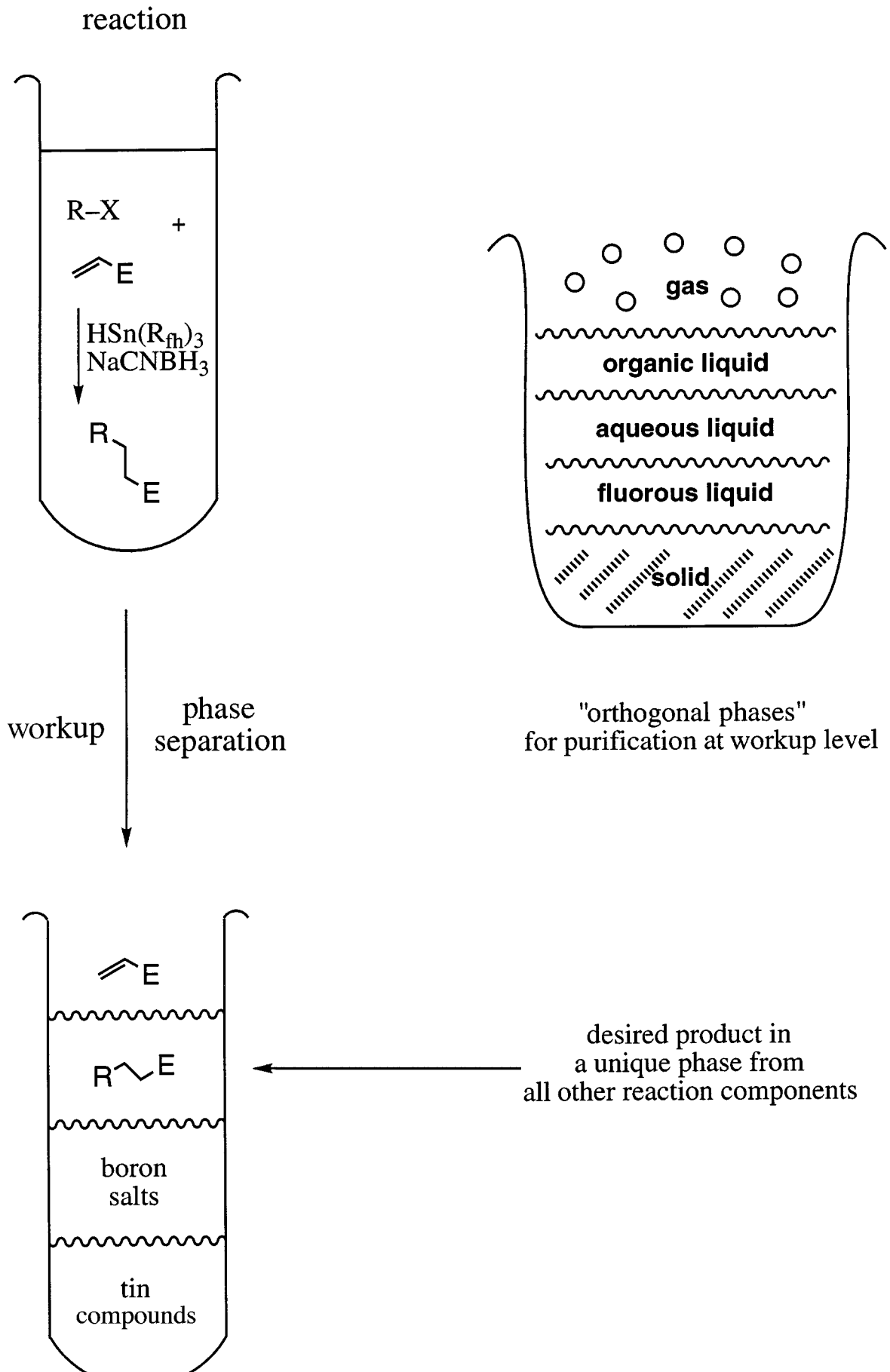

Strategy-Level Separations in Organic Synthesis: From Planning to Practice

Dennis P. Curran*

The yield and practicality of every reaction are limited by the ability to separate and recover the final pure product from the reaction mixture. Said another way, synthesis and separation are inseparable. However, over the years mainstream synthetic organic chemistry has tended to divorce synthesis from separation by treating separation as a technical issue. Advances in the field of separation have enabled modern synthetic chemists to contemplate and then synthesize molecules of remarkable complexity. At the same time, the power of modern separations has instilled a complacency in some. The expectation is that we can separate anything these days. However, separation advances notwithstanding, this expectation is no more realistic than the expectation (held by some outside the synthesis community) that we can synthesize anything we desire. On the process-chemistry front, we are expected not only to synthesize the desired compound, but to synthesize it cheaply, efficiently, and safely. Furthermore, with the advent of combinatorial chemistry, synthesizing *anything* isn't good enough anymore, we are expected to synthesize *everything*—and quickly! To meet these high expectations, synthetic chemists have begun to formulate strategic plans at the beginning of a synthesis. In these plans synthesis dictates separation, and molecules in the final reaction mixture are designed to virtually separate themselves when processed in a purification stage. The best laid plans allow products to be isolated by using simple workup techniques such as evaporation, extraction, and filtration. There is an emerging field at the interface of synthesis and separation, and though it is firmly rooted in the past the field is anything but old-fashioned. A unified basis for strategic separation planning is constructed by bringing together under a single umbrella a number of results from apparently disparate areas such as acid–base chemistry, solid-phase synthesis, fluorous synthesis, and others. A vision for the future forms in which reactions and separations are remarried and work together to help meet the demanding expectations that the field of organic synthesis faces in its ever more challenging quest to produce useful chemical entities.

Keywords: combinatorial chemistry · fluorous synthesis · solid-phase synthesis · synthesis design

1. Introduction

1.1. Purification in Synthesis

The discipline of organic synthesis is essential to progress in many fields, and is therefore one of the core disciplines in chemistry. During the second half of this century, synthetic strategies and techniques have rapidly advanced,[1] and this has resulted in the discovery and characterization of millions of organic molecules of all sizes. However, the number of known organic compounds still pales in comparison to the diversity that is offered by structures based on the element carbon. The need for new organic molecules of relatively small size (relative molecular weights in the range 250–750) is especially acute in the pursuit of new drugs. In response to this need, the emerging disciplines of combinatorial synthesis and automated organic synthesis are beginning to provide new compounds at a greatly accelerated pace.[2] In this arena, speed is of the essence.

At the other end of the spectrum from discovery is the production of molecules that have useful functions. Here, the development of the safest, least expensive, and most environmentally friendly synthetic route possible is widely recognized as an important goal. Supporting both discovery and production work in organic synthesis is a large component of basic research in areas such as the synthesis of natural and unnatural products, the development of new synthetic methods, and the study of reaction mechanisms. This research continues to transform the field of synthesis by providing increasingly powerful strategies, reactions, and techniques to make even the most sophisticated of organic molecules.

Despite these sweeping changes in our ability to conduct and also to analyze reactions, one crucial aspect of synthesis has not been affected much over the last decades: purification. The initial purification of an organic reaction mixture by

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"workup" has changed little over the past 50 years. Subsequent purification by crystallization, distillation, chromatography, or other methods are fundamentally similar now to 20 years ago, although there have been notable improvements in these purification techniques, especially in the area of chromatography.

Indeed, the whole purification process is regarded as a technical one in the field of synthesis. Aspects of purification rarely emerge in the experimental sections of papers, and authoritative books on synthesis say little or nothing about purification. Synthesis, as we know, is about reactions and strategies for conducting reactions in sequence. There are strategies for making molecules, for chemo-, regio-, and stereoselectivity, for protecting groups, and for other aspects of the synthesis process. However, it would seem that there are no strategies for purification—one simply conducts a reaction and then tries the available purification techniques to see which work and how well.

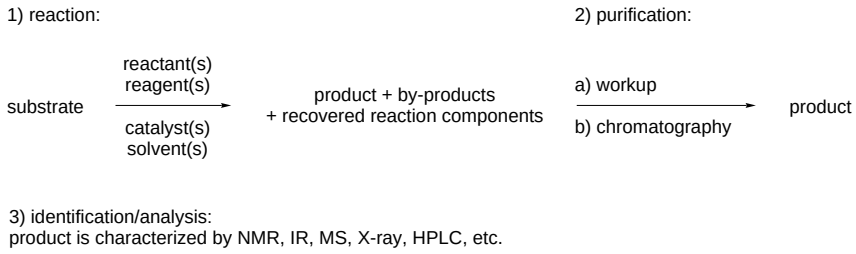
The advent of combinatorial chemistry and automated parallel synthesis is beginning to change the way synthesis is done. Combinatorial and parallel syntheses demand simple purification methods, and this demand has exposed huge gaps in the available techniques. These gaps are now being filled by promoting purification from a technical concern to a strategy-level concern. In other words, the plan for a reaction or sequence of reactions specifically takes into account separation at the design stage. Although rarely phrased in strategic terms, separation design is not new. The use of volatile or water-soluble reagents, acid–base extractions, and more recently solid-phase synthesis are all examples of designed separation. However, the field has lied fallow for sometime until recently, and existing applications—such as acid–base extractions—are so well established that they are almost treated as isolated techniques rather than as components of a larger strategy.

The purpose of this article is to provide guidelines for strategy-level separation planning, to show how these guidelines are now being implemented in practice, and thus to expedite work in this fast-moving field. This is not a review about combinatorial chemistry, about which many excellent reviews already exist.[2] Nor is it a review about solid-phase synthesis; solid-phase synthesis and allied techniques will be integrated into the big picture of separation planning. Thorough reviews are already available in the area of solid-phase synthesis,[3] and the citations in this paper are selected solely for illustration. Likewise, the use of water-soluble reaction components is commonplace and is not extensively reviewed here. Other areas are at an earlier stage of development, and an effort is made to be more complete in referencing.

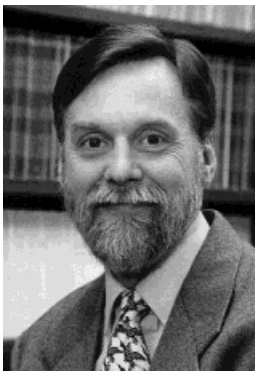
1.2. Stages in the Development of a Step in Organic Synthesis

The synthesis of an organic molecule of any size generally proceeds through a planned sequence of steps in which an initial starting material (substrate) is converted into a product by means of a chemical reaction. The product of the first reaction then becomes the substrate for the second reaction, and so on until the target product is made. Strategies to plan the sequence of steps for the synthesis of an organic molecule are now very sophisticated.[1] Although those of us who write the journal articles and books like to focus on reactions, those who do the experiments are quick to recognize that there is more to synthesis than reactions.

Each step in a synthetic sequence can usually be subdivided into three stages: reaction, purification, and identification/analysis (Scheme 1). The reaction stage consists of treating the substrate with appropriate reactants, reagents, or catalysts[4] under suitable conditions (temperature, sometimes pressure, light, etc.) to effect the transformation to the desired



Scheme 1. Stages of a step in an organic synthesis.



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product. Most reactions are conducted in the liquid phase with the aid of one or more solvents.

In the purification stage, the desired product is separated from any by-products and remaining reaction components. By-products can be obligatory, as with the remnants of a reactant consumed in the reaction (for example, Ph_3PO from a Wittig reaction), or they can result from undesired reaction pathways of the substrate or another reaction component. In the identification/analysis stage, the structure of the product is typically secured by spectroscopic and/or X-ray crystallographic means, and the purity of the product is ascertained by spectroscopic and/or chromatographic techniques. This three-stage classification is somewhat loose (for example, analysis can and often does take place at any of the three stages), but it is still representative of the majority of synthetic steps.

In modern organic synthesis, the purification stage is frequently subdivided into two sections: workup and chromatography. The workup stage uses simple phase-separation techniques such as extraction, filtration, and evaporation to make crude separations. The subsequent chromatographic stage is a more recent introduction that has greatly increased the power of organic synthesis by allowing the separation of organic compounds from other organic compounds based on various sophisticated types of phase partitioning. However, chromatography can be an expensive and time-consuming proposition, and chemists who make large quantities of organic compounds have always tried to use the time-honored techniques of distillation and crystallization or other simple methods in place of chromatography.[5] Purification is often the most costly stage in terms of time and resources.

2. Planning Separation Strategies

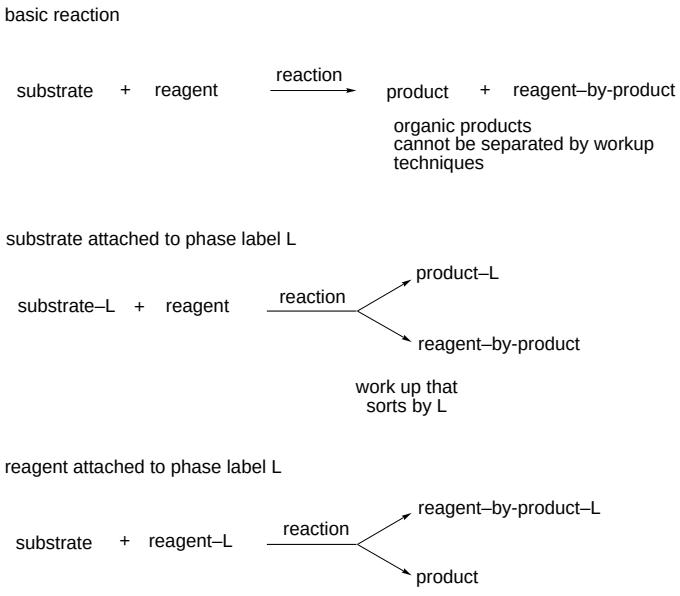
2.1. The Goal

The ultimate goal in organic synthesis is represented by Paul Wender's notion of an "ideal synthesis".[6] Taking this to the limit, I provide the following paraphrase of an ideal synthesis: You mix inexpensive, commercially available starting materials in the required stoichiometries and get the pure final product in quantitative yield. At this extreme case, the purification stage disappears; nothing is added to the "reaction mixture" except components that wind up in the final product. Wender's actual definition is more realistic, and allows for things such as catalysts—which immediately reintroduces the need for the purification stage since the catalyst must be separated from the product. However it is framed, the notion of an ideal synthesis represents a valuable "grail" for the synthesis community by exposing the fact that even though synthesis has come a long way, there is still a very long way to go. Phenomenal recent and future progress in reaction chemistry notwithstanding, there is no immediate prospect of the development of this chemistry to the point where it eclipses the need for a purification stage in most transformations.

