay!

2. Determine whether the problem is serious enough to warrant spending time to investigate and resolve it.

Troubleshooting requires time. What one individual views as a problem may not be a significant barrier to achieving the overall goal. It may be appropriate to check with management or someone who has an overview of the situation before investing time and resources to identify the cause of a problem and resolve the difficulty.

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TABLE 15.3. Confirming the Presence of a Problem

Potential problem	Actions
Quantitation or purity out of expected range	Confirm accuracy of analytical quantitative method for the amount of material assayed. Reassay originally prepared sample (reproducibility). Make another dilution of the original sample, and compare results. Obtain duplicate sample and assay.
Yield or mass balance out of expected range	Confirm weight of isolated product. Confirm accuracy of volume or weight measurements on mass of reaction. Confirm that a representative sample was withdrawn from reactor. Get another sample if there is any question. See above concerns on quantitation.
New impurity seen	Confirm existence and level by duplicate assay. Confirm no change in quality of input batches. New impurities are especially important for API.
Increased impurity level found	Examine the means of data analysis. For instance, in HPLC chromatography broad peaks or small peaks eluting on the shoulder of a large peak may require special integration parameters. Check for reproducibility with the same sample. Check the MDL and MQL: Less significance may be applied to the level of a peak that is quantitated just above the limit of detection.

3. Compare processing steps to those used in successful batches to determine where differences occur.

The most difficult part of troubleshooting is often identifying the true cause of a problem. There are four main barriers: incomplete data, conflicting data, confounding data, and opinion. The best way to identify the physical cause of a problem may be to view the operations firsthand. Once the true cause of a problem is known, designing experiments to resolve the difficulty is often straightforward.

Problems can often be identified by comparing the processing of successful runs to that of problematic runs. Ideally the appropriate data have been recorded in notebooks, batch records, or log sheets. Look for any special observations and any extended or delayed processing. Results from IPC testing can be very revealing. If conclusions from different sets of data are conflicting, it may be important to resolve the differences in order to identify the cause of the processing difficulties.

The start-up of the initial manufacturing process to prepare the phosphinyl acetic acid **6** by modified Arbuzov reaction (Figure 15.4) proceeded as anticipated. Subsequent manufacturing campaigns produced off-colored batches of **6**, and the reactions did not proceed to completion [2]. It was known that equal amounts of trimethylsilyl chloride (TMSCl, bp 57°C) and hexamethyldisilazane (HMDS, bp 125°C) were needed for rapid silylation [3]. To control the rate and hence exothermicity of the reaction, HMDS had been added to the TSMCl-containing

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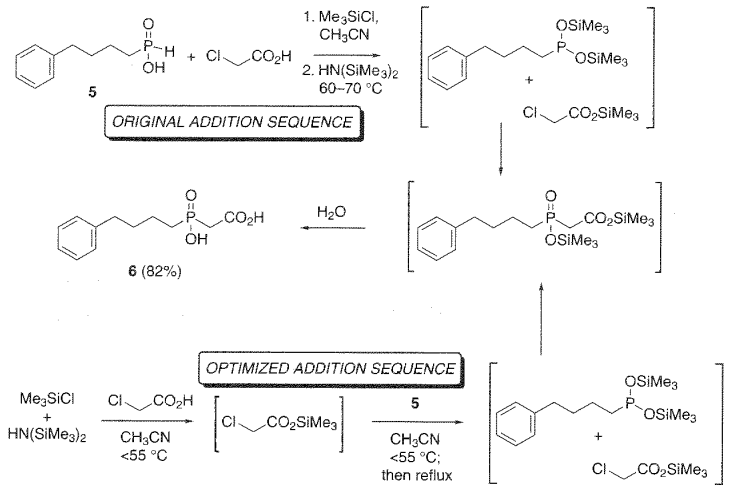


FIGURE 15.4. Altering an addition sequence to minimize loss of a reagent

reaction at 60–70°C as the limiting reaction component. Examining the batch records showed that the incomplete batches were formed when the addition of HMDS was extended or interrupted, and that during the processing of these batches acidic vapors (TMSCl and/or HCl) were released. Incomplete reactions were attributed to the loss of TMSCl. Conducting the process at lower temperatures did not lead to complete consumption of **5**. An alternative process was developed to contain the TMSCl by combining that reagent with HMDS. Then a solution of chloroacetic acid was added, followed by a solution of **5**, while maintaining the temperature below 55°C. To complete the reaction, the mixture was refluxed. Using the optimized process, the reactions were reliably completed, and no acidic vapors were released. Isolation of high-quality product was ensured by extraction into MIBK and crystallization; recrystallization of **6** had been developed as a patch to rework low-quality batches of **6**.

Confounding data can lead researchers unknowingly away from steps to resolve a difficulty. For example, an expensive rhodium-on-carbon catalyst was thought to be necessary to hydrogenate the acetylenic amine **7** with minimal generation of the hydrogenolyzed by-product **8** (Figure 15.5) [4]. Hydrogenolysis with Pd/C catalysts may have been facilitated due to the tendency of palladium to cause double bond migration [5]. Laboratory investigations with the Rh catalyst had been done using hydrogen at atmospheric pressure. By increasing the hydrogen pressure to about 20 psi when using the less expensive Pd/C catalyst, formation of the hydrogenolyzed impurity was decreased to less than 1%. A fresh approach such as this can help solve a problem.

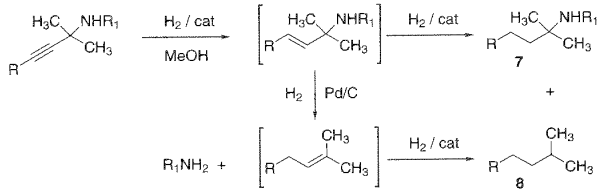


FIGURE 15.5. Metal-catalyzed reduction of an acetylenic amine

Emulsions sometimes cause processing problems during extractions on scale. One way to identify the physical or chemical factors causing the emulsion is to compare processing conditions in the laboratory and on scale. Emulsions may be encountered when a batch is stirred below the routine processing temperature. A cold emulsion may be broken by warming the batch slightly, with just enough agitation to aid heat transfer. Adjusting the pH may also break an emulsion. For instance, basic aqueous phases will sometimes emulsify with $PhCH_3$ or CH_2Cl_2. Filtration through a bed of diatomaceous earth may remove small particles that cause emulsions. A small amount of an electrolyte, e.g., NaCl, may be added to the aqueous phase to break emulsions. Adding a small amount of a more polar organic solvent, e.g., CH_3OH or EtOAc, may also break an emulsion [6]. Most of these approaches can be examined quickly by using a sample of the emulsion withdrawn from the reactor.

