1

INTRODUCTION TO PRACTICAL FUNCTIONAL GROUP SYNTHESIS

1.1 GENERAL APPROACHES FOR DESIGNING SYNTHESES

The construction of functionalized organic compounds remains one of the most challenging areas of synthetic chemistry, and scientists continue to redefine the limits of chemical reactions through the development of processes with increased chemoselectivity, enantioselectivity, and operational simplicity. In many cases, classic reactions are still the most effective means to generate the functional group of interest. Many of these reactions have been modernized to increase the tolerance to preexisting functional groups, decrease the required catalyst loading, increase the selectivity of the process, or minimize the waste generated from the process.

Despite years of education, many novice researchers flounder when trying to design a successful synthesis. They often get stuck on a specific step in a synthesis or are unable to purify an intermediate or product due to contamination by secondary products or solvent. While there are "chemistry" pitfalls that plague new synthetic methods, there are also a range of practical considerations that could render a clever synthesis unachievable. Other syntheses never get started because the starting materials are inaccessible. To help address these issues, a list of general questions for the design of a successful synthesis is provided below:

- What is the goal of the synthesis?
- How pure do the intermediates and products need to be?
- Are all of the reagents/catalysts/additives commercially available?
- If the starting materials are not commercially available, how long will it take to make them?
- Are there any reaction specific issues that need to be considered?

Practical Functional Group Synthesis, First Edition. Robert A. Stockland, Jr.

- How long will it take to complete the proposed synthesis?
- Is the shortest route really the most practical?
- Will the chemistry benefit from microwave irradiation?
- Is a glovebox required?
- Does the chemistry require the use of a vacuum/inert gas manifold?
- What are the safety concerns for this approach?
- Are the reagents/catalysts sensitive to light?
- Is a solvent needed?
- Do the solvents need to be rigorously dried?
- Will the solvents be easy to remove?
- Do the solvents need to be degassed/deoxygenated?
- Are the products stable to air?
- How will the products be purified?
- How will the products be stored?
- How will the products be characterized?

What is the goal of the synthesis? This might seem like an obvious question, but many researchers get bogged down with parts of the synthesis that are not relevant to why the compound will be prepared. If a few milligrams of a target compound are all that is needed in order to screen for a specific activity/property, it is not an appropriate use of time and resources to spend weeks searching the literature or running dozens of screening reactions to optimize the conditions. Simply find a decent synthesis, make the amount that is needed, and submit it for screening. Alternatively, if the project is focused on method development, and the product yields are critical for establishing the scope of the reaction, time needs to be spent optimizing the conditions so an accurate comparison between the new method and established protocols can be made.

How pure do the intermediates and products need to be? This might seem like another question with an obvious answer, but there are several aspects that need to be considered. It is rarely a good use of time and effort to prepare analytically pure samples of an intermediate in a multistep synthesis if that intermediate will simply be transformed into something else. If the next step in the synthesis will not be inhibited by the impurities in the crude reaction mixture, do not spend time purifying the intermediate. Instead, wait until the end of the synthesis and rigorously purify the final compound.

Are all of the reagents/catalysts/additives commercially available? If all of the starting materials are commercially available, the chemist will be able to begin work on the proposed synthesis quickly. Given the vast array of reagents and catalysts that are commercially available, the likelihood that the specific materials needed for the proposed synthesis is high. Arguably, this is the most important contributing factor when adopting a new synthesis.

If the materials are not commercially available, how long will it take to make the starting materials? If the starting materials are not available, the literature preparations must be

carefully analyzed to determine how long it will take to generate usable quantities of the starting materials and catalysts.

Are there any reaction specific issues that need to be considered? In some cases, the unintended reactivity of substrates, catalysts, and additives can complicate a reaction that looks reasonable on paper. Each component of the reaction needs to be evaluated against the remainder to anticipate unintended reaction pathways.

How long will it take to complete the proposed synthesis? Naturally, this is a bit of a tricky question. The level of difficulty of each step in the synthesis needs to be evaluated as well as how long it will take to make/purify the starting materials and any intermediates. After analyzing the individual steps and calculating a time frame, add 30% to the total because something will not work as planned. Once the overall calculation is complete, an accurate assessment of the approach can be made.

Is the shortest route really the most practical? In many cases, adding one or two operationally trivial steps to a synthesis is much easier than fighting with a single challenging reaction.

Will the chemistry benefit from microwave irradiation? Fundamentally, if a reaction needs to be heated, it is likely to be more efficient, cleaner, and faster in a microwave reactor. Since time is one of the most precious commodities in the modern synthetic lab, getting to the target compound quickly is critical.

Is a glovebox required? For most reactions, needing to use a glovebox will be a guaranteed hassle. All of the glassware needs to be flame dried before taking it into the glovebox, all solvents need to be rigorously dry and degassed, and everything needs to be pumped into the box. Some of the issues with solvents are mitigated by connecting a Grubbs style solvent drying system to the glovebox and pumping dry deoxygenated solvent into the box under pressure. Additionally, unwanted volatile organics are often found in gloveboxes. Unless your research team rigorously maintains the glovebox and routinely checks the quality of the atmosphere, it is often easier to keep a vacuum manifold free of contaminants.

Does the chemistry require the use of a vacuum/inert gas manifold? Most modern synthetic laboratories have several manifolds dedicated to synthetic chemistry. As a result, most modern preparations assume that one will be available. As a result, if a vacuum/inert atmosphere manifold is not available for the proposed synthesis, each step must be carefully screened to ensure that one will not be needed.

What are the safety concerns for this approach? While most chemists associate safety with flammability or risk of explosion, the toxicity of the reagents and products needs to be evaluated. For example, if a published preparation using phosgene as a reagent would cut the total synthesis time by 50%, it should still never be adopted by researchers who are not specifically trained on how to handle such a dangerous reagent.

Are the reagents/catalysts sensitive to light? While it is relatively rare that an organic product will be sensitive to light, it is quite common for metal catalysts to be light sensitive. Many gold(I) compounds are quite sensitive and will degrade upon exposure to light.