Planning for purification at the strategy level is based on the following goal for the "ideal purification": The product should be separated into a different phase from everything else that is present in the final reaction mixture. When this goal is met, the reaction mixture can be quickly subjected to one or more simple phase-separation techniques to provide a pure product. This is a time-honored goal that is only implemented occasionally.[5] For example, acylation of an amine with an acid chloride followed by a series of simple acid–base extractions provides the product amide (neutral phase) free from any unchanged amine (acid phase) or acid chloride (hydrolyzed to the acid and in the base phase). These simple notions will be generalized below to the concept of purification by "phase switching."

With this goal, separation at the strategy level becomes an exercise in "phase planning". This begins with the recognition that all molecules have a "natural" phase into which they will generally partition in a simple phase separation. Most molecules of interest in synthesis are "naturally" organic. We use the term organic here and throughout the rest of the article in a more restricted sense than the standard definition: Molecules are "organic" with respect to a phase-separation technique if they end up in the organic liquid phase. In other words, for a liquid–liquid extraction between diethyl ether and 1N HCl, the amide and the acid are organic (they partition to the ether phase) whereas the amine is basic (it partitions to the acid phase). In the case of an extraction with diethyl ether and 1N NaOH, the amide and the amine are organic, but the acid is not. The natural phase of a molecule must therefore be specified with reference to a given phase-separation technique. This qualitative behavior is quantified by a partition coefficient. In this section, we take the unrealistic view that all the partition coefficients are 100% into the natural phase. A more realistic view of partition coefficients is given in Section 3, which deals with the "practice".

In principle, the natural phase of any molecule with respect to a given separation can be modified by a process that we call "phase labeling".[7] The basic notion is shown in Scheme 2, where L is some type of chemical-phase label that can be attached to any reaction component before (Scheme 2),

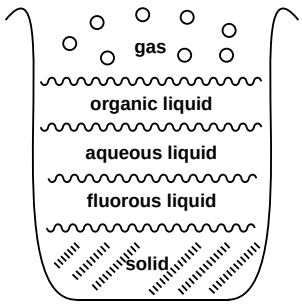


Scheme 2. Separation by phase labeling.

during, or after a reaction. For example, the attachment of a protected amino acid to a polymer support renders this naturally "organic" compound and all its subsequent reaction products in a "solid" with respect to the phase-separation technique of filtration. Phase labeling is a chemical process, so the attachment that alters the phase of the amino acid in the purification also can have profound consequences not only at the purification stage but also at the reaction and identification/analysis stages. Solid-phase synthesis provides an extreme example of this; the labeled substrates are generally insoluble at all times. While this facilitates separation, it can complicate reaction, identification, and analysis. Ideally, phase labeling should allow simple separations without compromising the reaction, identification, and analysis stages of a synthetic step.

2.2. The Simple Phase-Separation Techniques

Four phases are commonly used in simple workup-level purification techniques: the gas phase, the organic liquid phase, the aqueous liquid phase, and the solid phase. These four phases are orthogonal to each other (Scheme 3) as well as



phase label	phase	separation technique
none	organic	evaporation, extraction, filtration
ionized group	aqueous	liquid–liquid or solid-phase extraction
insoluble polymer	solid	filtration
soluble polymer	solid	precipitation–filtration
highly fluorinated group	fluorous	liquid–liquid or solid-phase extraction

Scheme 3. A simplified view of mutually immiscible phases that can be separated by evaporation, extraction, or filtration.

to the fifth, less commonly used fluorous liquid phase.[8] Each of these phases can be separated from any other in simple and very general ways.

Since the natural phase of a compound can be specified only with reference to a phase-separation technique, phase planning starts with the techniques. Most of the simple phase-separation techniques are well known to organic chemists and are based on partitioning between gas, liquid, and solid phases. Essentially all separation techniques involve some kind of phase separation, but the scope here is restricted to simple workup-level techniques.

Evaporation partitions a mixture into volatile and nonvolatile compounds. It is routinely used to separate solvents from crude or purified reaction components, and has limited utility for separating volatile from nonvolatile reaction components. Its use is restricted to a small range of "naturally volatile" compounds since there is no general method to "label" compounds as volatile by a chemical process.

Filtration partitions a mixture into a solid and a liquid phase. In classical organic synthesis, a filtration follows a crystallization (or, more generally speaking, a precipitation); the precipitation creates two phases that are separated by the filtration. Many of today's modern solid phase synthesis techniques dispense with the precipitation event since the polymer-bound substrates never dissolve in the first place.

Extraction partitions a mixture into two (or more) liquid phases. The process is routinely conducted with the aid of volatile solvents, and evaporation then follows extraction to separate the nonvolatile components from the solvent. Two types of extractions are important for purification of reaction mixtures: liquid–liquid extraction and solid–liquid extraction. Liquid–liquid extractions predate the field of organic synthesis and have remained an integral part of most workup procedures for more than a century. Yet only three types of liquid–liquid extractions are common: A mixture is partitioned between an organic solvent and an aqueous phase that is either neutral, acidic, or basic. Simply said, an organic–aqueous extraction partitions a mixture into organic and inorganic (or better, water-soluble) fractions. Basic components can be extracted into acid and vice versa, forming the basis of the "phase switch" by acid–base extraction described above.

There are a number of organic phases that are immiscible (for example, hexane is not miscible with either acetonitrile or methanol), and these pairs can be used in extractions. These "exotic" extractions have limited utility at this point, although the concept of phase labeling could possibly be applied to extend their usefulness. However, there is one class of exotic extractions that does have significant potential. It has been known for half a century that perfluorocarbon (and some very highly fluorinated) liquids are immiscible with water and many common organic solvents.[9, 10] Some properties of two common fluorocarbon solvents are summarized in Scheme 4. In a simple view, highly fluorinated solvents and compounds that partition into them form a separate phase called the "fluorous phase",[8, 11] in which organic and inorganic compounds have little or no tendency to dissolve. Therefore, phase labeling a compound or subset of compounds as fluorous is all that is required for a successful extraction.

The presence of three mutually immiscible liquid phases rather than two has a number of consequences. First, more types of extractions are possible since there are now seven basic types of two-phase extractions (one organic–fluorous, three organic–aqueous, and three fluorous–aqueous; the aqueous phase can be either neutral, acidic, or basic) and three types of three-phase extractions (organic–fluorous–aqueous). Each of these ten extractions provides its own set of separation capabilities.

Related to liquid–liquid extraction is the technique of solid-phase extraction (SPE). Though only now becoming

perfluoromethylcyclohexane
- M_r = 350
- bp = 76°C
- $\rho \approx 1.8$ g cm^{-3}

immiscible with
- EtOAc
- CH_2Cl_2
- H_2O
- CH_3CN

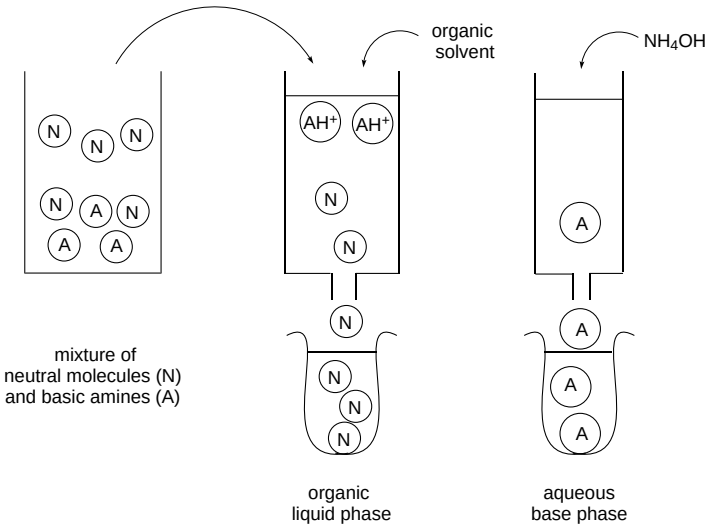
partially soluble in
- Et_2O, THF
- CCl_4

perfluorohexanes (FC-72 3M)
- bp ≈ 56°C
- mixture of isomers, mostly linear
- M_r = 338
- $\rho \approx 1.8$ g cm^{-3}

Scheme 4. The fluorous phase. Perfluorocarbons are nonpolar, nontoxic, and immiscible with many common organic solvents or water.

popular in synthesis, it has been a staple in analytical chemistry for some time. The technique sits on the fence between filtration and extraction, but we classify it here as an extraction since it functions in many ways like a liquid–liquid extraction and since it frequently provides the separated reaction mixture in two liquid phases.

Solid-phase extractions are popular in chemical analysis. For example, in the analysis of compound mixtures (e.g. of organic amines) a solid-phase extraction analogous to an acid–base extraction is often conducted. A mixture containing the amine or amines to be analyzed is injected onto an acidic ion-exchange column (Scheme 5). The amines are



Scheme 5. Schematic representaion of a solid-phase extraction.

affixed onto the column by protonation by the supported acid. Elution with a suitable organic solvent then quickly removes all the organic (neutral) impurities. Subsequent elution with a basic solvent then provides a second liquid phase containing the amines, which are then further analyzed. In this "prepurification" process, the amines are "extracted" from the first eluent onto the solid phase of the column as salts, and then extracted back off with a second eluent.

Currently, the potential for preparative purification by solid-phase extraction is largely untapped. In execution, solid-phase extractions resemble filtrations, and they are probably easier to conduct in parallel than liquid–liquid extractions. However, the advantages are more than technical. Solid-phase extractions can in principle provide better separations than liquid–liquid extractions. As the separation by solid-phase extraction becomes poorer and poorer, the "extraction" becomes at some point a "chromatography." This transition is roughly analogous to the conversion of a separation by "evaporation" into a "distillation" as the boiling points of two liquids converge. The goal of a solid-phase extraction is often to use a phase label to control the extraction behavior. The partitioning of compounds onto and off of the column is determined not by the structure of the compounds themselves but by whether they contain a phase label or not. Rephrased in chromatography terms, all compounds ideally have retention factors (R_f values) of 1 or 0 (with or without the label). Among other applications, SPE may be useful in the combinatorial synthesis of aggregate mixtures of soluble molecules,[12] which are now generally used without purification.[13]

The above description of phases and techniques is not exhaustive. Present challenges in the field including developing new ways to use common separation techniques as well as harnessing other separation techniques for strategic separation purposes. In the case of the latter, the allied methods of dendrimer synthesis and size-exclusion chromatography will be highlighted below as examples.

2.3. Features of Phase-Separation Techniques

The overwhelming popularity of solid-phase synthesis has led to frequent discussions about the advantages of solid-phase methods over traditional methods, and there are indeed significant advantages. However, there has been little clear discussion about which of these advantages are associated with solid–liquid separations and which with solid–solid separations. Yet the difference is crucial, since features of solid–liquid separations are shared in principle by all phase-separation techniques, whereas solid–solid features are unique.

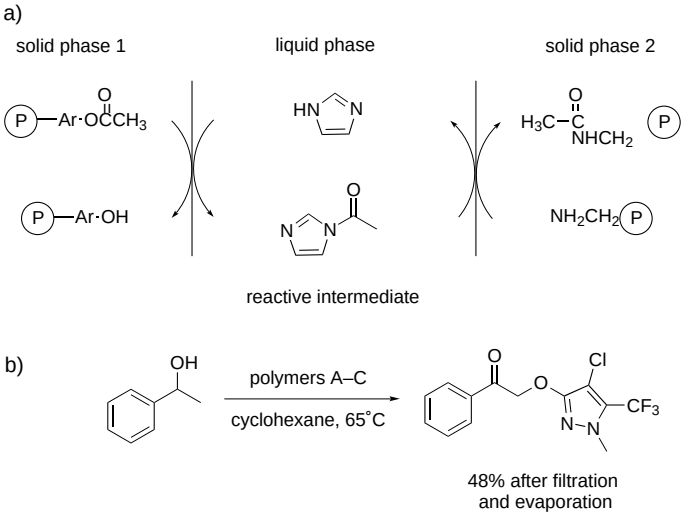
The basic feature of all the above methods is a simple separation technique, be it evaporation, extraction, or filtration. Likewise, excess reaction components of any type can be used with impunity in any reaction that meets the conditions of phase isolation. This oft-sited feature of solid-phase synthesis is by no means unique: All methods in which the substrate and the product are in the same phase can afford pure products at the end of a reaction, provided that the reaction occurs in quantitative yield based on the substrate and that none of the other reaction components or by-products derived therefrom is in the same phase as the product.

There are, however, powerful features associated with solid-phase synthesis that are not shared by other methods and that are directly attributable to solid–solid separations. Particles of any kind can be separated from one another by a

variety of triaging procedures. Indeed, arguably the most famous separation process of all time is a solid–solid separation: Pasteur resolved tartaric acid by sorting the enantiomeric crystals with tweezers under a microscope. The now popular technique of "split synthesis" is also based on a solid–solid separation.[2, 3, 14] Each bead in a synthesis contains a single compound and can be physically separated from every other bead. Although spilt synthesis shares the solid–solid separation features of the resolution of tartaric acid, it also requires the polymer, which in effect serves as an "internal reaction vessel" to hold a group of attached substrates together.

Split-synthesis techniques[14] then rely on three separate features: 1) The solid–liquid (and solid–gas) separations allow excess reagents to be used and provide for easy separation of products from other reaction components, 2) the solid–solid separation provides separation of one product (bead) from another, and 3) the chemical attachment of multiple substrate copies to the polymer provides enough product per bead for detection and analysis. This third feature is crucial, but it does not rely on phase separation.