TIP: Examine any tendency for emulsion formation in the laboratory. Processing can be delayed by hours if emulsions are encountered on scale.

A common cause of emulsions is overagitation. Excessive agitation can sometimes lead to emulsification. The tendency to form emulsions can be investigated in the laboratory by rapidly agitating the mixture with an overhead mechanical stirrer. Small particles can also cause an emulsion. Changing to another solvent may agglomerate the solids so that these contaminants can be removed. When a *t*-butyl ester was formed by reacting an acid with isobutylene in CH_2Cl_2 (Figure 15.6), an unbreakable emulsion layer formed upon extraction. When the organic phase containing the emulsion was withdrawn and the solvent was exchanged for

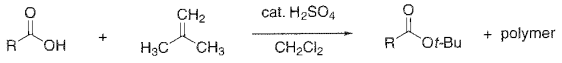


FIGURE 15.6. Formation of particles during esterification with isobutylene and catalytic acid

EtOH, a polymeric material, perhaps polyisobutylene, precipitated. Routine filtration removed these solids [7]. The usefulness of electrolytes and polar solvents to avoid emulsions can also be examined in the laboratory.

4. Use processing intuition to sort out which changes are most likely to have a negative impact.

Experience with the process and troubleshooting problems on scale are very valuable to decrease the amount of time needed for troubleshooting. Those who have developed the process are usually most familiar with the nuances and pitfalls of the process. These people often can very quickly troubleshoot a problem with their process by relying on their experience and intuition. Sometimes it is necessary to enlist the help of those who did not develop the troubled process. People with different and perhaps broader experiences may be able to see beyond the subtle processing effects that are too familiar for others to recognize. Having no vested interest in defending the development of this process, the "outside expert" may solve the problem dispassionately and quickly.

5. Propose the probable cause of the problem.

Once the true cause of a problem has been identified, devising a solution that avoids these difficulties in subsequent batches is usually straightforward. In many cases it is necessary to isolate and identify a new impurity in order to determine the reason behind suboptimal yields.

The initial process in Figure 15.7 produced the sulfamate **10** in high quality at 65–72% yield on a scale of up to 700 g of starting material [8]. When the process

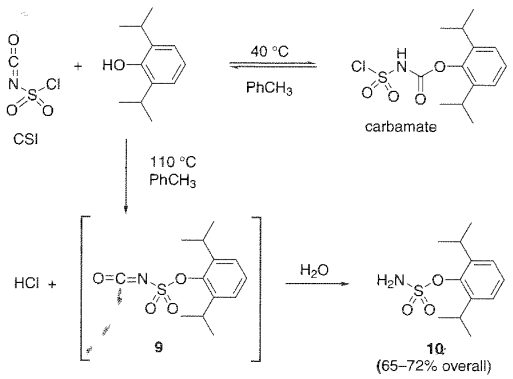


FIGURE 15.7. Reaction intermediates in the preparation of a sulfamate from CSI

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was scaled up to run 12 kg of starting material, the product was colored and only about 75% pure. Two recrystallizations with activated carbon improved the quality, but the overall yield was only 32%. UV-absorbing particles were found in crude **10**, and these were identified as having arisen from degradation of the heat exchanger by contact with chlorosulfonyl isocyanate (CSI). Important safety issues were at stake if degradation allowed the coolant to leak into a batch that contained CSI!

The lower yield was correlated with incomplete formation of the isocyanate intermediate **9**. In-process FTIR demonstrated that at low temperatures the starting materials were in equilibrium with the carbamate. At higher temperatures the isocyanate **9** and HCl were formed. In the laboratory the reaction had been conducted under a vigorous reflux, but on scale there was a gentle reflux and very little head space in the reactor. Therefore the scale-up conditions did not encourage the loss of HCl, which then drove the formation of **9**. With rapid agitation and suitable equipment modifications, the process was conducted with 24 kg inputs of starting material and returned **10** in 65–68% yields after recrystallization. In an optimized process the reaction was conducted in refluxing heptane and monitored by in-process IR; H_2O was added to quench excess CSI and hydrolyze **9**, and after decarboxylation the **10** that precipitated was dissolved with the addition of a small amount of THF. Impurities were removed by washing the organic phase with H_2O at 68–75°C, and upon cooling, the crystallized **10** was isolated in 86% yield on scale [8].

The importance of maintaining conditions that will expel a volatile amine by-product were noted with the preparation of the disphosphonate **14** (Figure 15.8) [9]. In the best-mode example of this patent, it is stressed that the reaction was

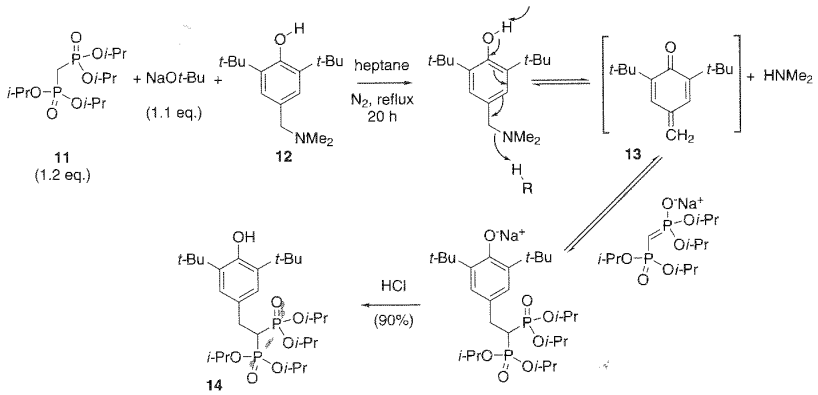


FIGURE 15.8. Preparation of a diphosphonate driven by loss of dimethylamine

stirred under reflux with a slow nitrogen purge. The reaction intermediates are probably in equilibrium with each other, but the reaction can be driven to completion by the loss of dimethylamine. For suitable scale-up of this process, it would be necessary to use conditions to encourage the loss of the by-product dimethylamine.