Naturally, this is quite substrate dependent, and while some catalysts will degrade within a few seconds upon exposure to light, others are quite stable. As a result, the individual compounds need to be evaluated for stability. Many researchers have spent far too much time attempting to determine why a catalyst was not as active as it should be when it was simply partially decomposed due to exposure to light.

Is a solvent needed? This is a critical question that is worth investigating. Most historical preparations of organic compounds employ a solvent. However, that does not mean that those are the highest-yielding procedures or that the solvent is really required. If the reaction is successful without the addition of solvent, removing it will significantly simplify the operational procedures since issues surrounding the use of a solvent will be eliminated. Carrying out the reaction under solvent-free conditions has its own challenges; however, they are often offset by the advantages of the approach.

Do the solvents need to be rigorously dried? With the widespread adoption of solvent purification systems, drying solvents is significantly easier than it was a few decades ago. It should be noted that some solvents are unable to be effectively dried using these systems and must still be dried using alternative methods. If anhydrous solvents are needed and a solvent purification system is not available, activated molecular sieves could be the most practical solution. Studies have shown that the water content of the solvents dried using molecular sieves is similar or lower than solvents dried with traditional methods [1]. Remember to take into account the time that it will take to activate the sieves prior to adding them to the solvent.

Will the solvents be easy to remove? If your reaction requires the use of a solvent, the ability to remove it after the reaction is over is a critical concern. Low-boiling solvents such as diethyl ether are often easily evaporated under vacuum; however, high-boiling solvents can be more challenging to remove.

Do the solvents need to be degassed/deoxygenated? If the answer is yes, there are two common approaches that are used. If oxygen is the only problematic gas, simply sparging the solvent with nitrogen or argon for 30 min will likely be sufficient to deoxygenate the solvent. Care must be taken not to introduce water into the vessel when sparging since the vessel could become quite cold due to solvent evaporation and moisture could condense. This is normally avoided by performing the sparging in septa-sealed vessels using a long needle or a specially designed glass frit to bubble the nitrogen or argon through the reaction mixture. A smaller needle is inserted into the septa at top of the vessel that will serve as the vent. If the solvent needs to be completely degassed, this is commonly achieved through several freeze–pump–thaw cycles. These steps consist freezing the dry solvent in a specially designed flask. Once frozen, the flask is placed under a static vacuum and warmed until the solvent melts. This process is repeated several times until no gas is evolved. This endpoint can be challenging to determine when low-boiling solvents are used. In general, three to four freeze–pump–thaw cycles are needed to degas the solvent. The prerequisite for this work is an outstanding vacuum line. If the vacuum is poor, this approach will not work as effectively. Additionally, the vacuum line needs to be pristine since contaminants from inside the vacuum line could contaminate the solvent. Special glassware has been designed specifically for this application. While deoxygenating solvents using a nitrogen purge is

quite successful using needles, *degassing* solvents using several freeze–pump–thaw cycles should not be attempted using needles plunged through septa.

Are the products stable to air? This is commonly encountered with organophosphines since many of these compounds often oxidize in air to generate organophosphine oxides. If the target phosphine is not stable to air, the purification will be quite challenging, and purification by column chromatography will be nearly impossible. For compounds that are especially sensitive to air, specific details will be provided in the sections dealing with those compounds. It is important to identify when an air-sensitive product will be generated. If the equipment is not in place to handle and store the air-sensitive materials, it might be advantageous to devise an alternative approach.

How will the products be purified? The most common methods for the purification of organic compounds are column chromatography, distillation, sublimation, and crystallization. Column chromatography can be the most time-consuming of the purification methods, but it can be the most effective. Distillation is often an excellent method for the separation of volatile compounds from a crude reaction mixture. In many cases, compounds with relatively high boiling points can still be separated using a vacuum distillation. Sublimation is also a relatively straightforward approach to the purification of many organic compounds, and a host of sublimators are commercially available. Crystallization is a popular method for the purification of solid organic compounds. However, devising a successful approach to the crystallization of a new compound can be challenging.

How will the products be stored? This is a critical concern when working with compounds that readily oxidize in air, absorb moisture, or decompose at room temperature or upon exposure to light. When reading a literature synthesis for a catalyst/starting material/product that is air sensitive and needs to be stored at low temperature, it would be logical to store the compound in the glovebox freezer. However, if your glovebox does not have a freezer or you do not have a glovebox, the synthesis will be much more complex and challenging. It might be more practical to search for a different approach.

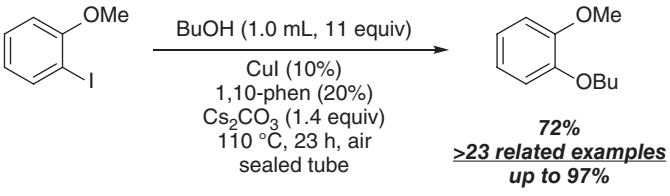
How will the products be characterized? The characterization methods need to be addressed when planning a synthesis. If the piece of equipment is not available for a critical characterization of the starting material, intermediate, or final product, it will not be possible to complete the synthesis. The type and complexity of the characterization methods will vary according to the synthesis. The author instructions for journals such as *Organic Letters* and the *Journal of Organic Chemistry* are often excellent places to find a list of the characterizations typically required for reporting the synthesis of new compounds. Additionally, it is important to use as many techniques as possible when characterizing synthetic targets. Trying to publish IR data for stable new organic compounds as the only method of characterization is typically unacceptable. The connectivity of new compounds must be rigorously investigated and questioned until all methods of characterization have been exhausted. This will aid in ensuring that the connectivity and chirality have been correctly assigned.