Solid–solid separations and chemical attachment also provide unique features that can be collected under the term "site isolation". For example, in Rebek's famous three-phase test (Scheme 6a),[15] a reactive intermediate such as acetyl



Scheme 6. a) An example of the three-phase test; no reaction occurs between solid phases in the absence of imidazole. b) Simultaneous multistep synthesis with polymer reagents; polymer A: poly(4-vinylpyridinium dichromate), oxidizes (secondary) alcohols to ketones; polymer B: perbromide on Amberlyst A-26, brominates ketones; polymer C: Amberlite IRA-900 ((4-chloro-1-methyl-5-trifluoromethyl)-1*H*-pyrazol-3-ol), displaces bromide.

imidazole is released from one polymer into solution and trapped on another polymer. In a related way, otherwise incompatible reagents can be mixed. For example, polymeric reagents can coexist and simultaneously operate on substrates in solution without reacting with each other (Scheme 6b).[16] These effects again result from solid–solid separations. Finally, especially in more rigid polymers, attached substrates are isolated not only from substrates on another bead but to some extent also from substrates on the same bead. Solid–solid separations prevent functional groups on different particles from reacting with each other, but effective molarity[17] retards functional groups on the same particle from reacting with each other.

2.4. The "Strategy" in Strategy-Level Separation Planning

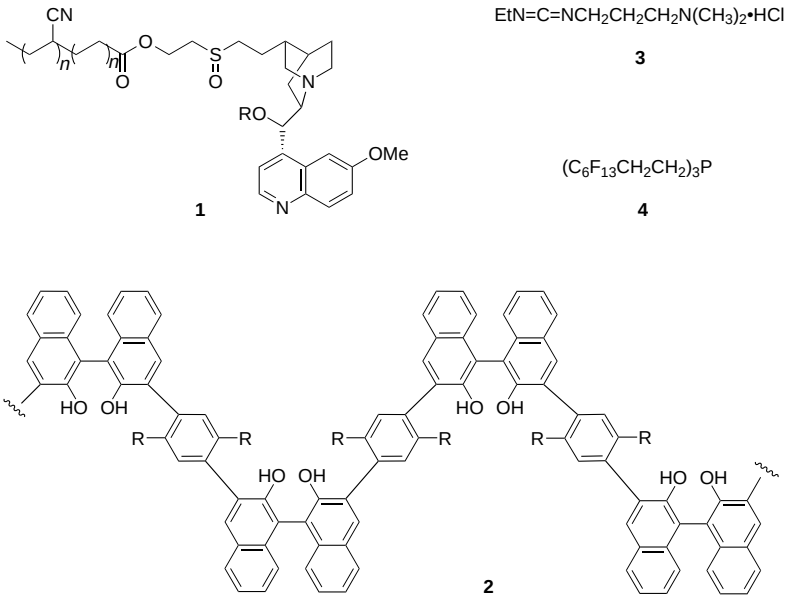
To reach the goal of isolating the product in a unique phase requires that separation be promoted from its current "technical" status to a strategy-level concern. In other words, synthetic chemistry dictates separation, and the planning of each step in a reaction sequence incorporates a designed strategy for purification. In the area of parallel synthesis, the separation strategy should be identically applicable across all members of the library. Strategic planning of separations is an exercise in matching separation techniques with the natural and labeled tendencies of all the expected components of the final reaction mixture. Additional levels of planning are associated with how and when phase labels are attached and detached (phase switching), and what other roles phase labels are required to play (as protecting groups or directors of stereo-, regio-, or chemoselectivity).

Exploiting the natural tendencies of molecules in simple phase-separation techniques formed the basis for the earliest separations, and this time-honored approach can still be used for classes of reactions that pair nonvolatile organic substrates with volatile or water-soluble reaction components. Separations for such reactions are already trivial, but these types of reactions are relatively uncommon. The development of phase-labeling techniques is now making the goal of applying simple workup-level separation techniques a reality for many more kinds of reactions.

2.5. Methods of Phase Labeling

The natural phase of any type of reaction component can be overridden by attachment to a phase label, or changed by a chemical process such as polymerization. We provide below a loose classification of phase labels taken largely from solid-phase synthesis. The basic concepts can be extended to any kind of phase-separation technique.

Permanent labeling: Reaction components such as reagents, catalysts, and additives that are not transferred to the final organic product of a reaction sequence can be rendered permanently solid, fluorous, or acid/base-soluble. The resulting modified reagents find use in any area of synthesis, because they facilitate purification of the reaction product as well as recovery of the labeled reaction component for reuse. A number of techniques for doing this are well appreciated.[5] For example, an organic reagent can be rendered solid either by attaching it to a polymer backbone,[18] as in the case of the asymmetric dihydroxylation catalyst **1** (Scheme 7),[19] or by fashioning a polymer of the reagent itself, as illustrated by the polymeric binaphthol (BINOL) derivative **2**.[20] Similarly, many standard reagents now have water-soluble (or acid- or base-soluble) variants: Water-soluble *N*′-(3-dimethylamino-

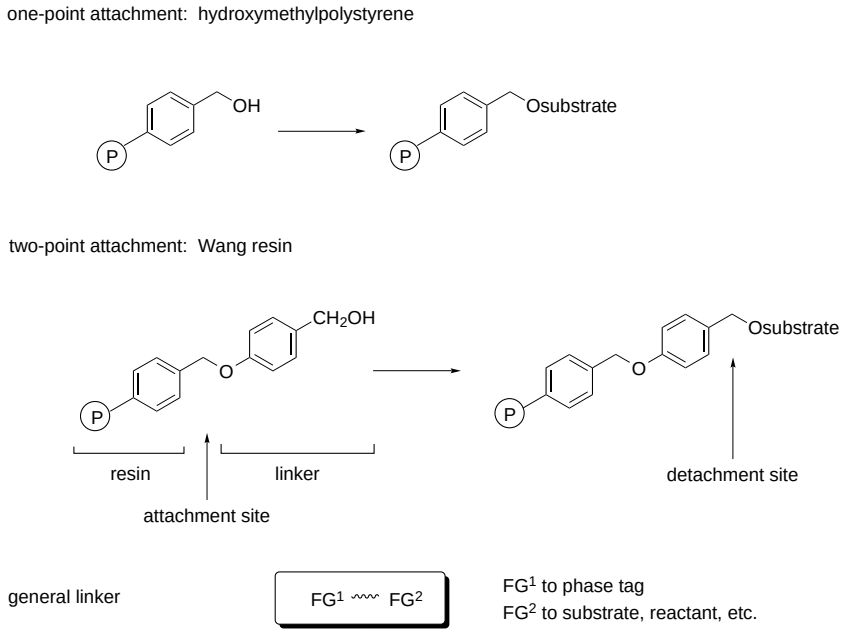


Scheme 7. Representative examples of permanently labeled reagents and catalysts: a catalyst with a polymer backbone (**1**), an integral polymer catalyst (**2**), a water-soluble reagent (**3**), and a fluorous reagent (**4**).

propyl)-*N*-ethylcarbodiimide (EDCI, **3**) can often be substituted for an organic carbodiimide in dehydrations,[21] and phosphane **4** can be viewed as a fluorous version of a standard trialkylphosphane.[8]

Temporary labeling: When instead reaction substrates and products are labeled, the labeling must be temporary because the initial and final products are organic. Temporary attachments can be accomplished in a number of different ways, two of which are illustrated in Scheme 8. In the simplest version, labels are attached and detached at the same site. Such a strategy resembles closely the standard use of protecting groups in many cases, as in solid-phase synthesis. Attachment and detachment at the same site is an especially good strategy for recycling the phase label.

In a number of applications, there are advantages to separating the sites of attachment and detachment. The separating groups are often called linkers. In polymer chemistry, linkers are valuable because a relatively large number of groups with different features can be generated from a few basic polymers. The linker is often anchored permanently by a robust bond to the polymer, and a separate bond (cleavable under certain, defined conditions) is then made to the substrate. The two steps can also be conducted in the reverse order. In solid-phase synthesis, linkers can also fulfill other roles, such as helping to expose linked substrates to reagents in solution. In the broadest sense, linkers are nothing more than difunctional molecules that bridge a substrate, and a phase label by attaching to each through one functional group. As discussed below, the role of linkers is now expanding beyond solid-phase synthesis.



Scheme 8. Examples of temporary labeling in solid-phase synthesis.

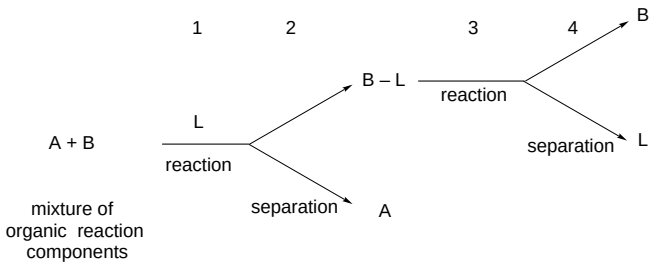
2.6. Establishing Different Phase Behavior at the Reaction and Purification Stages

It is frequently desirable for reaction components to exhibit different phase behaviors at the reaction and purification stages. Although biphasic reactions are purposefully used to advantage for some kinds of reactions, it is more common to conduct reactions that (ideally) occur in a homogeneous liquid phase. In contrast, at least two phases are required for any kind of separation. In solid-phase synthesis with insoluble polymers, it is not possible to establish a homogeneous liquid phase. This problem is being overcome by designing polymers that better mimic solution behavior and by developing reaction conditions that are optimized for solid–liquid reactions.

In most other applications not involving insoluble polymers, it is often possible to establish homogenous reaction conditions and then to cause a phase separation during purification. Because the phase behavior of a compound depends on both the compound and the phase-separation technique, a phase separation can be accomplished either by changing the technique or changing the compound. In perhaps the simplest example, the reaction itself converts a soluble substrate into an insoluble product, and a solid–liquid separation occurs. Product precipitation is highly sought after in process chemistry but has limited generality. Precipitations of specific compounds are also commonly effected by changing solvents or temperatures.

The use of soluble polymers represents a much more general approach to the problem of separation by precipitation or filtration. Some polymers are soluble under certain reaction conditions (solvent, temperature, etc.), but can be precipitated by changing the solvent or conditions.[22g, 23] When these polymers are used as phase labels, the precipitation can be controlled by the polymeric phase label and not by the labeled substrate or reagent. Fluorous approaches can also provide for one phase at the reaction stage and two phases at the separation stage either by alternative heating and cooling or by using different solvents at each stage.[8] Indeed, techniques based on soluble polymers and fluorous compounds are often classified together under the term "liquid-phase synthesis". However, since soluble polymers, fluorous tags, and the like are used for separation and not for synthesis, we prefer to classify these techniques according to their different phase behavior in separation.

It is also possible to switch the phase of one or more reaction components in a designed fashion, so that they become separable from another component or subset of components from which they were previously inseparable. We call this technique "phase switching" (Scheme 9). As mentioned above, phase switching can be as simple as an acid–base extraction. Here, the phase-switching "event" is the chemical protonation or deprotonation of a base or an acid.



Scheme 9. Stages in phase switching: 1) selective labeling of a component B with a label L (by protonation, deprotonation, conjugation to a polymer, fluorous group, etc.); 2) phase separation based on the presence or absence of L; 3) and 4) removal of L and repeated separation (only if isolation of B is required).

Complementing this classical technique are new methods based on chemoselective reactions of reaction components to attach or remove phase labels such as polymers or fluorous groups. The attachment/removal can be accomplished before the reaction, as a direct result of the reaction, or after the reaction. Any reaction component can be subjected to phase switching to effect purification. Probably the most powerful types of phase switches involve reaction products; if the product can be selectively switched into a unique phase, it can be isolated in pure form independent of the absolute yield of the reaction.

3. Strategy-Level Separation—Practice

3.1. Classification of Purification Schemes

The various purification strategies listed in the following are classified by whether or not phase switches are involved, and are further sorted by the natural phase (at the separation stage) of the substrate and/or product of a reaction as "organic synthesis", "solid-phase synthesis", "fluorous synthesis", etc. This classification is based on the notion that there are two fundamentally different strategies to effect a phase separation of a homogeneous reaction mixture: 1) The reaction conditions (solvent, temperature, etc.) can be modified to effect a partition, and 2) one or more components of the reaction mixture can be chemically modified to change the phase behavior of the mixture with respect to a given phase-separation process. In the classification scheme, acid–base extractions and related techniques are listed as phase switches, and protonation or deprotonation becomes the phase-switching event.

3.2. Fundamental Methods Not Involving Phase Switches

In most synthetic applications, the natural phase of the substrates and products of a multistep synthesis is either never changed or changed only at the beginning and the end of a sequence. This results then in a relatively small number (at present) of fundamental ways to conduct organic synthesis. The choice of a fundamental method for a synthesis is made at the highest level of strategic planning. Indeed, until the advent of solid-phase synthesis, the "choice" of a fundamental method was essentially made by default since it was not recognized that there were any choices. For lack of a better name, standard methods based on "unlabeled" substrates and products are classified under the umbrella of "organic synthesis", where the term "organic" refers again to small organic molecules that generally partition into the organic liquid phase. Other methods are classified according to the nature of the label that is attached to the substrate at the outset. The features of each method at the reaction, the purification, and the identification/analysis stages of a synthetic step will be briefly evaluated.

3.2.1. Organic Synthesis

The original and still by far the most common fundamental strategy is to directly use organic molecules themselves. During the course of a sequence of reactions, intermediate products are chemically modified for all sorts of purposes including setting up subsequent bond-forming reactions, protecting reactive functional groups, and controlling stereo- and regioselectivity. However, they are not modified in a general way to change their phase behavior.