TIPS: For rapid troubleshooting:
- Balance the equation.
- Apply the snapshot principle.

6. Identify an assay to monitor key processing.

The existing IPC method may serve to quickly monitor key processing steps. It may be necessary to develop a new assay if the existing one does not enable the type of investigations that troubleshooting requires. The accuracy and reliability of the new method are more important than convenience.

7. Examine processing to determine if the problem has been identified.

Monitor the processing to determine if the cause of the problem has in fact been identified and if suitable changes can be implemented. This can often be done in the lab, which offers greater convenience in controlling and monitoring most reactions. It may be necessary to extend the processing in the lab to mimic what occurred in the plant. The ideal location to examine a problem may be at the site the problem occurred: in this way, there is no additional step to transfer the optimized process.

8. Confirm that the cause of the problem has been identified.

Once the cause of the problem has been located in Step 7, it is valuable to confirm this identification. It may be necessary to analyze data from additional batches or to run a confirming use-test. Considerable resources (and professional reputations) are at risk if large-scale operations are resumed based on hasty conclusions.

9. Propose alternative treatments to eliminate the problem, and institute these steps

Once the true cause of a problem has been clearly identified, selecting improved processing conditions is usually straightforward. To quickly confirm the value of the new conditions, these process changes should be introduced at the site where the problem occurred.

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10. Monitor the results of the changed processing to confirm whether the changes are effective

By closely following the introduction of the optimized steps at the site where the problem occurred, one can monitor the results immediately and quickly make any further adjustments that are needed. If the modified operations did not solve the problem, it is necessary to begin the troubleshooting process again.

IV. DEBOTTLENECKING A PROCESS

To maximize productivity in a manufacturing operation, the amount of time that equipment is idle must be minimized. Therefore in ideal circumstances as soon as equipment has been suitably cleaned it is used to process the next batch. Processing subsequent batches will be delayed if the operations for the first batch have not been completed when the process stream from the second batch is ready. This situation creates a process bottleneck.

A hypothetical example serves to illustrate this situation (Figure 15.9). Let us suppose that a reaction is carried out in reactor R1 over a period of about 8 hours. When the reaction is complete, the reaction mixture is transferred to vessels R2 and R3 for an extractive work-up that requires about 6 hours. Then the rich extract is transferred to R4 for concentration and crystallizing, which takes about 16 hours. Filtration on centrifuge C1 requires 4 hours, and the product is dried in dryer D1 for 8 hours. When the reaction mixture has left R1, the vessel and staging area can be cleaned. If the equipment is to be used to make the same material that was generated in that vessel in the prior run, simple rinsing of R1 may suffice to ready the vessel for the second batch.

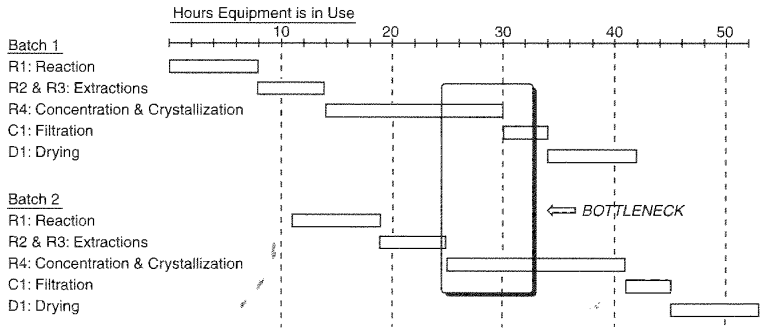


FIGURE 15.9. Identifying an operations bottleneck

Suppose that that the operators are ready to begin the second batch 3 hours after batch one was transferred from R1. Beginning the operations for the second batch will lead to a bottleneck in R4, because processing of the first batch will not be complete at the point that the second batch is expected to be ready for concentrating. Under these conditions the second batch should be started about 9 hours after the first batch has left R1, and in a manufacturing facility this is a significant amount of wasted time. If the concentration and crystallization operations in R4 can be reduced to about 8 hours, this bottleneck can be eliminated.

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CHAPTER 16

Chiral Syntheses

I. INTRODUCTION

The majority of drugs recently approved worldwide (Table 16.1) [1] and 54% of the 500 best-selling drugs worldwide in 1997 were single enantiomers [2]. The negative influence of the undesired enantiomer in racemic drug substances was recognized after 1960, when hundreds of deformed babies were born to mothers who had taken the sedative thalidomide during pregnancy. The teratogenic activity

TABLE 16.1. Importance of Single Enantiomer Drugs Approved Worldwide in 1994–1998[a,b]

Approved Drugs	1994	1995	1996	1997	1998
Single Enantiomer	26	23	29		
Racemic	7	5	6		
Achiral	14	11	16		

[a]Stinson, S. C., "Chiral Drug Market Shows Signs of Maturity." *Chem. Eng. News* **1997**, *75(41)*, 38.
[b]Technology Catalysts Incorporated

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was localized in the "evil, mirror-image twin" of the active compound [3]. The impetus to develop single-enantiomer API springs from a desire to avoid potential toxicology problems from less active compounds, to decrease the burden on biological systems by having to metabolize inactive compounds, to minimize the dosing required for patients, and to increase plant productivity by preparing only the most active compound. Such concerns have created an emerging industry for a "racemic switch," in which the active enantiomer (eutomer [4]) of a racemic drug is developed as a drug [5]. Developing a racemic switch has in effect prolonged the lifetime of compounds such as Prozac® [6, 7]. The financial impact of single-enantiomer drugs is huge.

II. SOME EXAMPLES OF MOLECULES PREPARED BY ASYMMETRIC SYNTHESIS

Some excellent texts have been published on approaches to preparing chiral compounds [8–13]. There are four basic approaches, shown in Table 16.2 [14]. A few examples and some perspective are worthwhile.