1.2 NEW VERSIONS OF "CLASSIC" ORGANIC REACTIONS

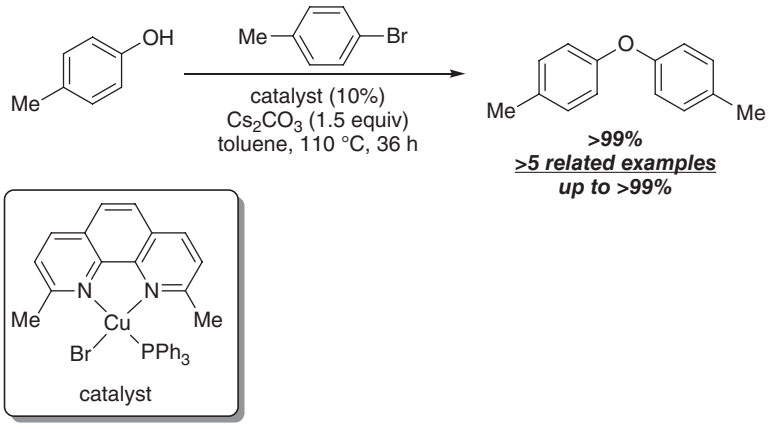
Synthetic chemistry is quite fluid and researchers are constantly devising new versions of classic reactions and generating catalysts with higher activities and increased selectivities. While many classic reactions remain the best methods for the preparation of a specific group of compounds, modifications of these classic reactions are constantly improving various aspects of the chemistry.

As a representative example of how the modernization of classic reactions can alter the design of a synthesis, consider the preparation of ethers through a copper-catalyzed coupling reaction. The Ullmann-type synthesis of ethers is one of the most well-known versions of this reaction. Historically, an Ullmann synthesis used a stoichiometric (or higher) amount of copper bronze to promote the reaction [2–4]. This resulted in a significant amount of copper waste that needed to be separated from the desired reaction products and disposed of. Furthermore, the temperatures required for the copper bronze-promoted Ullmann coupling were typically above 200 °C. Thus, it would be advantageous to develop a catalytic method for the synthesis of these compounds that functioned at lower temperatures. Reducing the copper to catalytic levels would make the removal of the copper as well as the isolation/purification of the desired diaryl ether significantly easier, while the lower temperature would facilitate the use of temperature-sensitive substrates. A significant step toward this goal was recently achieved by Buchwald and Venkataraman [5,6]. Buchwald's approach used common copper salts along with a solubilizing ligand to generate a catalytically active copper complex that promoted the coupling reaction (Scheme 1.1). Venkataraman used a discrete copper(I) species containing neocuproine as the chelating ligand (Scheme 1.2) to catalyze the reaction. The conditions for both approaches were quite mild (110 °C) relative to the classic Ullmann synthesis, and both approaches generated the desired ethers in excellent yield. The advantages of these modifications to the classic reaction included significantly reduced reaction temperatures and a significant reduction in the amount of copper needed to promote the reaction. The use of organotrifluoroborates as the coupling partners has also been reported (Scheme 1.3) [7] along with a microwave-assisted version of this reaction [8].

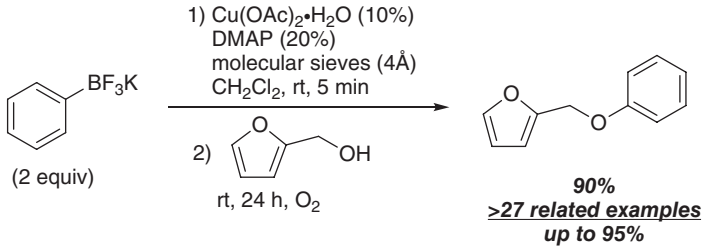
One of the most active areas of research is the conversion of reactions that are classically catalyzed by transition metals into metal-free versions. The economic issues that are driving this area of research revolve around the high cost of many catalysts as well as the challenges encountered when trying to recycle and reuse these catalysts in subsequent reactions. There are also toxicity issues to consider with some metals. However, significant reactivity issues can be encountered when trying to reproduce the unique reactivity that transition metal catalysts exhibit using nonmetallic systems. Several of the following chapters and sections will highlight recent developments in this area.



SCHEME 1.1 Synthesis of alkyl aryl ethers using the cuprous iodide/phen catalyst system [5].



SCHEME 1.2 Synthesis of diaryl ethers using a discrete copper complex [6].



SCHEME 1.3 Synthesis of alkyl aryl ethers using aryltrifluoroborate salts [7].

1.3 SOLVENT SELECTION AND SOLVENT-FREE REACTIONS

One of the biggest issues encountered when devising a synthetic strategy is the solvent selection. From a practical perspective, a good solvent will dissolve the components of a reaction that the chemist wishes to dissolve, not react with either the reagents or products, be easily removed, not be flammable, and not be toxic or harmful to the environment. Some solvents will satisfy all of those requirements, while others will only match a few.

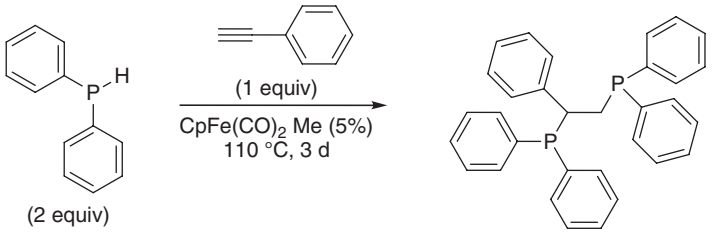
How easily the solvent can be removed from the crude reaction mixture remains one of the most important issues when considering a solvent. It will not be successful to design an elegant synthesis for a target molecule only to discover that small amounts of solvent cannot be removed. Low-boiling solvents such as dichloromethane and pentane are often easily removed under vacuum, although small amounts can be encapsulated in solid products. Trituration of the solid while under high vacuum can be an effective way to solve this issue. This is quite common when the products are foams. High-boiling solvents such as DMSO and NMP can be very challenging to remove from crude reaction mixtures. While it is common practice to remove these solvents under vacuum, this is often not practical. For very polar solvents such

as these, it might be possible to remove the solvents using an aqueous extraction. DMSO and NMP are quite soluble in water, while many of the organic products are not.

In some cases, it will be possible to recycle a solvent for use in additional reactions. Low-boiling solvents often work well since they can simply be distilled from the reaction mixture. For most synthetic laboratories, recycling the comparatively small amounts of solvents used for in synthesis of small molecules is often not economically feasible. However, recycling the liters of solvents used for column chromatography is quite common. Since the most common solvents used for this application are hexane/pentane and ethyl acetate, it is common to find a dedicated still for these solvents in many synthetic laboratories. It is also noteworthy to point out that many research groups do not take the time to try and separate hexane from ethyl acetate. The composition of the solvent mixture is determined after distillation and adjusted to provide the eluent for the next separation.