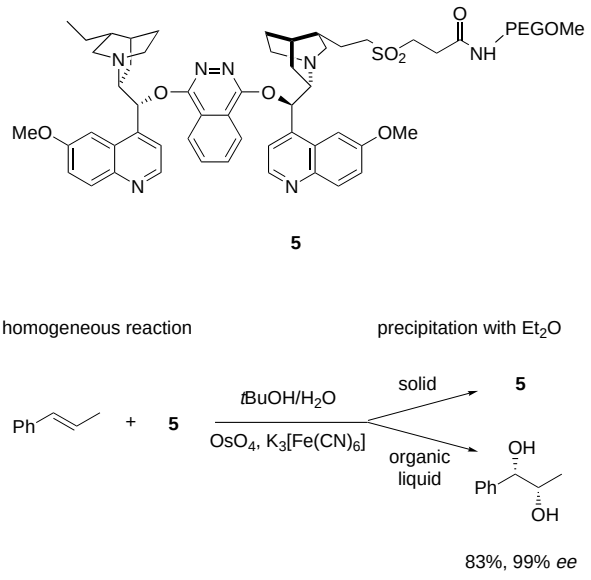
Backed by decades of intensive research and continuous improvements,[1] traditional organic synthesis is very strong at the reaction stage. It is also strong with respect to identification and analysis; there are many powerful spectroscopic and chromatographic methods that specifically address small organic molecules. However, traditional organic synthesis is weak at the purification stage—it is an exception rather than the rule that a single nonvolatile organic compound is present at the end of a reaction. The separation of one nonvolatile organic compound from another often requires chromatography, because most organic molecules partition together into

the organic liquid phase in any of the simple phase-separation techniques.

Although early methods for combinatorial synthesis were almost exclusively based on solid-phase techniques, "solution-phase" methods that use standard organic molecules as substrate and products are now making a comeback. In these methods, phase planning dictates that other additives to a reaction of a small organic molecule are chosen such that they all partition into a phase other than the organic liquid phase.[11]

Methods based on the gas phase (with volatile additives) and the aqueous phase (with inorganic or water-soluble additives) are well recognized by all practitioners, but are not covered here. Likewise, polymer-bound reagents have been used for more that two decades[22] and are becoming increasingly popular. In addition to allowing simple purification by filtration, these reagents can be used simultaneously (Scheme 6b). Furthermore, the reagents need not be polymer-bound; any type of insoluble solid will do. Heterogeneous metal catalysts, clay catalysts, and zeolites are examples of other types of insoluble solids that can promote reactions and then be separated from products by filtration.[5b]

Reagents attached to "soluble polymers" represent an especially useful class, because they can be made soluble at the reaction stage but precipitated at the purification stage by a change in solvent or temperature.[22g] The most popular and useful reagents to date in this class are bound on polyethylene glycol ethers (PEG).[23] PEG polymers arise from polymerization of ethylene oxide, and are available in varying molecular weights; they then have differing phase characteristics. PEG with a relative molecular weight (M_r) of 2000 to 20000 is soluble in many organic solvents, but can be precipitated by adding diethyl ether. A variety of reagents and catalysts are now available conjugated to PEG;[23] a representative example is shown in Scheme 10. The PEG-conjugated catalyst for asymmetric dihydroxylation (AD) provides superior results in representative Sharpless AD reactions, and is readily separated from the products and

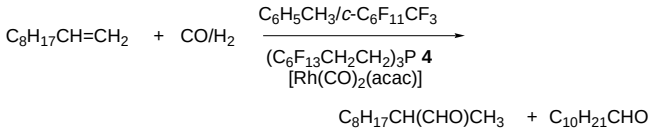


Scheme 10. A Sharpless AD catalyst tagged to a soluble PEG polymer.

recovered for reuse by precipitation.[24] Dendridic reagents may also offer interesting capabilities.[25]

Compared to other areas, the use of fluorous reagents to facilitate separations in traditional organic synthesis is in its infancy. It remains to be seen whether these methods will grow to complement more established alternatives. However, they do offer a significant potential advantage over methods based on polymer labeling or acid–base chemistry: The functionality present in the fluorous labels is highly inert and should therefore be stable under a wide range of reaction conditions.

Horváth and Rábai introduced "fluorous biphasic catalysis" by preparing the fluorous phosphane **4** and using it in the hydroformylation reaction shown in Scheme 11.[8] The reaction is conducted in a biphasic system of toluene and

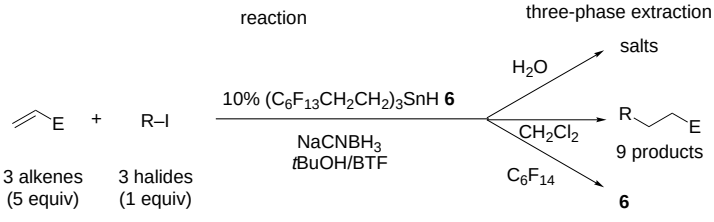


Scheme 11. Fluorous biphasic catalysis. acac = acetylacetonate.

perfluoromethylcyclohexane, and upon completion the two phases are separated. The hydroformylation products are recovered by evaporation of the toluene phase. There is no need to evaporate the perfluoromethylcylcohexane; the fluorous catalyst remains in this phase and can thus be reused in a subsequent reaction. A number of other catalysts for fluorous biphasic reactions have also been introduced, and the general strategy appears to have excellent potential.[8b, 26]

For more traditional syntheses including combinatorial applications, the use of immiscible phases in the reaction stage is often not desirable. Homogeneous reaction phases can be obtained upon use of organic solvents (such as ethers) that have a good dissolving power for fluorous compounds or upon use of miscible organic and fluorous solvents. Certain solvent pairs that are immiscible at room temperature become miscible on warming, and this is proving very useful for reactions with fluorous catalysts.[8b, 26d,f] Alternatively, one of the best ways to dissolve organic and fluorous compounds together is with "hybrid solvents". These are simply organic solvents that contain a few fluorine atoms; examples include benzotrifluoride ($\alpha\alpha\alpha$-trifluorotoluene, $C_6H_5CF_3$), 4-chloro- and 3,4-dichlorobenzotrifluoride, and trifluorethanol.

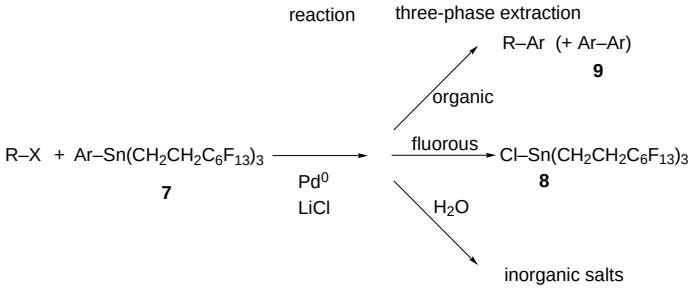
Scheme 12 shows the synthesis of a small library of radical-addition products formed in parallel Giese reactions mediated by fluoride-containing **6**.[27] This tin hydride is used in catalytic



Scheme 12. Fluorous reagents/catalysts: catalytic reactions of the fluorous tin hydride **6**.

amounts with sodium cyanoborohydride as the coreductant. Related reactions do not succeed in organic solvents such as benzene (because the tin hydride is insoluble) or fluorous solvents such as perfluorohexane (because the organic reactants are insoluble), but proceed smoothly in benzotrifluoride. In the case of the catalytic transformations, *tert*-butanol is added as a cosolvent to aid the dissolution of the sodium cyanoborohydride. At completion of the reaction, the reaction mixture is evaporated (which removes excess alkene) and partitioned between water, an organic solvent, and a fluorous solvent in a three-phase extraction. The aqueous layer containing the inorganic salts is discarded, whereas evaporation of the organic and fluorous layers gives the corresponding products. Nine different organic products are obtained in reasonable yield and excellent purity from the organic phases. Since the fluorous product is the starting tin hydride in all cases, the fluorous phases can be combined and evaporated to provide **6** for reuse.

In the above small library, **6** behaves as a catalyst and the sodium cyanoborohydride as a reagent; together they provide a constant component (a hydrogen atom) to each product. The fluorous version of the Stille coupling (Scheme 13) provides an example for the synthesis of a small library with use of a collection of fluorous reactants **7**.[28] Unlike reagents, reactants provide a variable piece of a library.[4] In this case, the Stille coupling detaches the aryl ring from the fluorous label to provide an organic product. The reactions are conducted with standard catalysts and ligands in DMF or DMF/THF. The starting tin reagents are not completely soluble in warm DMF, but do dissolve to some extent, and the reactions appear to become homogenous over several hours. Interestingly, LiCl is essential for rapid and clean Stille couplings of fluorous tin reagents.

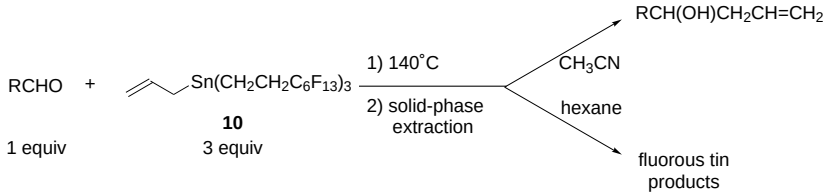


Scheme 13. Fluorous reactants: the Stille coupling.

Reaction mixtures are again purified by three-phase extraction, and the obligatory by-product from the tin reagent, fluorous tin chloride **8**, is recovered in excellent yield. In reactions such as this, the labeled reactant can be used in excess provided it is effective in forcing the partitioning of the tin reagent into the fluorous phase. Extraction experiments show that the starting tin reagents **7** do partition very well into fluorous solvents. However, analysis of the product mixture also shows that there is no aryltin reagent left at the end of the reaction. Furthermore, about the same yield of Stille coupled product is obtained with 1.1 equivalents of tin reagent as with 3 equivalents. In general it follows that for reactions in which the fluorous reactant is consumed the label need only be of sufficient size and fluorine content to force the obligatory by-product into the fluorous phase; the partitioning of the starting reagent is unimportant.

In addition to the unavoidable tin chloride by-product, there is a side product of these reactions, biaryl **9**, which results from the homocoupling of **7**. This product is "organic" with respect to a fluorous–organic liquid–liquid extraction and cannot be separated from the cross-coupled products by nonchromatographic methods. This is a general problem that is not unique to fluorous chemistry: When a side product is formed that detaches a reagent, reactant, or catalyst from its label, it is usually organic and passes through the phase-separation process with the desired organic product. In the case at hand, the problem was solved by optimizing the reaction conditions; addition of a copper salt or conduction of the reaction under microwave conditions (or both) suppress the formation of the homocoupled product.[29] The use of microwave techniques has the added benefit of reducing the reaction time to just a few minutes.

Allylations can be conducted under standard conditions with the allyl tin reagent **10** either thermally without solvent or with a standard catalyst in benzotrifluoride.[30] In the first case reaction mixtures (Scheme 14) were purified by standard liquid–liquid extraction and by a new technique, fluorous solid-phase extraction. This uses "fluorous reverse-phase silica gel",[31] which can be prepared by the standard silylation procedures that are used to prepare normal reverse-phase silica gel; our silica was silyated with $ClSi(Me)_2CH_2CH_2C_6F_{13}$. In the solid-phase extraction, the crude reaction mixture is loaded directly onto the fluorous column, which is then eluted with acetonitrile. Organic compounds cannot interact with the column and are eluted instantly. On the other hand, the same general, nonspecific interaction that allows one fluorous compound to dissolve in another helps to hold the fluorous tin reagents firmly to the column. However, this interaction is shattered by elution with a fluorous solvent (or even a very nonpolar organic solvent such as hexane), and the tin fraction then elutes immediately.



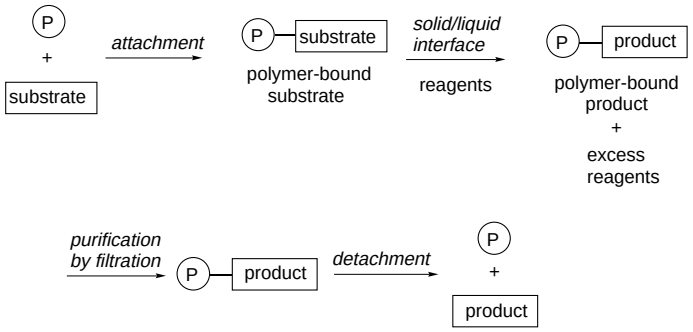
Scheme 14. Purification by fluorous solid-phase extraction. The solid-phase extraction is conducted with fluorous reverse-phase silica (silica–$OSiMe_2CH_2CH_2C_6F_{13}$).

Currently, Hindsgaul and co-workers are introducing the complementary technique of reverse solid phase extraction.[32] These and related techniques for solid-phase extraction provide technically simple yet substantive and general separations across a range of processes (see below).

3.2.2. Solid-Phase Synthesis

Solid-phase synthesis was the first fundamental strategic alternative to traditional organic synthesis from the standpoint of phase planning, and is still the only one of demonstrated generality. Techniques for solid-phase synthesis have exploded from their origins in peptide and oligonucleotide synthesis to encompass the synthesis of libraries of small molecules[2, 3] and, very recently, natural products.[33] Since the general approach is now familiar to most practicing chemists, no specific examples are provided here; we simply summarize the strategy within the larger picture of phase planning.

Schematic representations such as that in Scheme 15 are often used to reduce solid-phase synthesis to its bare bones. A small organic molecule is initially attached through a



Scheme 15. Solid-phase synthesis with polymer-bound substrates.

covalent bond to a polymer or another form of solid support. This is a phase-labeling event, and the substrate and all products until detachment are then fixed as solids in any solid–liquid (or solid–gas) separation. Most applications make use of insoluble polymers, and reactions are then conducted at the solid–liquid interface with a large excess of other reaction components. The use of these excesses is crucial in solid-phase synthesis since reactions can be more difficult to drive to completion. The purification of reaction mixtures from solid-phase syntheses is the essence of simplicity, and generally involves filtration to separate the insoluble products from soluble reaction components.

Purification is thus the overriding strength of solid-phase synthesis. In contrast to traditional syntheses of small molecules, however, solid-phase synthesis presents problems at the reaction stage owing to inhomogeneity. Additional constraints are added at the identification and analysis stage, because polymer-bound substrates are mixtures of large macromolecules. Standard chromatographic techniques provide no information on polymer-bound substrates. Whereas spectroscopic techniques such as IR and NMR can be used to great advantage, experiments are rarely easy to execute and sometimes do not provide as much information on polymer-bound substrates as they do on small organic molecules.