II.A. Products from Fermentation and the Chiral Pool

Fermentation has produced natural products such as antibiotics and the cholesterol-lowering agents pravastatin and lovastatin. Modification of fermentation products has led to semisynthetic compounds such as simvastatin (see Figure 1.2), penicillins, and cephalosporins. With increased capability in genetic engineering,

TABLE 16.2. Approaches for Producing Enantiomerically and Diastereomerically Pure Products

- Fermentation: isolation of natural and unnatural products
- Chiral carbon pool: preparation of intermediates
- Separating racemates
  - Preferential crystallization of one enantiomer (occurs for conglomerates, not true racemic crystals)
  - Kinetic resolution (enzymatic and nonenzymatic)
  - Crystallization of diastereomeric compounds (salts and covalent modifications)
- Asymmetric synthesis
  - Stoichiometric
  - Catalytic

microbial strains are producing higher yields of fermentation products, and unnatural products are also being made [15, 16].

The chiral pool has provided the backbone of many products. Carbohydrates [17] and amino acids are often used because of the high degree of functionality and the ready availability of these compounds from natural sources. Enalapril maleate contains the dipeptide L-alanyl-L-proline (Figure 16.1a) [18]. Aztreonam is derived from L-threonine (Figure 16.1b) [19]. The chiral ester **2** was prepared from an amino acid derivative **1** (Figure 16.1c) [20]. In this transformation the original chiral center from L-cysteine was destroyed, similar to self-immolative processes [21].

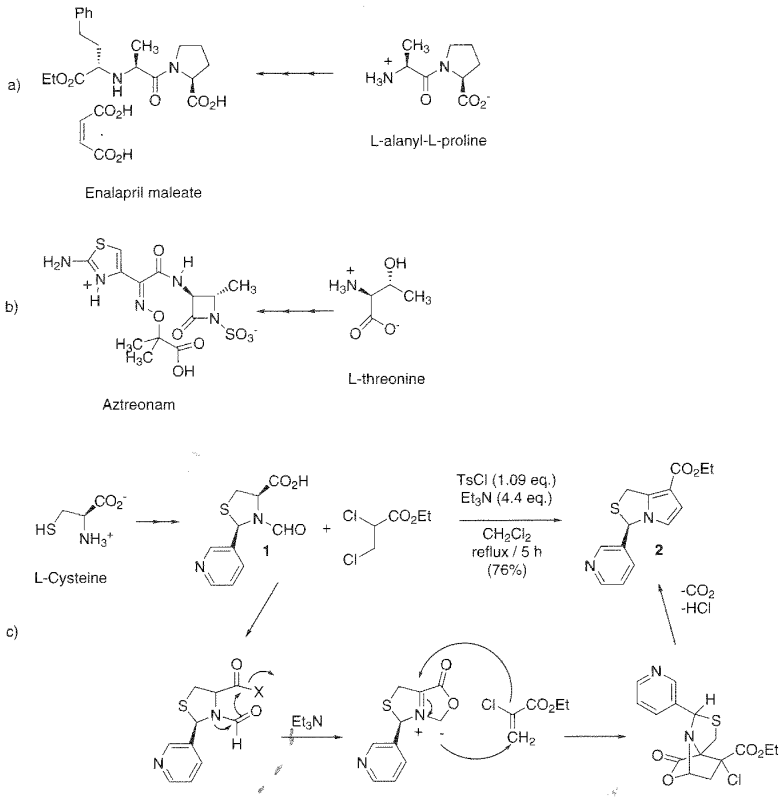


FIGURE 16.1. Preparation of chiral compounds from amino acids

The preparation of optically pure naproxen by the Zambon procedure (Figure 16.2) [22] is another example of a molecule from the chiral pool. Rearrangement of the tartaric acid-derived ketal **3** establishes the chiral center in naproxen, and the overall yield is excellent. However, this process does bear the burdens of recovering and regenerating the chiral tartrate auxiliary and of neutralizing the HBr generated by hydrogenolysis.

II.B. The Crystalline Nature of Enantiomeric Compounds and Approaches for Resolution

The two most common forms of crystals of racemic compounds are conglomerates and true racemates. Conglomerates are equimolar mixtures of crystals containing either one or the other enantiomer. A mixture of conglomerates has a decreased melting point and increased solubility as compared to the properties of either enantiomer. For racemates to form a true conglomerate, the melting point of either enantiomer must be at least 20°C above the melting point of the racemic mixture of crystals. True racemates are crystals containing equimolar amounts of each enantiomer in every unit cell. A racemic mixture has an increased melting point and decreased solubility as compared to either enantiomer. The third type of racemate crystals is termed a pseudoracemate or a solid

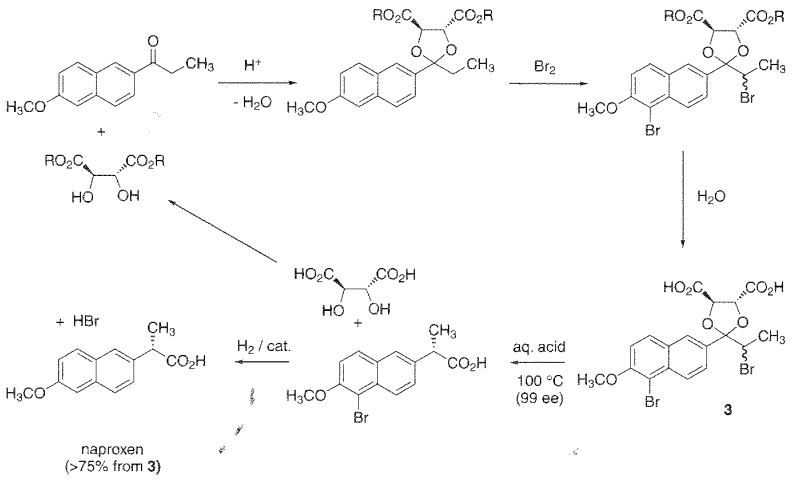


FIGURE 16.2. Preparation of optically pure naproxen by the Zambon synthesis

solution, and the solubility and melting point behavior of such compounds are little affected by the enantiomeric composition [23, 24]. The impacts of the crystal types of racemates are summarized in Table 16.3.