Before starting a synthesis, the chemistry should be evaluated to determine whether or not a solvent is actually needed. In many cases, reactions are faster, cleaner, and more efficient in the absence of a solvent. In the extreme case, the desired reaction will *only* occur in the absence of a solvent. The iron-catalyzed addition of secondary phosphines to alkynes is an example of such a reaction (Scheme 1.4) [9]. In the absence of solvent, this double addition reaction cleanly affords the 1,2-bisphosphine in excellent yield. When solvents were added to the reaction, the addition reaction was completely suppressed.

There are several operational issues to consider when performing solvent-free reactions. Most laboratory-scale reactions are carried out on 0.1–0.5 g scales. Under solvent-free conditions, the small amounts of reagents might be problematic for common round-bottom flasks since much of the material could be spun onto the sides of the flask and not actually be in contact with the other reagents. This is not typically encountered when using a solvent since the solvent will typically rinse down the sides of the flask. Instead of using round-bottom flasks, small vials are ideally suited to carry out solvent-free reactions. There are also a number of issues to consider when using vials. One of the most important issues is



solvent	% conv.
hexane	0
toluene	0
THF	0
acetonitrile	0
solvent free	94

SCHEME 1.4 Effect of solvent on the double hydrophosphination of alkynes [9].

the physical state of the reagents and products. If all of the reagents and products are liquids, using small flat-bottom vials and small stirring bars will likely be effective at mixing the reagents and the reaction will be successful. If one of the reagents or products is a solid and does not entirely dissolve in the other reagent, or tends to precipitate out of the reaction, flat-bottom vials with small stirring bars will not be as effective since the material will collect in the edges of the vial.

A reaction that contains a number of solid reagents, catalysts, additives, or products can be one of the most challenging to convert into a solvent-free version. For these reactions, achieving effective mixing could be difficult. In these cases, gently heating the reaction mixture could be successful or adding a very small amount of a solvent might also aid in the reaction. While this approach is a bit substrate dependent, a good general place to start is to add one mass equivalent of solvent per reagent.

A general approach to solvent-free reactions carried out on scales between 0.1 and 0.5 g is to use small vials with rounded bottoms and large stirring bars. Using small stirring bars will not effectively stir the material in the bottom of the vial. There are many inexpensive vials that are readily available from a range of vendors. One of the more attractive options is to use the vials sold by microwave manufacturers for running microwave-assisted reactions. As a representative example, the CEM reactor vials are shown in Figure 1.1. These are useful for solvent-free reactions since they have rounded bottoms, the tops can be crimp sealed with septa, and they will fit into standard centrifuges. It is worth noting that these vials can be used for reactions carried out in and out of the microwave. As mentioned earlier, one of the most important components to a solvent-free reaction is making sure all the reagents are thoroughly mixed and the desired stoichiometry is achieved. Spinning the vial in a centrifuge will concentrate the reagents at the bottom of the vial. This can be repeated many times if needed. Naturally, this is challenging to achieve with a round-bottom flask.

FIGURE 1.1 Solvent-free reaction using both a solid and a liquid reagent. *Source*: Image of the CEM microwave reactor vials was produced with permission from CEM Corporation.

Troubleshooting solvent-free reactions. *While it is not possible to predict every challenge that will arise during the course of a synthesis, the following observations and reaction requirements are typically encountered during a solvent-free synthesis.*

Observation/Issue/Goal	Possible Solution/Suggestion
The stirring bar is flinging the reagents onto the sides of the round-bottom flask under solvent-free conditions	Change from a round-bottom flask to a narrow vial with a rounded bottom and use a large stirring bar to triturate the reagents
All of the reagents and products are liquids	This is the ideal case for a solvent-free reaction—small vials with small stirring bars would be a good place to start
The reagents keep getting stuck on the bottom edges of the flat-bottom vial and do not appear to be properly mixing	Change to a small vial with a rounded bottom
After injecting the liquid reagents into the vial, they are sticking to the sides of the vial and not interacting with the other reagents at the bottom of the flask	Centrifuge the reaction tube to concentrate all of the reagents in the bottom of the tube
Despite being very careful, some of the solid is sticking to the sides of the vial	Use a rolled piece of weighing paper or a sleeve to aid in delivery of the solid catalyst to the bottom of the reactor vial. It might help to centrifuge the vial for a few minutes although this tends to be less effective with small amounts of solid catalysts
The reaction is not going to completion and is no longer stirring due to the formation of a gel or solid	If you have already changed to a larger stirring bar, it might be necessary to add a small amount of a solvent to the reaction mixture to inhibit the formation of the gel. While the amount of solvent needed to promote the reaction will vary, a good place to start is 1 mass equivalent per reagent
Improper mixing of solid reagents	Use as large a stirring bar as possible. If this is a microwave-assisted reaction, the length of the stirring bar should not exceed ¼ of the standing wave
At least one of the reagents or the product is a solid	There could be incomplete mixing of the solids. Vials with rounded bottoms and large stirring bars are a good place to start. If this is not effective, try adding a small amount of solvent to the reaction mixture
Sublimation of one or more of the reagents into the neck of the flask is occurring during the course of a reaction using conventional heating	Try to submerge as much of the vial as possible into the oil bath or block heater. Alternatively, use an external heating source to prevent the sublimation. In some cases, adding a small amount of solvent might be successful
Sublimation of one or more of the reagents is occurring during the course of the reaction using microwave heating	Since the reaction vessel is fully contained by the reactor, applying an external heating source to prevent the sublimation is not possible. Adding a small amount of solvent could circumvent the problem

(*Continued*)

(Continued)

Observation/Issue/Goal	Possible Solution/Suggestion
The mineral base is not fully mixing with the reagents	Change to a liquid base
A gas is generated during the reaction and pressure builds inside the vessel	This could generate an extremely dangerous situation. One solution would be to add an active purge to the reaction. A slow purge using an inert gas is often sufficient to inhibit a pressure buildup. If septa capped vessels are used for the reaction, simply adding a nitrogen/argon feed (needle) and vent needle could solve the problem

1.4 OPERATIONAL SIMPLICITY

The operational simplicity of a synthetic method remains one of the most critical parameters that should be considered when designing a synthesis. If the protocol is so complex that only an expert can get it to work 50% of the time, the approach is not very practical for a typical synthetic laboratory. A synthetic approach that is straightforward to carry out is more practical and likely to be adopted by the general community.