Like synthesis with insoluble polymers, the attachment of substrates to soluble polymers such as PEG is an outgrowth of polypetide synthesis. Gravert and Janda have shown that this method has many attractive features for the synthesis of libraries.[23] In addition to their ability to be dissolved at the reaction stage, PEG-bound substrates tend to be easier to identify than other polymer-bound substrates. The PEG substrates are bound only to the end(s) of the linear polymer, and since the end of one polymer is pretty much like the end of another, the molecules often behave like they are single entities even though they are not. For example, many PEG-labeled substrates give well-resolved, readily interpretable NMR spectra. Only the small region in the vicinity of the signal for the PEG methylene group is obscured. However, like fluorous synthesis described below, PEG-supported synthesis sacrifices the features of solid–solid separations and cannot be used for "one-bead, one-compound" split-synthesis techniques.

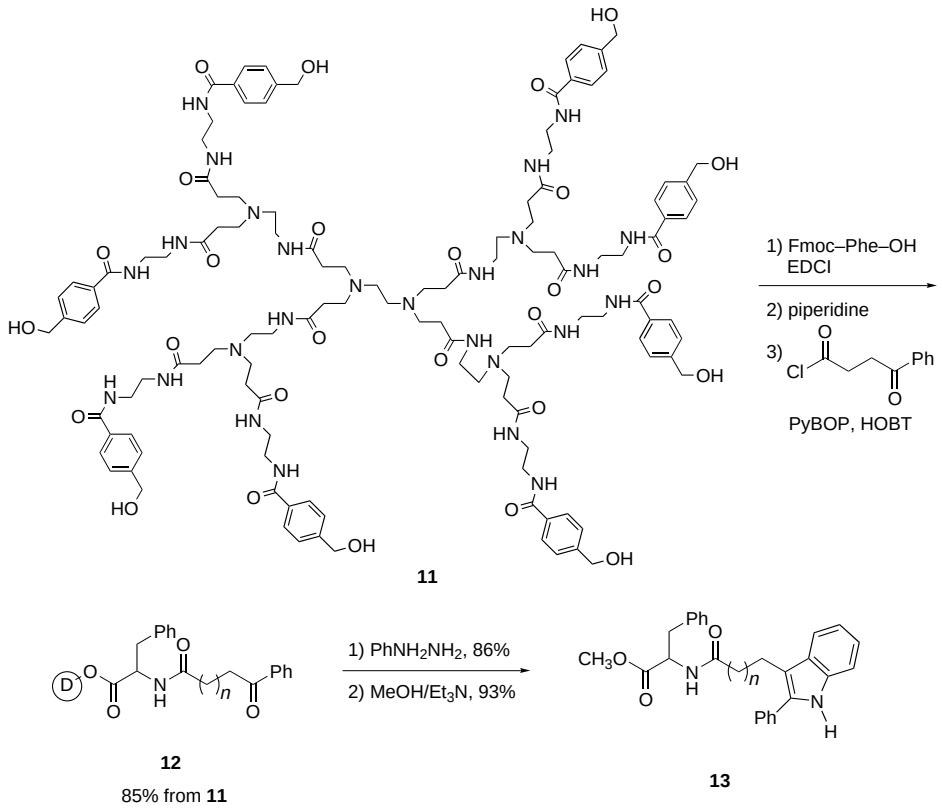
The rapid and overwhelming embrace of solid-phase synthesis as a mainstream technique speaks volumes for purification. In the early 1990s, organic chemists deemed it easier to solve the reaction, identification, and analysis problems in solid-phase synthesis than to solve the purification problems in the synthesis of small molecules. That collective decision—conscious or unconscious—has resulted in the development of solid-phase synthesis into a valuable mainstream method that is improving at a rapid pace.

3.2.3. Dendrimer Synthesis

Recently introduced by Kim and co-workers at Merck,[34] the technique of dendrimer synthesis allies labeling of substrates by dendrimers with size-exclusion chromatography. In size-exclusion chromatography, a suitable support is charged with a mixture to be purified and then eluted with a solvent. Smaller molecules are retained better by the column, while larger molecules move faster. In dendrimer synthesis, the technique is used in a crude way to separate large molecules from small ones, and the purification tends to resemble a filtration more than a chromatographic separation.

The features of the technique are illustrated in Scheme 16 for the Fisher indole synthesis; purification is accomplished at each stage by size-exclusion chromatography. The starting dendrimer **11** was prepared by conjugation of a first-generation poly(amidoamine) (PAMAM) Starburst dendrimer[35] to a hydroxymethylbenzoic acid linker. Acylation first with 9-Fmoc-phenyl alanine (Fmoc = 9-fluorenyloxycarbonyl) and then with 4-benzoylbutyric acid provides the substrate **12** for Fisher indole synthesis. Reaction of this substrate with phenylhydrazine followed by detachment from the linker provides the product **13** in excellent yield and purity.

Dendrimer synthesis has attractive features at all stages of the synthesis process. At the reaction stage, standard solution reaction conditions for the synthesis of small molecules should often be directly applicable, as dendrimers are generally soluble molecules. At the purification stage, size-exclusion chromatography provides a simple method to separate dendridic from non-dendridic molecules. At the identification and analysis stage, dendrimer synthesis is attractive because the products, while rather high in molecular weight, are still single entries[36] that are readily soluble. Although many standard chromatographic techniques are not applicable, the dendridic products are amenable to the same types of



Scheme 16. Dendrimer synthesis with the Starburst dendrimer **11**, which has linkers ready for eight substrates. PyBop = 1-benzotriazolyloxytripyrrolidinylphosphonium hexafluorophosphate; HOBT = 1-hydroxy-1*H*-benzotriazole.

spectroscopic analysis that are conducted for small molecules. Even mass spectra can be obtained by using the electrospray method. Finally, the "loading level" of substrates on a dendrimer is much higher than typical polymer loadings.

Split synthesis with dendrimers provides mixtures of compounds that can be analyzed or characterized in several ways. Kim and co-workers illustrated this with a 3×3 split-mix synthesis of 27 indoles in which the three variable components were the amino acid, the keto acid, and the arylhydrazine (Scheme 16). The final result was three mixtures of indoles that each contained one hydrazine fragment connected to the nine possible combinations of the other two fragments. Like with solid-phase synthesis, each individual dendrimer in any mixture (ideally) contains eight copies of the same indole. However, there is no way to capitalize on this at present since one dendrimer cannot be conveniently separated from another.

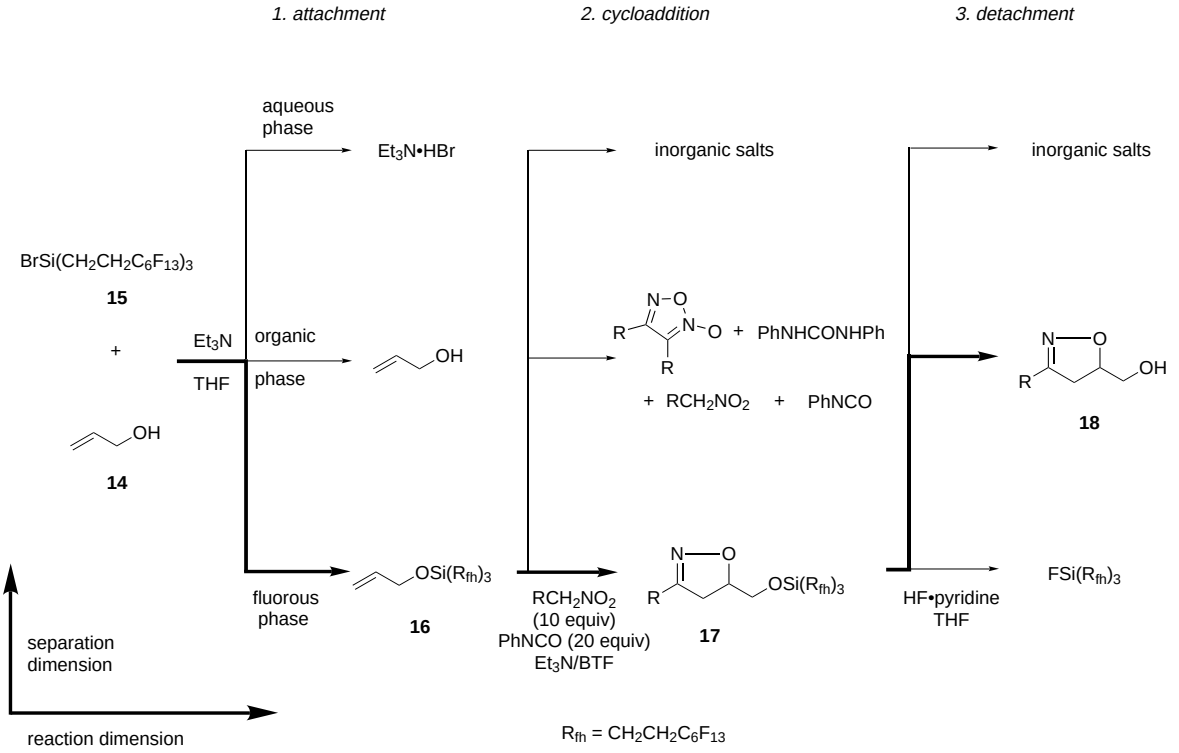
3.2.4. Fluorous Synthesis and Multilayer Reaction Schemes

The most recent addition to the list of fundamental synthesis techniques is fluorous synthesis, which we introduced in early 1997.[37] The approach is conceptually similar to solid-phase synthesis (especially the soluble variants such as PEG chemistry) and dendrimer synthesis. A substrate is attached to a fluorous phase label that has sufficient fluorine content to draw the labeled substrate and its subsequent products into the fluorous phase in a suitable separation technique. To date, we have only used fluorous–organic liquid–liquid extractions, but we expect the fluorous solid-phase extraction will be applied to advantage in due course. The substrate is then subjected to one or more reactions prior to removal of the fluorous label to give the desired small molecule.

The technique was first demonstrated with the synthesis of a series of isoxazoles and isoxazolines. These were initially prepared by the traditional method with isolation and chromatographic purification of all intermediates, and then the sequence was repeated on selected samples with purification only by fluorous–organic extraction (Scheme 17). Introduced in Scheme 17 is a "multilayered" organic reaction scheme that is intended to augment the traditional approach to writing schemes that places everything across a single line. The traditional scheme for notation of reactions is readily adapted to visualizing "two-phase" reactions such as polymer synthesis (solid–liquid filtration) and dendrimer synthesis (dendrimer/non-dendrimer filtration). In these two-phase methods, it is common to write substrates and products in front of and behind arrows, while reagents and other additives are written above and below arrows. This naturally separates, say, the final solid-phase reaction components from the final liquid-phase products. However, things start to become less clear when more than two phases are involved or phase switching is used.

Multilayer schemes like that in Scheme 17 divide the reaction and purification stages of a process into two different dimensions. In Scheme 17, the reaction dimension is horizontal. Purification then occurs in the vertical dimension, and a layer is drawn for each type of product. The lines in boldface track the progress of the target products. The reaction mixtures in Scheme 17 are all purified by three-phase extractions with water, an organic solvent, and a fluorous solvent. Each horizontal line represents the contents of one of the phases at the end of every step. In some of the schemes below, reagents will be written adjacent to the vertical arrows; these signify reagents that are added during or after the reaction to effect a phase switch of one or more of the components. These types of multilayer schemes are readily adaptable to the diverse array of purification methods, and help with both planning and visualization of the separation scheme.

The "organic" allyl alcohol **14** is rendered fluorous by silylation with the highly fluorinated silyl halide **15** (Scheme 17). The excess alcohol used to drive the reaction to completion (based on the tag) is removed into the organic



Scheme 17. Fluorous synthesis illustrated in a multilayer reaction scheme.

layer of the ensuing three-phase extraction. Nitrile oxide cycloaddition is then conducted by the Mukaiyama method with very large excesses of a nitro compound (10 equiv) and phenyl isocyanate (20 equiv). This ensures a quantitative yield of fluorous isoxazoline **17** (based on the precursor **16**). All unchanged reagents and side products derived therefrom are in the organic or aqueous phases. Desilylation of **17** returns the final product **18** to the organic phase in the last three-phase extraction.

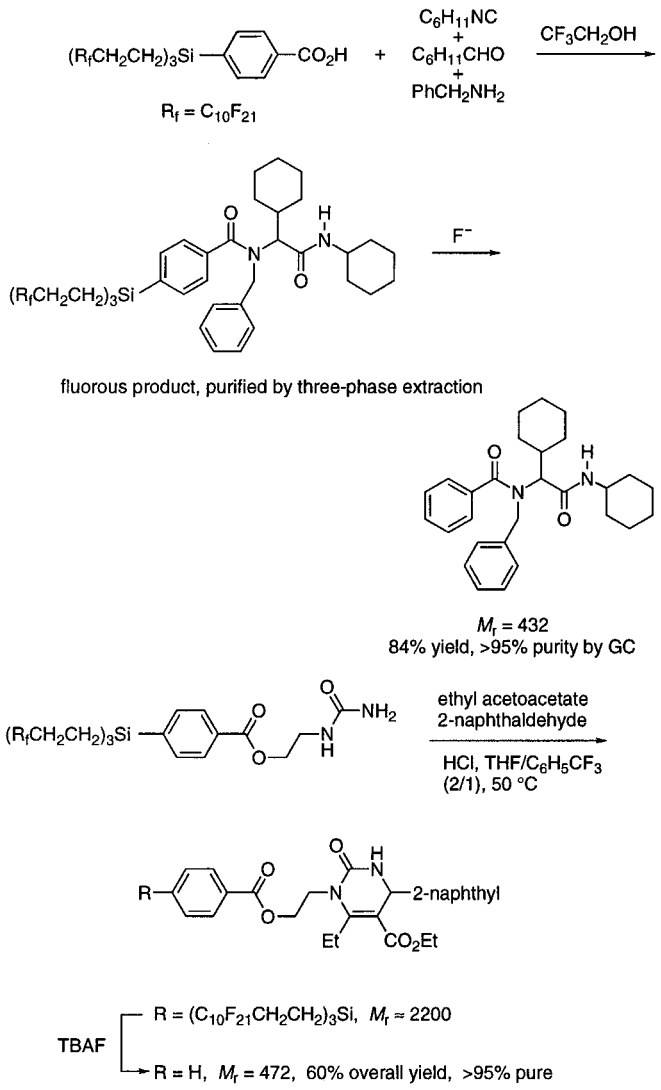
This nitrile oxide cycloaddition requires protection of the alcohol (which would otherwise react with the phenyl isocyanate). This might normally be accomplished with a trialkylsilyl ether; however, in this route all the intermediates on the fluorous (lower) level in Scheme 17 are organic and must be separated from all the other organic products on the organic (middle) level.