Different approaches to resolving compounds must be taken depending on whether the crystalline racemic material exists as a conglomerate or a true racemate. Conglomerates can be resolved by entrainment: Seeding a solution of racemic material with (*R*)-enantiomer leads to the selective crystallization of these crystals, enriching the mother liquor in the (*S*)-enantiomer. Seeding the mother liquor with the (*S*)-enantiomer leads to crystallization of those crystals, with subsequent enrichment of the mother liquor in the (*R*)-enantiomer. This process can be repeated until the buildup of impurities in the mother liquors leads to processing difficulties [25]. Resolution of compounds that crystallize as true racemates requires the use of chiral adjuvants, generally chiral amines or acids (see Section II.B.2), to separate compounds by crystallization of the diastereomeric salts. Due to the high cost of resolving agents for large-scale operations, it has been stated that "[o]nly resolution through direct crystallization of enantiomers is likely to answer to industrial requirements" [26].

No more than 10% of racemic compounds have been shown to crystallize as conglomerates [27]. If a racemic mixture does not crystallize as a conglomerate, it may be possible to generate conglomerate crystals by forming salts of the chiral compounds with achiral acids or amines [28]. DSC can provide a useful tool for selecting resolving agents [29].

TABLE 16.3. Characteristics of Crystals of Enantiomeric Compounds

Characteristic	Conglomerate	True racemate	Psuedoracemate or racemic solid solution
Contents of crystal unit cell for racemic mixture	One enantiomer in each unit cell of a crystal; enantiomers found in different crystals	Both enantiomers in unit cell	Both enantiomers in unit cell
Characteristics of racemic crystals relative to a pure enantiomer	Decreased mp Increased solubility	Increased mp Decreased solubility	Very little change
Occurrence	≤ 10%	Most common	Very rare
Approaches for resolution by crystallizing[a]	Entrainment	Generate diastereomers by salt formation or covalent modification	NA
Effect of racemic switch	Increased mp Decreased solubility	Decreased mp Increased solubility	Very little change

[a]Resolution can also be accomplished through kinetic resolution and second-order asymmetric transformations.

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II.B.1. Second-Order Asymmetric Transformation

Second-order asymmetric transformation involves resolution by racemizing the material in solution as the chiral product crystallizes [30]. Under these circumstances the *in situ* formation of a derivative renders a molecule more prone to racemization, and the application of heat, acid, or base leads to racemization. With *in situ* deprotection, the racemic component is generated, and the formation of the diastereomeric salts can lead to crystallization of one compound. This procedure has been demonstrated on scale by the resolution of the amine **4** as the camphorsulfonic acid salt **5** (Figure 16.3a) [31]. Under more stringent conditions L-proline is racemized, and D-proline crystallizes as the (unnatural) tartaric acid salt **6** (Figure 16.3b) [32]. A second-order asymmetric transformation could be applied to resolution of a compound with two chiral centers if the compound is broken down and reformed by reversible reactions. Reformation of the desired product in a chiral environment could effect a resolution. In an achiral environment a mixture of aldol **7** and its enantiomer are in equilibrium with the retro-aldol products (Figure 16.3c). Treating a mixture of **7** and *ent*-**7** with antibody 38C2 led to enrichment of **7** through retro-aldol reaction and selective aldol formation [33]. Lipase-catalyzed hydrolysis of thioesters was also carried out under conditions in which the unreacted thioester enantiomer was racemized; this approach may hold promise in resolutions of electron-poor carboxylic acids and esters [34]. When applicable, a second-order asymmetric transformation can be the most economically feasible approach to resolution, as in principle a quantitative yield can be obtained with only one product isolation.

II.B.2. Resolution of True Racemates

Resolution of compounds that crystallize as true racemates requires the use of chiral adjuvants. Generally chiral amines or acids are used to separate compounds by crystallization of the diastereomeric salts [35, 36]. Covalent modification may also be employed, either by reacting the racemic compound with a chiral reagent and selective crystallization of the desired diastereomer [37] or through kinetic resolution using enzymes [38] or chemical approaches [39]. The drawback of covalent modification is that regenerating the resolved product from the modified product is generally more difficult than removing the resolving agent from a salt ("splitting the salt").

Key factors for successful crystallization and isolation of diastereomeric salts are the selection of crystallization conditions and the rate at which the two diastereomers crystallize. Water and alcohols have been used as solvents in the majority of resolutions, and the solvent that has been recommended for initial solvent screening is 96% aq. EtOH [40]. Controlling the amount of water may be important to encourage the formation of the desired hydrate at the desired crystallization rate [41] (see Figure 11.11). Adjusting the solvent content may be necessary to ensure