In many cases, the operational difficulties of a specific approach can be mitigated through the careful selection of solvents, catalysts, and reagents. However, in some cases, the complexity of the synthesis is a result of the chemistry itself. In these cases, cleverly devising completely different strategies might be the only way to circumvent a problematic step. As listed previously, increasing the overall length of a synthesis by the addition of a few easy steps can often be much more practical than struggling with one challenging reaction.

An example of how a chemical discovery has greatly reduced the operational difficulty of a synthetic approach is provided by the synthesis of dialkylbiarylphosphine ligands (Buchwald ligands) [10]. Dialkylbiarylphosphines are a valuable class of monodentate phosphine ligands that stabilize/solubilize a number of metal centers and promote transition metal-catalyzed reactions (Figure 1.2). These supporting ligands have been successfully used in a range of carbon–heteroatom bond-forming reactions [11–14]. Although these

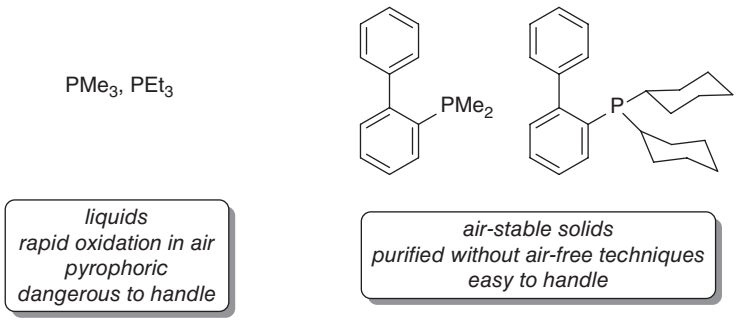


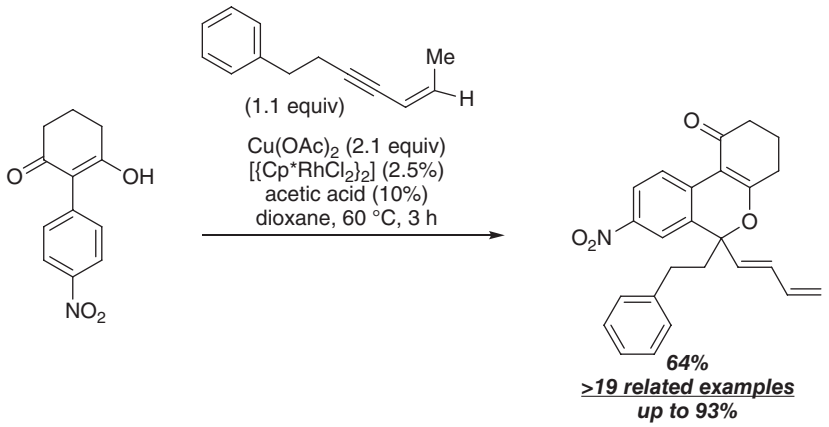
FIGURE 1.2 Stability of common trialkylphosphines and dialkylbiarylphosphines.

compounds are useful, the discovery that they are remarkably stable to air [15] has catapulted this class of ligands to be one of the most practical choices for synthetic chemists. This stability stands in stark contrast to the extreme air sensitivity of many alkylphosphines. For example, tricyclohexylphosphine is a very strong ligand for a host of metal centers, but it must be stored and handled under an inert atmosphere to prevent rapid oxidation. Many trialkylphosphines are so sensitive to air that they will spontaneously ignite. The vast majority of the dialkylbiarylphosphines can be handled, loaded into reaction flasks in air, and stored at ambient temperature for years. Virtually every synthetic lab working on metal-catalyzed coupling chemistry has several of these ligands on the shelf.

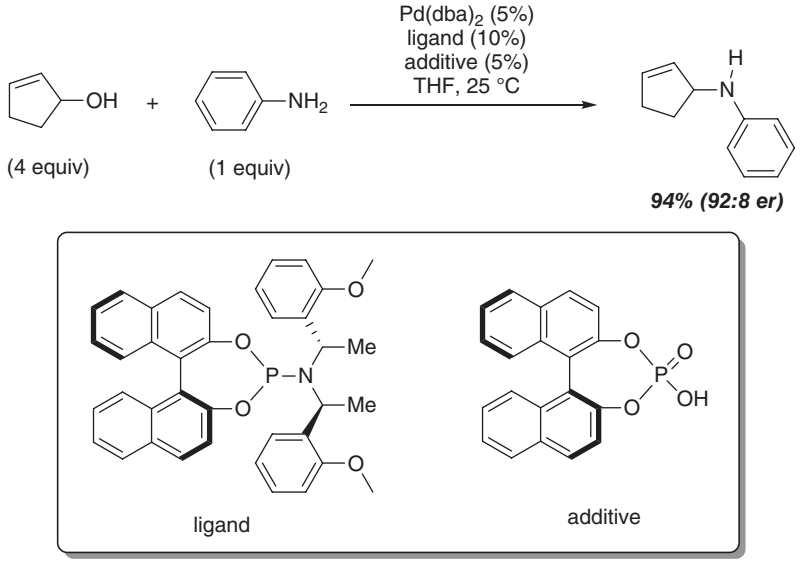
This discovery reaches far beyond the use of dialkylbiarylphosphine ligands in catalytic reactions. It has changed the way in which chemists think about the synthesis of new alkylphosphines. As long as the biaryl fragment is present, there is a reasonable expectation of some air stability [15]. The other groups on the phosphorus center could be highly electron donating, and the resulting phosphine would still have some stability to air. The dialkylbiarylphosphine that might be predicted to be highly reactive toward oxygen would contain small donating alkyl groups such as methyl. Indeed, high-yielding syntheses of methyl-containing phosphines remain rare, and trimethylphosphine is known to spontaneously ignite in air. However, when one of the methyl groups on PMe_3 was exchanged for the biaryl fragment, the resulting compound, dimethylbiphenylphosphine, was quite stable to air [16]. Naturally, the level of stability will vary from group to group; however, dialkylbiarylphosphines are unlikely to be pyrophoric. Why this chemistry has had such an impact can be found in the classic approaches to the synthesis of alkylphosphine ligands. The historical approaches to the preparation of these compounds are complicated by the sensitivity of the reagents, intermediates, and products to air. This requires all of the various steps and purifications required to form the desired phosphine to be carried out with rigorous exclusion of air. Naturally, many of the approaches to the synthesis of the dialkylbiarylphosphine ligands still require an oxygen-free environment; however, their isolation/purification can often be carried out without rigorous exclusion of oxygen. Setting up the reactions in a deoxygenated environment without a glovebox can be difficult, but it is still possible for many synthetic laboratories. However, purification of an air-sensitive phosphine such as PCy_3 or PMe_3 by column chromatography without a glovebox is remarkably difficult. Historically, most chemists might have looked upon the lack of a glovebox as a reason to not even consider alkylphosphine syntheses. Currently, if a synthetic laboratory does not have a glovebox and is interested in making new phosphine ligands, a very practical approach would be to simply try and add a biaryl group to the phosphorus center and modify the remainder of the fragments on the phosphorus center to suit the needs of the desired application.