The silyl bromide **15**, containing 39 fluorine atoms, has been used to render small organic molecules ($M_r < 200$) fluorous with respect to liquid–liquid extractions, but larger molecules begin to partition into the organic phase. However, the use of labels with more fluorine atoms favors partitioning of even relatively large molecules into the fluorous phase. For example, the fluorous acid and urea shown in Scheme 18 were subjected to Ugi and Biginelli reactions, respectively.[37a,c] In both cases, very large excesses of organic components were used, and the organic components that had not (or only partially) reacted were separated from the desired fluorous products by liquid–liquid extraction. Final desilylation of the fluorous products then provided the organic Ugi and Biginelli products shown. A number of other products in the molecular-weight range of about 300–500 were synthesized by these procedures.

While there is still much to be learned before fluorous synthesis can be applied more generally, it does offer a number of attractive features that should stimulate research in this area. At the reaction stage, fluorous synthesis offers the potential for homogeneous reactions to be conducted under standard conditions, although solvents must sometimes be adapted to ensure that all reactions components are sufficiently soluble. For example, in the nitrile oxide cycloaddition in Scheme 17 benzotrifluoride was used in place of a standard solvent such as benzene or toluene, whereas in the Ugi reaction in Scheme 18 trifluoroethanol was used in place of methanol or ethanol.

In the purification stage, the fluorous label allows tagged molecules to be separated from untagged molecules by liquid–liquid or solid-phase extraction. However, the nature of the tag is substantially different from the polymers and dendrimers used to date. Perfluoroalkyl chains are much more stable under organic reaction conditions than most polymers and dendrimers, and the tagging strategy resembles the protection of functional groups. Therefore, fluorous labels are generally expected to expand, rather than contract, the range of reaction conditions to which a labeled substrate can be exposed. Although linkers may be useful for some applications, they are generally not needed. Like protecting groups, the fluorous labels are attached and detached at the same site. This makes recycling of the labels convenient.

At the identification and analysis stage, fluorous substrates resemble small organic molecules much more closely than with the other techniques. Although their relative molecular weights are high (1000–2500), the substrates in fluorous synthesis are all soluble entities that can be identified and analyzed by the full battery of techniques for small molecules.



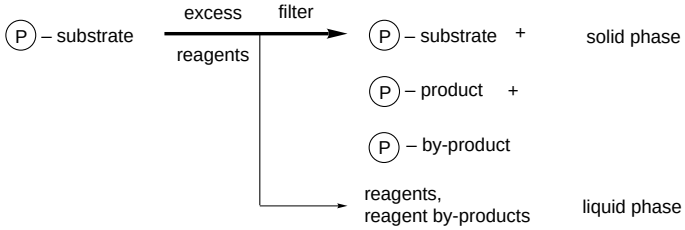
Scheme 18. Fluorous Ugi and Biginelli reactions.

With the exception of spin–spin coupling to nearby nuclei, the fluorine atoms are silent; the ^1H and ^{13}C NMR spectra of the fluorous substrates in Schemes 17 and 18 resemble standard protected organic molecules. Owing to the volatility of organofluorine compounds, electrospray methods are not needed to obtain mass spectra; standard electronic impact and chemical ionization techniques suffice, and both low- and high-resolution spectra can be obtained.

Potential advantages also accrue because fluorous synthesis links a single substrate to a label, as opposed to most other methods which attach multiple substrates per label. Reactions can be followed by thin-layer chromatography, and products can be analyzed by HPLC or other standard techniques (but generally not gas chromatography). Although fluorous techniques are designed to minimize purification, standard chromatographic purification of fluorous compounds is still possible. Polymers cannot generally be purified beyond washing. While it may be possible to purify dendrimers in reactions that do not occur in quantitative yield (based on a bound substrate), the purification is pointless because each individual dendrimer would itself contain a mixture of bound products.

3.3. Phase-Switching Techniques

There are two well-recognized problems with using any single fundamental method of synthesis continuously for a sequence of reactions: 1) Reagents and reactants having the same natural phase as the substrate cannot be used, and 2) reactions must occur in quantitative conversion and yield (based on the substrate). The first problem is most acute for traditional organic synthesis; despite active research there are currently not nearly enough reaction components (polymer, fluorous, dendridic, etc.) available to contemplate a complex multistep synthesis starting with a soluble organic molecule without adding or forming another organic molecule besides the desired product. The second problem is more insidious and cuts across all areas. It is illustrated in Scheme 19 for polymer-bound substrates. If a



Scheme 19. The Achilles heel of one-phase synthesis (illustrated with polymers).

polymer-bound substrate is left unchanged in a given reaction, it cannot be separated from the polymer-bound product; if the polymer-bound substrate is consumed but gives two products, these cannot be separated from each other. The problem is similar for soluble and insoluble polymers and dendrimers. When substrates and products are organic or fluorous, the separation is often possible by chromatography, but the whole point of the synthesis design is to render this unnecessary.

These two problems are solved by the technique of phase switching. To address the first problem, phase switching of reactants, reagents, or by-products therefrom (in other words, anything but substrates and products) is used. This provides methods to separate substrate and products from other reaction components. If the reaction occurs in quantitative yield and the phase switch succeeds, the product is isolated in pure form. The second problem is addressed by phase switching of substrates or products derived from substrates. These techniques are more powerful because they permit the isolation of pure products in reactions that do not occur in quantitative yield. This is attractive for library synthesis because even "optimized" reaction conditions are unlikely to provide quantitative yields and conversions for hundreds of different reaction partners.

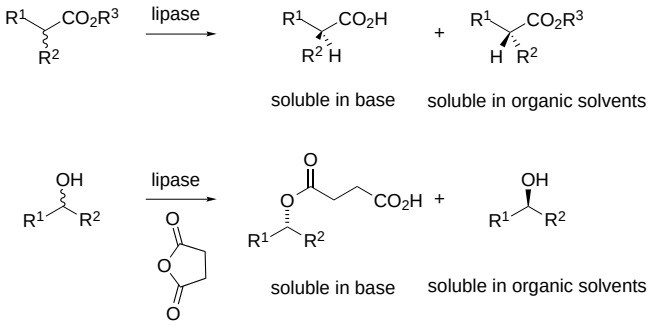
A number of techniques of phase switching are summarized below and organized according to the form of "nonorganic" phase from or into which a given product or subset of products is switched. Emphasis is placed on the use of linkers which allow phase switches to occur indirectly.

3.3.1. Acid–Base Chemistry

Acid–base extractions have long been used for workup-level purifications, but have changed very little until recently.

As mentioned above, the phase switch of an acid–base extraction is accomplished by protonation or deprotonation. This ionization step frequently transfers molecules from the organic to the aqueous phase in a liquid–liquid extraction. Acid–base chemistry is not generally thought of as providing substantive purifications, but recent results show that the power of acid–base purification extends well beyond its traditional bounds.

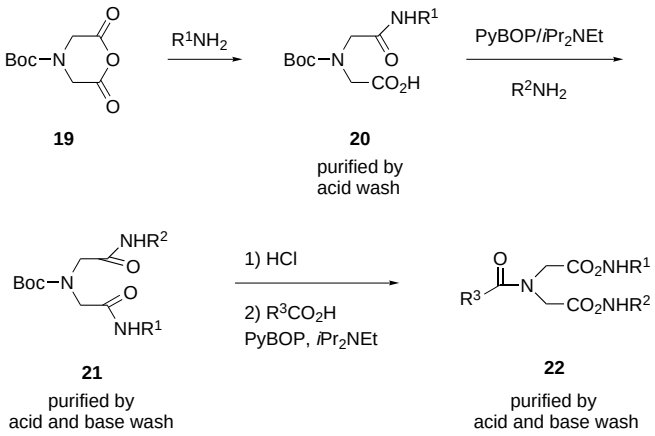
A classical example of an acid–base switch is shown in Scheme 20. Hydrolysis of a racemic mixture of esters with a lipase provides an acid from one enantiomer while leaving the



Scheme 20. Enantioselective acid–base phase switches.

other substantially unchanged.[38] In highly efficient kinetic resolutions of this type, the two products can be isolated in enantiomerically pure form by a suitable acid–base extraction. When ionizable functionalities are not directly involved, they can be "linked" to the process in question to effect a phase switch. For example, enzyme-catalyzed acylation of racemic alcohols typically provides two organic products, a recovered alcohol and an ester. However, if the esterifying reagent is something like succinic anhydride, the process of acylation links an acid group selectively to one of the products.[39] An acid–base extraction then separates the products into organic-soluble and water-soluble fractions based on the stereoselection in the acylation step. In both of these simple examples, the separation is directly coupled to the prior chemistry; the enantioselective reactions dictate the phase switch. In the subsequent examples, chemoselection is commonly used.

In seminal work on solution-phase synthesis of libraries of individual, pure compounds, Boger and co-workers prepared a number of "universal" dipeptide mimetics.[40] A representative example of the approach is shown in Scheme 21. Template **19** is allowed to react with a first amine used in excess to form the acid amide **20**. Purification by acid extraction causes the excess amine to switch phases to the aqueous layer in an organic–aqueous extraction, and pure **20** can be obtained from the organic phase. Coupling with a second amine in the presence of PyBOP reagent is the next step. Sequential acid and base extractions remove leftover amine, PyBOP and associated by-products to leave pure amide **21** in the final organic phase. Acid-promoted cleavage of the *tert*-butoxycarbonyl (Boc) groups, renewed coupling with an acid in the presence of PyBOP, and acid–base washing provides the final compounds **22**.

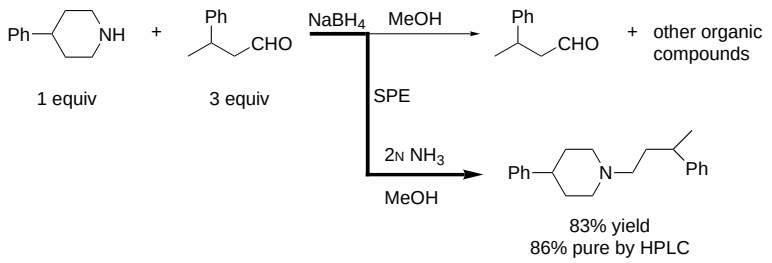


Scheme 21. Parallel synthesis of soluble organic products with purification by acid–base extraction.

In this sequence the acid–base extractions are used to remove reagents (PyBOP) and by-products derived therefrom as well as variable reactants (acids and amines) that are used in excess to drive reactions to completion and unchanged starting materials that are ionizable. The actual products are retained in the organic phase at all times, presumably because the reactions proceed in such high yields that purification of these products by phase switching is not needed. However, some of the products are ionizable and could at least in principle be purified by a suitable acid–base technique. This approach dictates that everything that is added to the substrate either is water-soluble or can be made so by protonation or deprotonation; it has been used to make libraries of over 1000 compounds in tens to hundreds of milligram quantities in excellent crude purities (typically $>90\,\%$).

Research groups at Lilly,[41] Signal,[42] Monsanto,[43] Bristol Myers,[44] Roche,[45] and Argonaut[46] have recently reported examples in which solid-phase extraction replaces liquid–liquid extraction as the separation technique for executing acid–base switches. Solid-phase extractions are easier to automate and conduct in parallel than liquid–liquid extractions, and possible complications with emulsions are avoided. Furthermore, not all ionized organic compounds partition out of an organic liquid phase and into an aqueous phase, but methods for solid-phase extraction should still at least provide some measure of separation of neutral molecules from ionized ones. Details about the technique of solid-phase extraction were illustrated in Scheme 5. In general, the ionized component is retained on the column during the first pass to provide a neutral fraction. When the desired product is neutral, the columns can then simply be discarded (at least in small-scale work). When the desired product is an ionic species, it must then be eluted from the column in a second pass with a suitable complementary eluent. For example, a solution of ammonia could be used to elute an amine from an acidic ion-exchange resin, or acetic acid could be used to elute an acid from a basic resin.