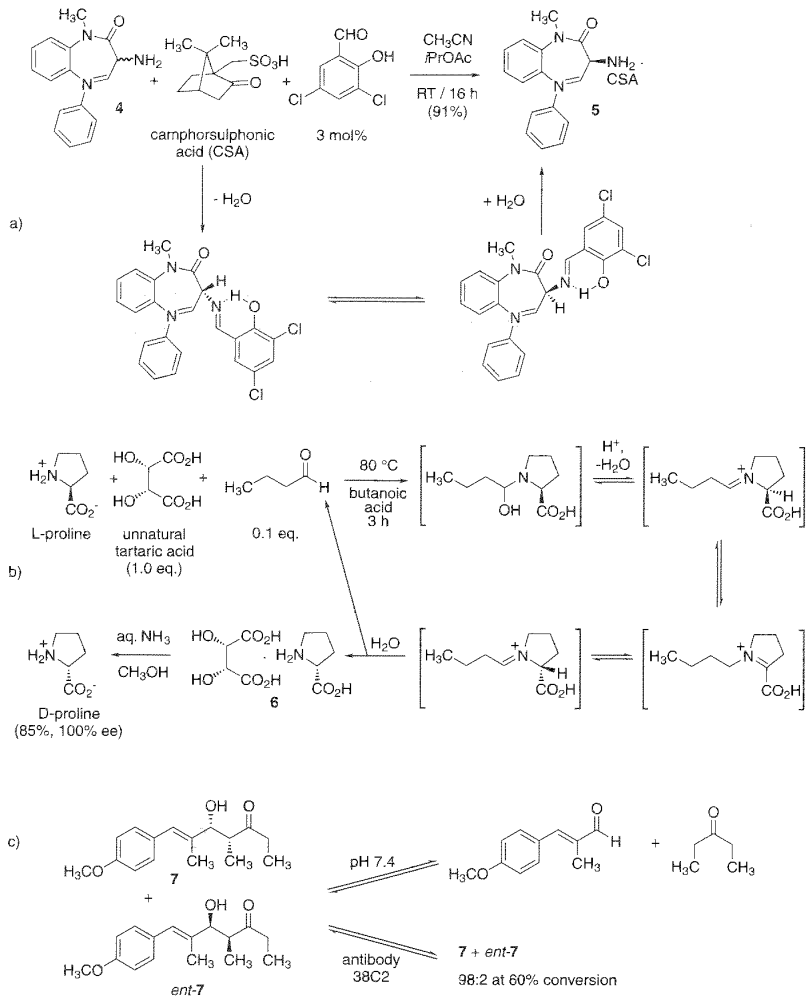


FIGURE 16.3. Examples of second-order asymmetric transformations

the dissolution of the undesired diastereomer. The crystallization rates of the desired diastereomer must be sufficiently greater than that of the undesired diastereomer; otherwise, extended operations on scale may lead to co-crystallization of the undesired diastereomer [41]. The crystallization rate may also be determined

by the concentration: at higher concentrations, the crystal growth rate of the desired racemate pair **8** was slowed, suggesting that the unwanted enantiomeric pair **9** was acting to dissolve **8** (Figure 16.4) [42]. Close attention to details may be required to develop a reproducible crystallization of diastereomers (and enantiomers).

> **TIP:** In developing a crystallization of diastereomeric compounds, scale-up difficulties may be anticipated by extending the laboratory crystallization and monitoring the quality of the crystals. If the crystallization rates of diastereomers are very similar, there may be a small time period to complete processing and obtain the desired product yield and quality of product.

The conventional approach to prepare a diastereomeric salt is to examine crystallization of the desired enantiomer in the presence of one resolving agent. Despite attempts to formulate guidelines for a systematic approach, selecting the optimal resolving agent largely occurs through trial and error [43]. Resolution has been demonstrated by adding two or three closely related resolving agents to racemic amines or acids. Salts were quickly formed as crystals containing more than one resolving agent in stable, nonstoichiometric ratios (Figure 16.5) [44]. This approach may have applicability for rapid resolution of chiral amines and acids.

Salts may be split by dissolving in an aqueous-organic solvent mixture and by adjusting the pH to selectively partition the two components into the two phases.

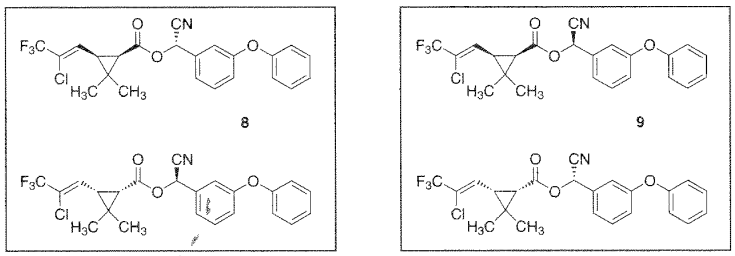
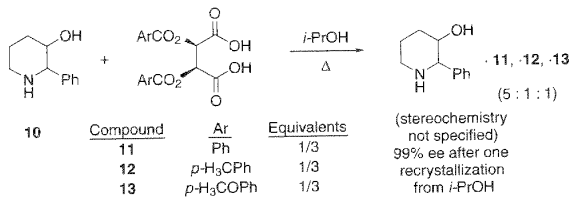


FIGURE 16.4. Enantiomeric pairs that acted as solvents during crystallization



10	Compound	Ar	Equivalents
	11	Ph	1/3
	12	*p*-H_3CPh	1/3
	13	*p*-H_3COPh	1/3

FIGURE 16.5. Resolution by using a mixture of di-o-aroyl tartrates

The resolved enantiomer can then be recovered by conventional isolation techniques. Due to solubility in the undesired phase or through losses during isolation, product may be lost from such operations. To minimize losses one approach is to crystallize the product in the presence of the resolving agent; this was nicely demonstrated by recovery of the resolved amino acid **14** by crystallization from aqueous THF (Figure 16.6) [45].

III. COMPOUNDS PREPARED BY ASYMMETRIC SYNTHESIS

Most of the examples mentioned in this book involve asymmetric synthesis using carefully designed conditions and reagents, and some elegant chemistry in this area has been published over the years. As one example, the chloroketone **17** was

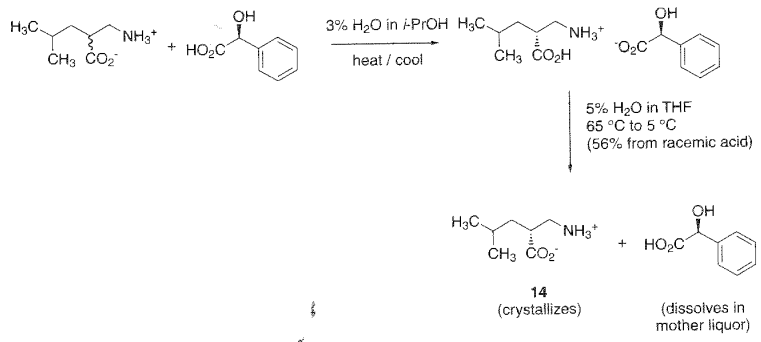


FIGURE 16.6. Recovery of a resolved product by crystallization in the presence of the resolving agent