1.5 METAL-CATALYZED TRANSFORMATIONS

The use of transition metal catalysts to promote carbon–carbon and carbon–heteroelement bond-forming reactions has significantly increased over the past few decades. These metal complexes often promote unique reactions that are challenging or impossible to achieve using classic organic methodology. Representative examples of metal-catalyzed carbon–heteroelement bond-forming reactions are shown in Schemes 1.5–1.9. One of the current challenges in this field includes the design of metal complexes that exhibit high catalytic activities and selectivities while being stable to moisture and oxygen.

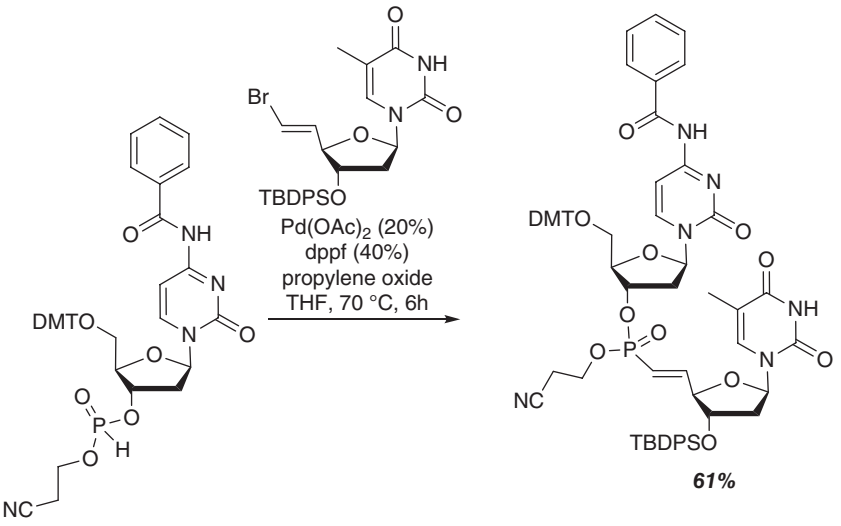


SCHEME 1.5 Example of a rhodium-catalyzed carbon–oxygen bond-forming reaction [17].

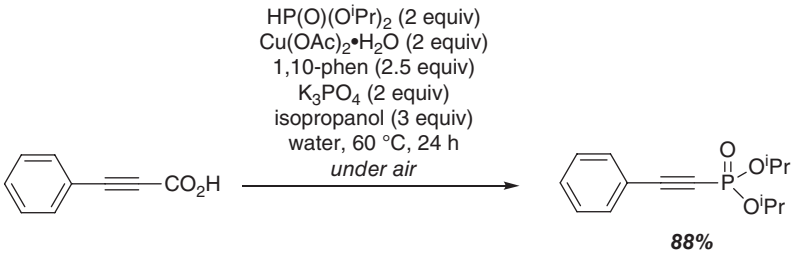


SCHEME 1.6 Example of an asymmetric palladium-catalyzed carbon–nitrogen bond-forming reaction [18].

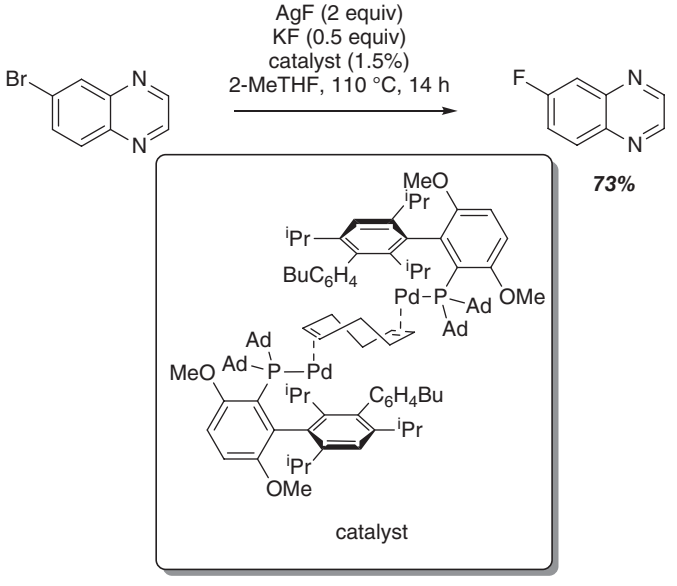
The importance of designing operationally simple catalyst syntheses cannot be overstated. Ideally, the metal complexes should be robust species that will remain intact until converted into the active species during the course of the reaction. It is also advantageous for the purity of the metal complexes to be easily determined. In some cases, researchers add a "catalyst" of unknown purity and composition to reactions and are confused when they obtain strange results. This is often the case when using highly insoluble metal precursors such as cuprous iodide or ferric chloride. The former tends to readily generate the oxide upon exposure to air, and if the contaminated copper iodide is used in a Sonogashira coupling reaction, it could promote the formation of



SCHEME 1.7 Example of a palladium-catalyzed carbon–phosphorus bond-forming reaction [19].