An example of an ion-exchange process is shown in Scheme 22. The straightforward reaction and purification sequence has been used at Lilly[41] to make hundreds of



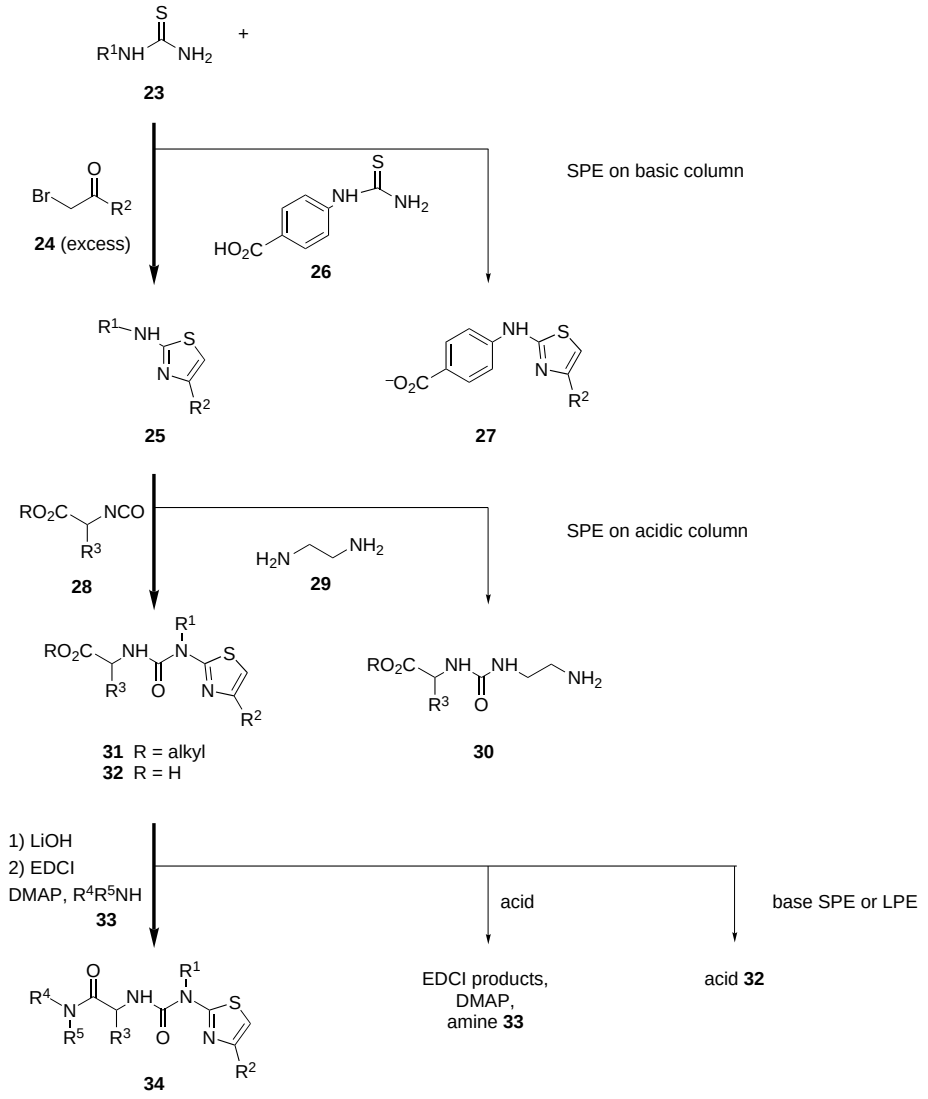
Scheme 22. Solid-phase extraction on an acidic ion-exchange column.

secondary and tertiary amines by an assortment of different alkylation reactions. Purities typically range from 85 to 95% or better. Other groups have related comparable successes in different reactions.[42–46]

The separation of two nonionizable reaction components can be accomplished by a linking strategy. In the example in Scheme 22, the ionizable group was introduced in one of the original reaction components. However, it can also be conjugated after the reaction by adding a suitable linker (scavenger) that will react quickly and chemoselectively with the target functional group (or groups).[41, 43] Once again, the chemistry dictates the separation. Scheme 23 shows a four-step library synthesis that features solid-phase extractions at three steps and a linking strategy in two of these steps.[45] A multilayer scheme is used with reactions in the vertical direction and separations in the horizontal direction. Reaction of thiourea **23** with excess bromomethyl ketone **24** provides thiazole **25**. Excess thiourea **26** was then added at the end of the reaction to convert the neutral bromoketone **24** into the acidic thiazole **27**, which was removed by solid-phase extraction. In the subsequent coupling of **25** with isocyanate **28**, the excess isocyanate was linked after the reaction to ethylene diamine **29**, and the resulting amino urea **30** was separated from the desired product **31** by solid-phase extraction. The hydrolysis that follows is a classical example of a purification that requires only removal of inorganic by-products, and this is accomplished by liquid–liquid extraction (not shown). Finally, the acid **32** is coupled with excess amine **33** in the presence of EDCI (**3**). Purification by suitable acid–base techniques leaves **34** as the only organic compound.

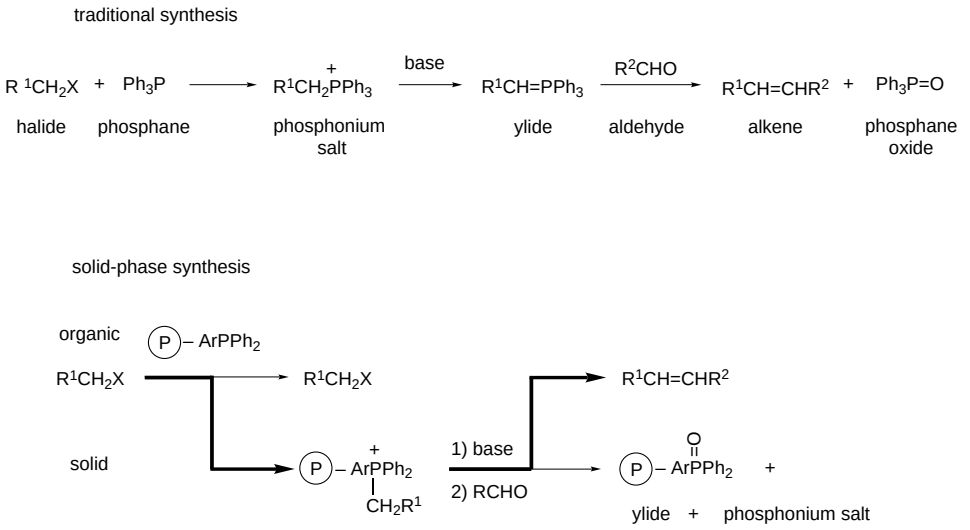
An attractive feature of the linker strategy is that suitable linkers can be added to capture any type of reaction component, including one or more of the starting materials or a known (or expected) by-product. Thus, pure products can be obtained from reactions that do not occur in quantitative yield. From the standpoint of purification, the most attractive method is to link the product itself. Provided this can be done selectively and the separation technique succeeds, a pure product is isolated independent of the yield of the reaction or the nature of the by-products.

Although the use of linkers dramatically extends the generality of acid–base switches, there are still limitations. The molecule (or molecules) being separated must be stable to brief exposure to moderate or strong acid, base, or both. Furthermore, it (they) cannot have any ionizable functionalities that are complementary to the purification techniques. A library that is being freed of amines, for example, cannot have any members that are ionized by acid. Like the other methods discussed below, acid–base methods sometimes involve a "double phase switch". An amine, for example, is



Scheme 23. Purification by solid-phase extraction with linkers.

transferred to the aqueous phase by protonation and back to the organic phase by deprotonation. There are then two opportunities for purification, but acid–base chemistry capitalizes almost exclusively on the first phase switch in terms of purification; the second is simply to recover the product that was transferred. The polymer (solid) and fluorous switches described below follow analogously from the principle of acid phase switches, but they have unique attractive features that allow them to both supplement and complement acid–base switches.



Scheme 24. Comparison of the traditional Wittig reaction with the solid phase switch variant.

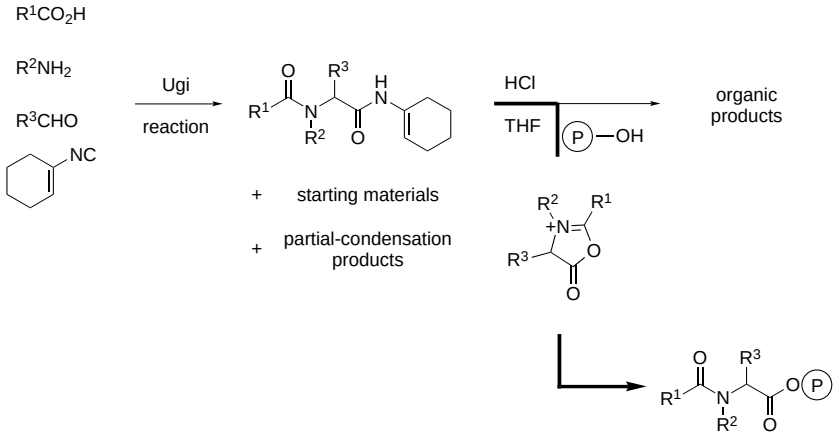
3.3.2. Solid Phase Switches

In traditional solid-phase synthesis, a substrate is attached to the linker and then processed through a sequence of steps prior to detachment. Although the attachment and detachment steps are switches to and from the solid phase, they rarely exhibit substantive features of purification. However, these features can be expressed by attaching reaction components to the solid phase during a reaction or detaching them from the solid phase after completion of a reaction. A number of these features were recognized in the early days of solid-phase synthesis, and some pioneering experiments have been summarized by Hodge under the name of "fishing out".[22e]

The Wittig reaction was one of the first C–C bond forming reactions to be studied on the solid phase,[47] and it nicely exemplifies some of the attractive features of solid phase switches. A standard solution Wittig reaction is shown in the top part of Scheme 24. Assuming that the aldehyde is the limiting reagent that provides the alkene product in quantitative yield, the alkene must still be separated from triphenylphosphane oxide and any unchanged triphenylphosphane, ylide or phosphonium salt, and halide. A successful solid-phase synthesis provides for all these separations.

Reaction of an organic halide with a polymer-bound phosphane provides the intermediate phosphonium salt, which can be separated from unchanged halide by filtration because the substrate is switched from organic to solid. The solid-phase Wittig reaction then switches the substrate from solid back to organic. The bound reagent and all its derivatives (phosphane, phosphonium salt, ylide, phosphane oxide) are solids throughout and are readily separated from the organic product. However, the process also allows the separation of one of the organic substrates (the halide) from the organic product (the alkene) because of the intervening double phase switch. The intermediate oxyphosphonium salt can also be separated from any unchanged aldehyde by filtration. The reaction nicely illustrates the power of a reaction designed such that the phase of an intermediate product is different from that of the starting and final products. In such a process, a reaction component is drawn out of one phase, physically transferred away from it to effect purification, and then allowed to react with another reaction component of the same phase as the original phase. The "three phase test" (see Scheme 6a) bridges two solid-phase components by a liquid-phase component, whereas the Wittig reaction bridges two liquid-phase components by a solid-phase component.

With a technique dubbed "resin capture", Armstrong and co-workers conducted Ugi reactions in solution and then captured the products on the solid phase by acylation (Scheme 25).[48] While one of the components could have been (and indeed has been[3]) linked to the solid phase prior to the Ugi reaction, the resin-capture



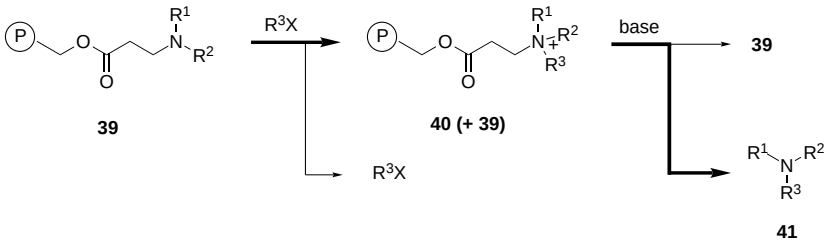
Scheme 25. Resin capture of Ugi reaction products: a solid phase switch that selectively targets products.

strategy allows the complex multistep Ugi reaction to occur in solution, while simpler, more rapid reaction (acylation) is forced to occur at the solid–liquid interface.

An especially attractive feature of this process is that it does not target any one of the original reaction components; the whole Ugi product is required for acylation. Thus, pure products can be obtained in nonquantitative reactions. In contrast, standard solid-phase variants of the Ugi reaction require quantitative yield (based on the solid-phase component) to provide pure products. Since the process in Scheme 25 requires an initial cyclization for subsequent switching to the solid phase to take place, it is the logical reversal of "cyclative cleavage" (cleavage of a component from a solid phase that is induced by cyclization of the component, see below). It is also analogous to the acid–base applications described in Section 3.3.1 and fluorous phase switches in Section 3.3.3; since the alcohol trapping agent bears a polymer rather than an ionizable group, a filtration is called for rather than an acid–base (or fluorous–organic) extraction.

It was recognized early on in solid-phase synthesis that cyclative cleavage had the unusual feature of providing pure final products after resin capture in reactions sequences that had not occurred in quantitative yields. A typical example of a cyclative cleavage is shown in Scheme 26.[49] Only products **37**, in which the amino acid **35** and the isomer **36** were incorporated in the synthesis sequence, will be removed from the solid phase in the final step. In a broader sense, cyclative cleavage is an example of a solid-organic phase switch. As with the resin-capture process described above, the selectivity of this technique relies on the following: Only the intermediate that contains the multiple components of the product reacts further. The message is clear: the more chemoselective a phase-switching process is for the product as opposed to impurities, the better. Processes that target a single functional group in one of the starting components are still valuable, because they allow the switching of organic soluble reaction components to other phases, but processes that target features unique to the product are even more valuable.

Cyclative cleavage is not the only way to trigger a selective solid–organic switch. Morphy and co-workers described the solid-phase synthesis of tertiary amines (Scheme 27).[50a] Quaternization of the resin-bound amine **39** provides the salt **40**, which is then freed from the resin in a selective phase

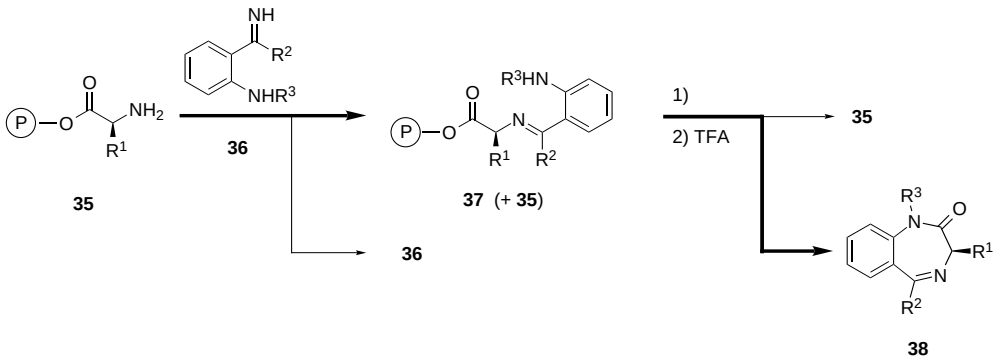


Scheme 27. A solid–organic switch that targets ammonium salts.