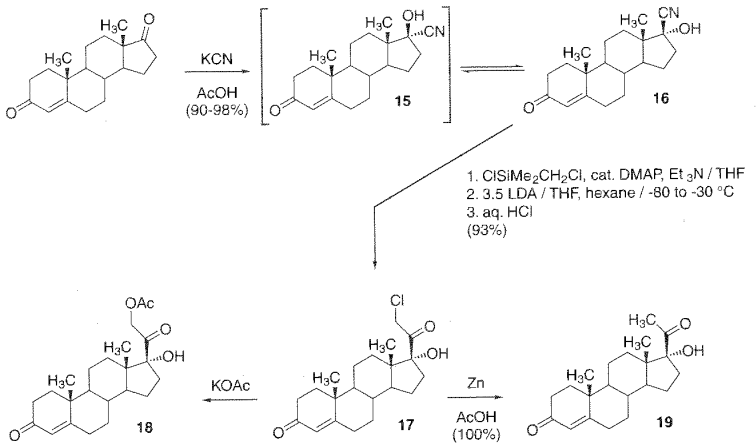


FIGURE 16.7. Diastereoselective synthesis of steroids

elaborated in one step from the ß-cyanohydrin **16**; one reaction of **17** produced the corticosteroid **18** or 17-α-hydroxy-progesterone, **19** (Figure 16.7) [46]. The usefulness of this approach to **18** and **19** is based on the high-yield preparation of **16**. Formation of the ß-cyanohydrin **16** is in equilibrium with the α-cyanohydrin **15**, and the desired diasteromer **16** selectively crystallizes [46].

A short, enantioselective synthesis of (*R*)-fluoxetine, **24**, has been described (Figure 16.8) [47]. The asymmetry was established in the first step, which is key

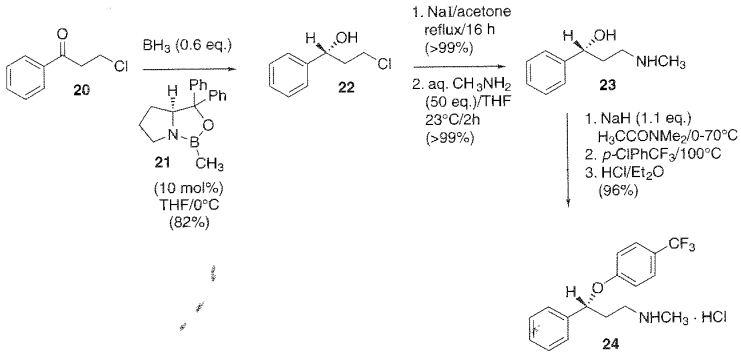


FIGURE 16.8. Enantioselective synthesis of (*R*)-fluoxetine

for an economical preparation. For this reduction the ketone **20** was added over 20 minutes to a solution of BH_3 and 10 mol% of the catalyst **21**. Finklestein reaction of **22** and treatment with aqueous methylamine gave the amino alcohol **23** in almost quantitative yield, and arylation with NaH in dimethylacetamide led to **24**.

Asymmetric synthesis by asymmetric induction is shown in the route to manufacture indinavir sulfate (Figure 16.9). Four of the five chiral centers were established by asymmetric induction, beginning with asymmetric epoxidation to form

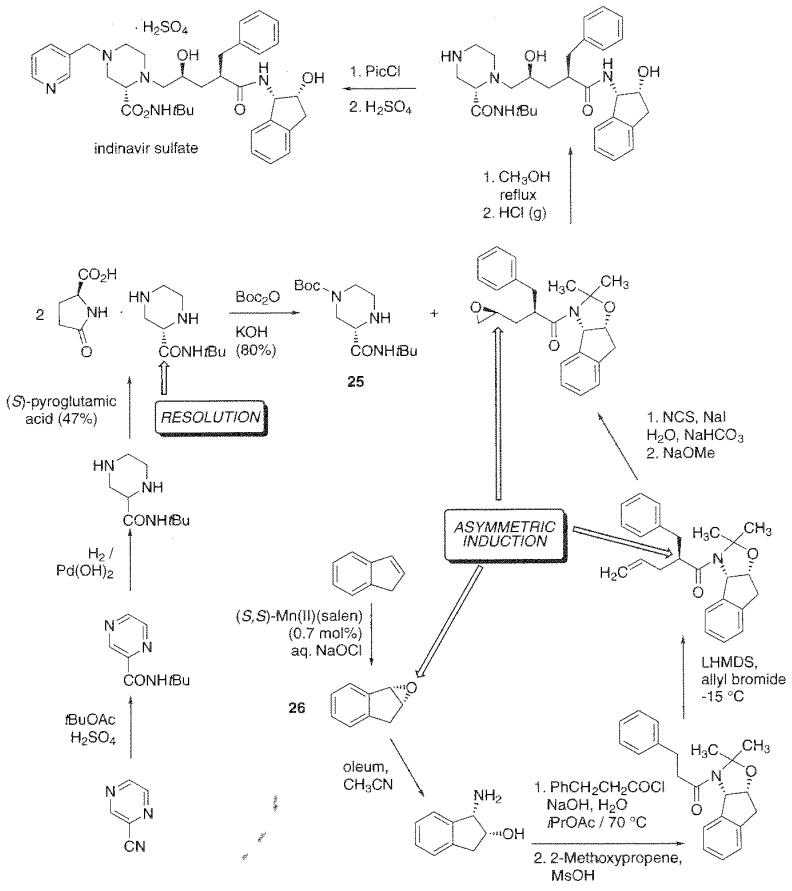


FIGURE 16.9. Asymmetric synthesis of indinavir sulfate

26. Classical resolution provided the fifth stereocenter, found in the piperazine **25** [47].

Discussion of the routes to prepare captopril (Figure 16.10) illustrates many of the points made earlier. Early *in vitro* studies showed that captopril was 100 times more potent than the diastereomeric methyl compound **29** and eight times more potent than the des-methyl compound (not shown) [48, 49]. The original preparation used the racemic acid chloride **27**, and captopril was separated from the