SCHEME 1.8 Example of a decarboxylative copper-promoted carbon–phosphorus bond-forming reaction [20].



SCHEME 1.9 Examples of a palladium-catalyzed carbon–fluorine bond-forming reaction [21].

diynes instead of the desired cross-coupling. If the metal complexes are thermally unstable or rapidly decompose in the light, the evaluation of the reaction results will always be suspect. The worst-case scenario would be for the results to be unrepeatable in other laboratories.

Chemists often devote considerable amounts of time and resources on the design and synthesis of new and more exotic ligands that will increase the activity or selectivity of a specific transition metal-catalyzed reaction. A researcher may spend years optimizing the synthesis of the new ligand. However, if the ligand dissociates from the metal center during the course of the reaction, interpreting the results of the catalysis will be challenging since the dissociated ligand may not behave as an innocent species in the reaction mixture. This is also true for additives, cocatalysts, and promoters. As a general rule, it is critically important to make sure that all materials are clean and free of contaminants. It will be well worth the time, and the effects of the foreign materials can always be determined by adding controlled amounts of materials to the reactions mixtures after the baseline reactivity with clean materials has been established.

Several examples highlight the importance trying to rigorously characterize catalysts. The first example involves the use of $Pd_2(dba)_3$ (dba = dibenzylideneacetone) solvates. These compounds are commercially available and remain popular sources of palladium(0). Thousands of reactions have been reported using this palladium source. In a typical reaction, this compound is treated with a supporting ligand such as a phosphine in order to displace the dba and generate the desired metal–ligand complex. In addition to the possibility that the dba could reversibly coordinate to the metal center and alter the activity of the catalyst, the possibility that commercially available samples as well as "in-house" prepared material could be contaminated by nanoparticle palladium is a significant concern [22]. While some of the contamination levels have varied according to the sample, levels as high as 40% have been found. Depending upon the reaction medium, the solubility of this material can be quite different from the $Pd_2(dba)_3$ solvate. If the nanoparticle palladium is never solubilized, this results in a lower level of available palladium being added to the reaction and could significantly alter the outcome of the catalysis. Naturally, this altered stoichiometry could result in unrepeatable results since many palladium-catalyzed reactions are quite sensitive to the Pd/L ratio. This contamination could also lead to TON and TOF that are not a true reflection of the activity of the ligated palladium species. In addition to these issues, if the nanoparticle palladium is truly insoluble and a heterogeneous solution is formed, this material could conceivably catalyze an entirely different reaction pathway.

While it might seem reasonable to attempt to characterize the catalyst using ^{1}H NMR spectroscopy, the ^{1}H NMR spectrum of Pd_2dba_3 solvates can contain a vast number of resonances due to coordinated and free dba. An elegant solution to this NMR problem that combined detailed one- and two-dimensional NMR investigations including diffusion studies was reported by Ananikov [22]. Elemental analysis is also an option; however, unless the analyzer is located in-house, there will always be uncertainty associated with the results due to potential decomposition while in transit. In the ideal case, both elemental analysis and the spectroscopic data should be used to provide a more accurate picture of the composition of these metal complexes. As with many metal catalysts, it is advantageous to prepare them immediately prior to use. While some reactions are not as sensitive as others, this issue could cause problems for enantioselective synthesis due to the presence of resolved Lewis base (chiral ligand) in solution.

A second example that illustrates the importance of rigorously characterizing catalysts and is focused on the use of iron salts as catalysts for organic transformations. One of the most popular ways of generating a catalytically active species was to solubilize a common iron salt such as $FeCl_3$ with a chelating ligand. A variety of diamines have proven successful in this role, and a number of organic reactions have been catalyzed using this approach. The issue with this chemistry is the potential for trace contaminants in the ferric chloride to serve as the true catalyst in the reaction. Buchwald and Bolm demonstrated that even 10 ppm copper(I) oxide could dramatically increase the yields in a number of reactions [23]. Key to this investigation was the observation that 99.99% pure $FeCl_3$ was much less active, and only upon the addition of the copper salt was significant conversion observed. Thus, even small amounts of trace metal contamination could lead to incorrect conclusions regarding the outcome of the reactions.

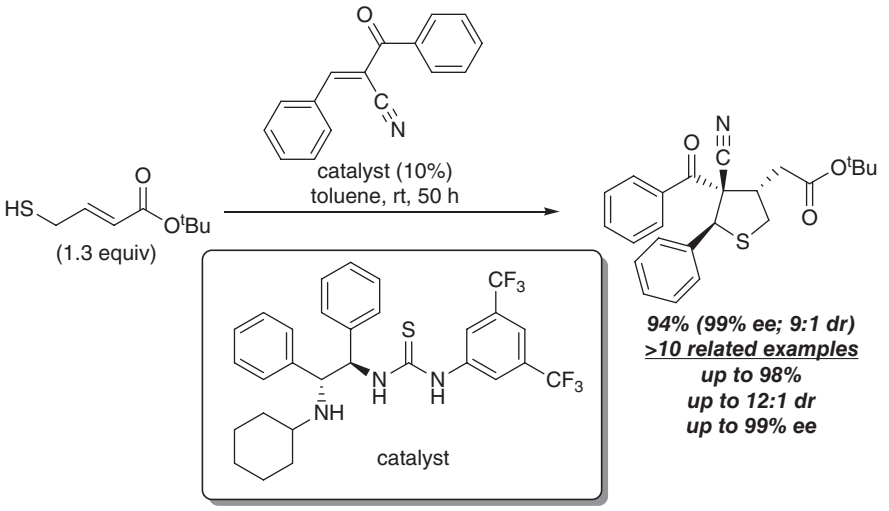
Ideally, when metal salts are used to generate active catalysts in solution, they should be of the highest grade when establishing baselines for reactivity, selectivity, and substrate scope. A representative sample of each lot should also be analyzed for the presence of trace impurities. For contamination due to metal salts, this is most commonly accomplished by ICP-AES. For many metal salts, the level of detection for this technique is in the ppm range. Although this will not completely eliminate the possibility of contamination, it will provide other researchers with an idea of what is present. Ideally, the results of contamination screen should be included in the supplementary materials of published reports. Once the baselines have been established, it would be valuable to the synthetic community to screen the metal salts of lower purity in order to determine if there are any differences between the grades.