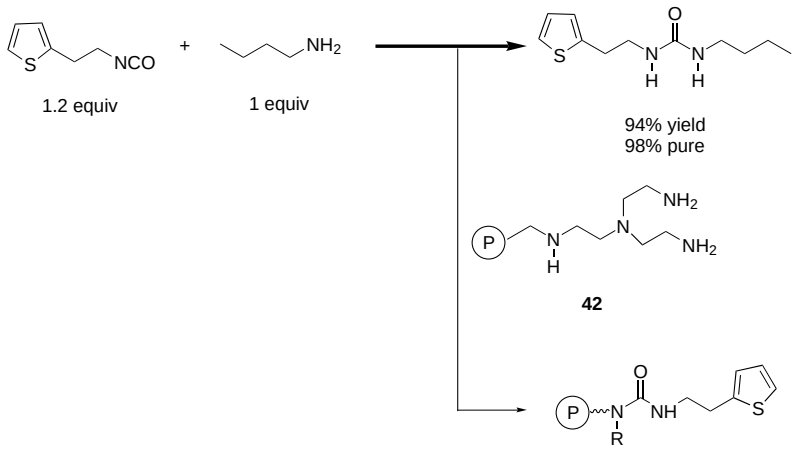
switch by β-elimination to give **41**. This process targets quaternary ammonium salts **40**, and other impurities such as tertiary amines **39** resulting from incomplete *N*-alkylation are left on the solid phase. Another very recent example of a solid–organic switch was provided by Ito and Ogawa. They loaded two monosaccharides onto a polymer and then cut them off with concommitant linking to each other to make a disaccharide with a β-mannose linkage.[50b]

A solid phase switch can be conducted without ever binding a target product to a polymer.[4f, 4b, 51] Solid phase switches that remove excess reagents, reactants, and by-products are only just emerging, but it is already evident that these are among the simplest and therefore most powerful techniques. For example, polymeric acid chlorides can function as general traps for nucleophiles, whereas polymeric amines can function as traps for electrophiles. An example from the work of Booth and Hodges is shown in Scheme 28.[51] In a design that borrows from dendrimers, polymeric primary diamine **42** was prepared in order to double the quenching capacity of standard aminomethyl polystyrene resin. Resin **42** can be used to remove isonitriles, acid chlorides, and other reactive electrophiles used in excess. The process occurs in a batch mode and is therefore even simpler to execute than solid-phase extraction. A quenching resin is added to a reaction mixture, and, after allowing time for the phase switch to complete, the reaction is filtered and the product is isolated by evaporation of the organic phase.

Solid phase switches of all sorts will benefit from the use of linkers. As in the acid–base chemistry, one end of the linker



Scheme 26. Cyclative cleavage, an example of a selective solid–organic phase switch. TFA = trifluoroacetic acid.



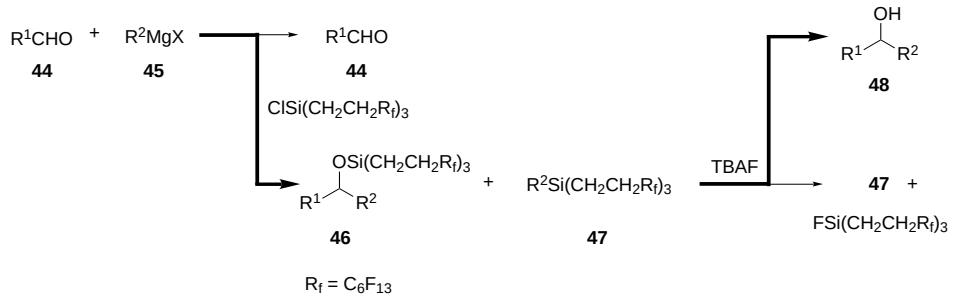
Scheme 28. Polymer-supported quenching: removal of impurities by organic–solid switching.

targets the functionality to be purified. Furthermore, the other end targets a complementary functional group or combination of groups in the polymer. This allows the use of a simple, rapid (biphasic) reaction to conjugate to the polymer. Also, by varying one end of the linker, a relatively large number of quenching processes can be conducted with just a few types of polymers. In traditional solid-phase synthesis, the linker is connected to the polymer and then the organic compounds is connected to the linker. However, mixing and matching of the order of these steps introduces valuable new options for both synthesis and separation.

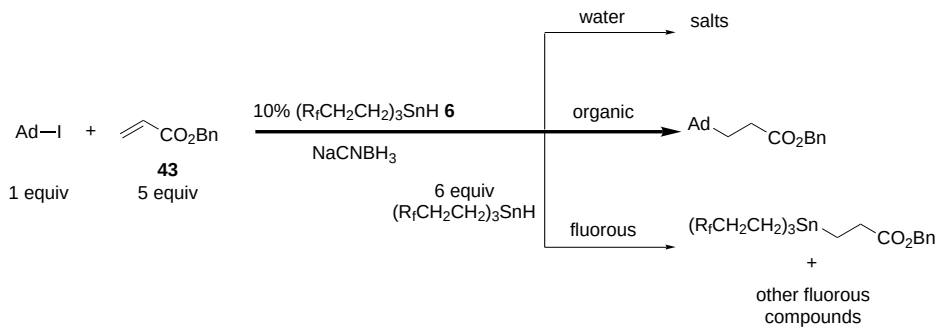
3.3.3. *Fluorous Phase Switches*

Fluorous phase switches can in principle be designed based on any of the elements outlined above by replacing the polymer or ionizable functional groups with a fluorous group. For example, we executed the fluorous quench shown in Scheme 29 for removing excess alkenes by hydrostannation.[52] This is an extension of the process given in Scheme 12, in which an excess of volatile alkenes was used and then removed by evaporation. In Scheme 29, an excess of nonvolatile alkene **43** is used, and additional fluorous tin hydride **6** is added at the end of the reaction to consume the unchanged alkene **43**. Fluorous–organic extraction then provides the pure products in the organic phase. The process is generalizable to any reaction as long as the products do not react with the tin hydride and alkenes are involved that do.

We also introduced a number of simple fluorous switches that exhibit interesting separation features and are generalizable to other methods. For example, the standard Grignard reaction shown in Scheme 30 can be coupled with a silylation of the intermediate alkoxide by the fluorous silyl ether. The resulting organic–fluorous–organic "double switch" resembles in many ways an acid–base extraction. However, unlike acid–base processes, the act of switching from fluorous back to organic is not the reverse of going from organic to fluorous. In other words, each phase switch is a distinct event with its own purification opportunities based on chemoselection. An example is a reaction with excess aldehyde **44**. After silylation and separation, the excess aldehyde **44** is removed in the organic phase, and the conversion from fluorous ether **46** to organic alcohol **48** by desilylation with fluoride provides no additional purification. However, when the Grignard reagent **45** is used in excess, the second step effects the purification: **46** is converted into **48**, but **47** remains fluorous. For reactions that are incomplete (as in Scheme 30), both steps effect independent separations. In short, well-planned double switches can be especially powerful.

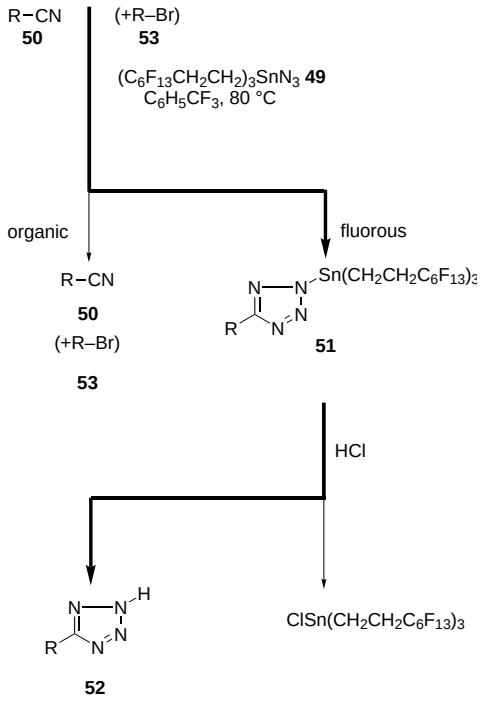


Scheme 30. A double phase switch (organic–fluorous/fluorous–organic). TBAF = tetrabutylammonium fluoride.



Scheme 29. Quenching by hydrostannation with a fluorous reagent. Ad = adamantyl.

Scheme 31 provides a simple example of how a reagent, in this case fluorous azide **49**, can provide purification of the target compound based on chemoselection. Reaction of three equivalents of nitrile **50** with the azide **49** provides tetrazole **51** in the fluorous phase, and excess nitriles are left behind in the organic phase in a fluorous-organic liquid–liquid extraction. Unlike the silylation in



Scheme 31. Use of fluorous **49** as reagent and label.

Scheme 30 or the resin capture in Scheme 25, this process does not separate the reaction at hand from the labeling step. Only azides (or more generally, products formed by reaction with **49** and retaining the tin) are labeled as fluorous in the process. This, and indeed any process that switches the phase of the desired product, has the feature of being able to "correct" prior purification problems in a synthesis. For example, if the nitrile **50** was made from a bromide **53** and that prior alkylation was incomplete, a mixture of a nitrile and bromide would result (because both are organic). However, for the ensuing tetrazole synthesis, there is no need to separate this mixture since the bromide **53** does not react with azide **49**. This shows the power of phase switches of products as opposed to that of any other reaction component. As parallel syntheses become longer and more complex, occasional phase switches of products will become key features of purification planning.

4. Summary and Outlook

This review makes the case that purification is a strategy-level concern that should be addressed in the planning stage of any synthesis. From the purification standpoint, the "ideal synthesis" is designed such that only simple separation techniques such as evaporation, filtration, and extraction are needed for separation. A basis for phase planning is presented by bringing together a number of apparently disparate concepts and results. At the most fundamental level, many of the concepts that have been used in acid–base chemistry, polymer synthesis, and the more recently introduced methods of dendrimer synthesis and fluorous synthesis are more or less interchangeable. Multilayer reaction schemes are introduced to facilitate the phase planning and to illustrate a number of the more powerful techniques. These techniques are often designed such that reaction chemistry dictates separation.

A number of the techniques call for excess reagents coupled with the addition of quenching reagents, and these are inherently wasteful from the standpoint of "atom economy". Such applications are targeted primarily towards parallel and combinatorial synthesis, where the scales are small and it is time rather than "atoms" that is being economized. However, many of the other techniques are applicable across the whole field of synthesis from discovery to production. Even "wasteful" techniques such as quenching to remove by-products might still be more economical on a production scale than other alternatives for purification. The best techniques provide not one but two or more products in separate phases at the end of a phase-separation scheme. One of the products is of course the target of the synthesis, while the other is a catalyst or some form of a recovered reagent that can be reused at a later date.

Many of the existing techniques and concepts of strategic purification need to be extended and generalized to reach their full potential. For example, the quenching techniques were illustrated with amide chemistry, but the quenching approaches outlined above are more fundamental and can be applied to a range of organic syntheses by allying them with suitable reaction chemistry. The use of linkers, which heretofore played mostly a specialized role to connect substrates to polymers at the beginning of a solid-phase synthesis, is especially ripe for development in conjunction with new phase switches. Phase-switching techniques that involves substrates, intermediates, or products have much untapped potential; with suitable planning and execution they can be used to provide pure products from sequences of reactions that do not occur in quantitative yields. This is important in library synthesis, where it may be more efficient from the standpoint of time simply to design an effective synthesis and purification scheme than to optimize all reaction conditions. Especially prized are phase switches that are coupled with one or more steps in the synthetic sequence or that target functionalities present only in one set of products.

This review offers fours general strategies for rendering erstwhile organic molecules "nonorganic" with respect to a given phase-separation technique in a process called phase labeling: acid–base, solid, dendrimer, and fluorous. Surely there are other fundamental ways to accomplish this, and the identification of these ways is a valuable goal. For example, Ramage et al. attached heptacyclic analogues of Fmoc to amino acids in peptide synthesis, and then separated labeled from unlabeled peptides by absorption of the former on porous graphitized carbon.[53] In principle, this technique could be generalized beyond peptide synthesis. Likewise, the recent use by Hindsgaul et al. of long hydrocarbon tags to label carbohydrates and effect polar/apolar separations over reverse-phase silica may also represent a generalizable approach.[32]

The design of new methods couples a suitable label with a given separation technique, which in the ideal case separates molecules into fractions based on the presence or absence of the label. Along these lines, techniques based on molecular

recognition appear ripe for development. For example, one could view fluorous solid-phase extraction as a case of (very nonspecific) molecular recognition in which a fluorinated tag (guest) is recognized by the bonded phase of the column (host). More selective techniques making use of smaller labels would be useful. In this view, the labeling process begins to resemble affinity chromatography.

The yield in any given reaction sequence is limited not only by the efficiency of the chemical process or processes, but also by the ability to recover the desired product from the reaction mixture after each process. Ideally, the reaction mixture *is* the pure product, but this idealized scenario is and will continue to be extremely rare. Along with all the other accepted features, well-planned syntheses should incorporate designed strategies for separation that provide pure products and simultaneously minimize time (for discovery-oriented syntheses) as well as cost and waste (for production-oriented syntheses).

I am very grateful to the talented and enthusiastic students and postdoctoral fellows in my group who have taken up the challenge of fluorous chemistry, especially the pioneers in 1995: Dr. Sabine Hadida, Dr. Masahide Hoshino, and Dr. Armido Studer. I also warmly thank Professors Anders Hallberg, Marty Newcomb, Tara Meyer, Ilhyong Ryu, and Peter Wipf and their co-workers for their invaluable collaborative efforts. The ideas in this article took shape in part as a result of stimulating discussions with several industrial groups investigating parallel synthesis; I thank Dr. John Saunders (CombiChem), Dr. John Hodges (Parke-Davis), and Dr. Steven Kaldor (Lilly) for sharing their problems, ideas, and results. Finally, I am most grateful to the National Institutes of Health and the National Science Foundation as well as Parke-Davis, CombiChem, and OxyChem for providing research funds.

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