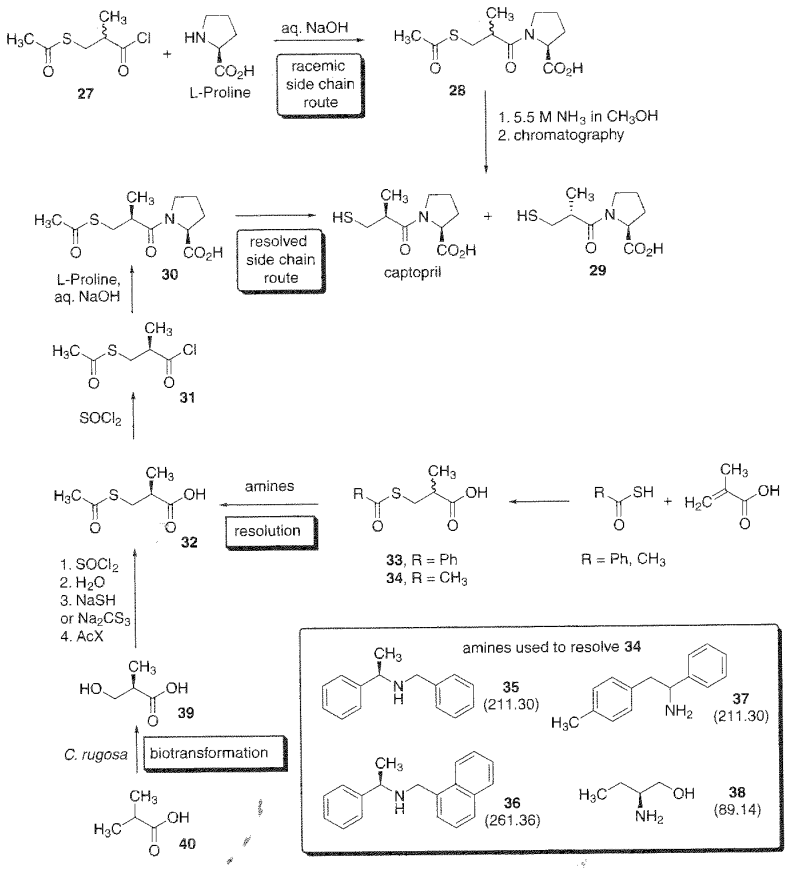


FIGURE 16.10. Routes to prepare captopril

diastereomer **29** by chromatography [50]. Although the racemic side chain route conveniently provided both captopril and **29** for testing, obviously the wasted resources spent in preparing the ballast **29** makes this route inappropriate for scale-up. By preparing the desired chiral acid **32** the syntheses became more efficient. Resolution of the S-benzoyl acid **33** was relatively straightforward [51]; unfortunately, resolution of the S-acetyl acid **34**,the intermediate filed with the FDA, was not easy to accomplish [52]. A number of chiral amines were used to resolve **34**, including **35** [52], **36** [53], **37** [54], and **38** [55]. Based only on molecular weight considerations, the smallest amine **38** would be preferred in order to maximize the amount of **34** that could be charged to a vessel. Intermediate **32** was also prepared by biotransformation of prochiral isobutyric acid (**40**) to the chiral hydroxy acid **39** [56–58] and subsequent conversion of the hydroxyl group to the S-acetyl group [56]. In preparing **32** using biotransformation, four chemical steps are necessary, for a total of five steps from inexpensive starting materials, whereas by resolving **34**, only two chemical steps are needed. Many factors, including cost of starting material, overall yield, cost of waste disposal, productivity, and processing reliability, would need to be considered to choose the preferred manufacturing route between the biotransformation route and classical resolution to prepare **32**.

IV. PERSPECTIVE ON ASYMMETRIC SYNTHESIS

At the inception of a project, the key is to provide enough material for early testing. Early in the development process, when speeding the compound to market is the primary goal, preparing an active ingredient by any expedient synthetic route is justifiable. Later in the development of a compound, when cost-effective routes are selected, the synthetic route may change. Some forethought into developing an efficient asymmetric synthesis early in the development of a compound may decrease the time needed to develop a suitable manufacturing process.

From an industrial perspective the most elegant chemistry is the most economical chemistry. Synthesis through resolutions are less glamorous than those in which the stereochemistry is set through asymmetric synthesis; nonetheless, resolutions have been shown to be more economically effective in some cases [8, 45, 60]. With asymmetric synthesis the desired stereochemistry must be efficiently introduced. If it is not, the undesired stereoisomers may complicate isolations and reduce the yield of the desired product. Many of the features of a route that need to be considered were mentioned in Chapter 2. Comparing product costs through spreadsheets may be extremely valuable [61].

Sun Ex. 1022

TIPS: Guidelines for Asymmetric Syntheses

- Yields are important, but minimizing the number of steps can have greater impact than increasing yields on a multistep route. This is particularly true for multistep routes on scale, where the cumulative risk and impact of processing problems increase.
- High-molecular-weight auxiliaries for asymmetric induction may prove less economical than a resolution. Recovery and recycling of auxiliaries will be important for minimizing long-term costs.
- Asymmetric synthesis may be more efficient than syntheses from the chiral pool. Key is the number of steps required overall.
- Resolutions may be more effective than asymmetric syntheses; i.e., it may be better to rely on resolutions than on the asymmetry inducible from reagents or other parts of the molecule.
- Resolutions are most economically placed early in a synthetic sequence unless a dynamic resolution is used to increase the yield of the step.

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Practical Process Research & Development

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Bringing a compound to market quickly and profitably requires efficient and cost-effective processes for preparing large amounts of the target compound and intermediates. The key to rapid and successful process development is avoiding scale-up problems. However, an understanding of scale-up issues is rarely taught in academia and may take years of industrial experience to acquire.

Practical Process Research & Development teaches how to anticipate and avoid these problems when processes are being scaled up from the research lab or pilot plant. The approach is pragmatic, with a minimum of theory and over 100 practical scale-up tips. Many tables and detailed reaction schemes allow the reader to identify critical processing steps quickly. This practical guide is essential reading for chemists and chemical engineers involved in industrial process research and/or process development and for anyone seeking a clearer understanding of how and why process R&D is conducted in the pharmaceutical and fine chemicals industries.

KEY FEATURES

- Provides insights into generating rugged, practical, cost-effective processes for the chemical preparation of "small molecules"
- Breaks down process optimization into route, reagent, and solvent selection, development of reaction conditions, workup, crystallizations, and more
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- Discusses guidelines for the timely development of processes
- Illuminates principles with examples from the recent literature
- Includes over 100 tips for rapid process development
- Presents guidelines for implementing and troubleshooting processes
- Written by an author with over 22 years of experience in process R&D in the pharmaceutical industry

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