It remains critically important to determine the precise identities of the active species and elucidate as many of the mechanistic details as possible. Such investigations enable the design of second- and third-generation catalysts with enhanced reactivity. The undeniable conclusion resulting from even a cursory survey of the literature is that it is often remarkably difficult to determine the precise identity of the active species that catalyzes a specific reaction. The metal complex that is added to the flask is rarely the active species. However, following common practice, the compound that is added to the flask will be referred to as the "catalyst" for the purposes of this text. Naturally, it would be more accurate to refer to these compounds as precatalysts or precursors.

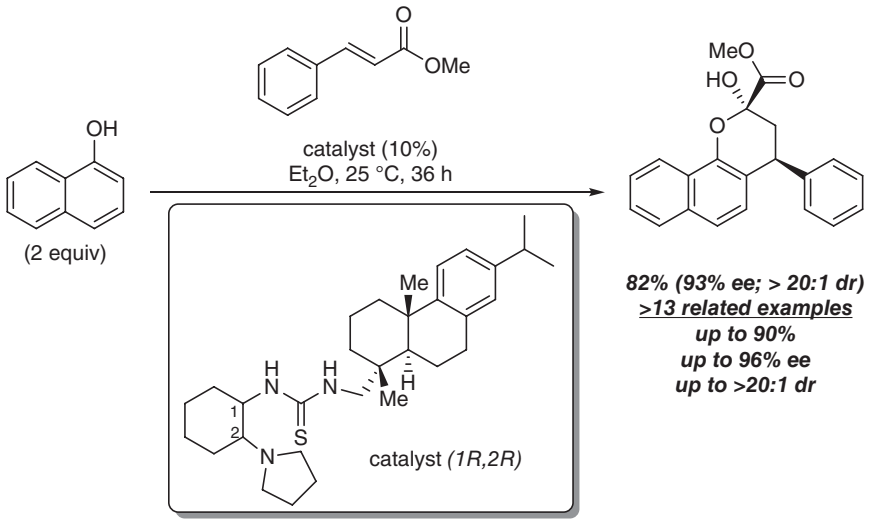
1.6 ORGANOCATALYSIS

The ability of a transition metal catalyst to promote unique reactions that are not accessible with classic organic methodology as well as the potential to direct the selectivity of a reaction remains one of the major driving forces for the development of new metal catalysts. However, there are considerable challenges that must be overcome when using a few of the popular catalyst systems. Many transition metal catalysts must be handled and stored over an inert atmosphere such as nitrogen or argon. Some of these catalysts can be rendered inactive upon exposure to moisture. For a number of catalysts, the toxicity of the metal can be a concern. Over the past few years, a considerable amount of effort has been devoted to the conversion of metal-promoted synthetic strategies into approaches that use entirely organic compounds as catalysts [24–34].

Practical advantages of an organocatalyst can include an increased tolerance of the catalyst and catalytic reactions to moisture and air, greater selectivity, and the minimization



SCHEME 1.10 Organocatalytic asymmetric synthesis of functionalized tetrahydrothiophenes [35].

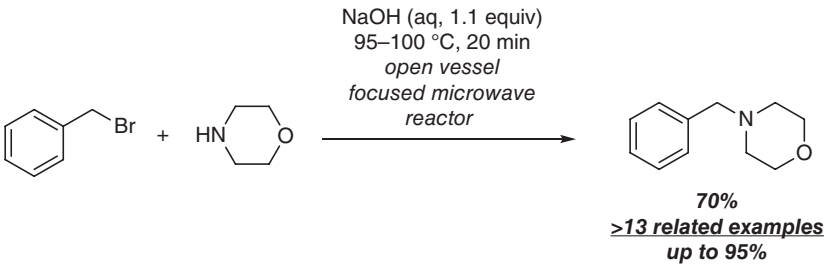


SCHEME 1.11 Organocatalytic asymmetric synthesis of chromane derivatives [36].

of secondary reaction pathways. A few representative examples of organocatalyzed carbon–heteroelement bond-forming reactions are shown in Schemes 1.10 and 1.11.

1.7 MICROWAVE- AND ULTRASOUND-ASSISTED CHEMISTRY

Over the past decade, focused microwave reactors have revolutionized how synthetic chemists approach the preparation of chemical compounds. Due to their ability to rapidly heat reactions on small to moderate scales, microwave-assisted chemistry has become



SCHEME 1.12 Microwave-assisted aqueous alkylation of amines using an open vessel [47].

"first choice" for synthetic chemists. A number of excellent reviews have been published on microwave-assisted synthesis [37–46]. The following sections provide a brief outline of the practical considerations when designing a microwave-assisted approach.

Many of the early examples of microwave-assisted chemistry used domestic microwaves with holes cut through the casing in order to accommodate condensers. This approach suffered from poor reproducibility due to the nonhomogeneity of the microwave field. Rather than cutting holes in the microwave oven, reactions were performed under solvent-free conditions on silica or other solid supports. A typical reaction was carried out by suspending the silica in a solution of the reagents followed by removal of the solvent. Irradiation of the resulting mixture generated products. This silica-supported approach also suffered from poor reproducibility, and some of the reactions carried out on dry silica that were reported to be microwave-assisted reactions were actually complete prior to irradiation. The heating needed to remove the solvent promoted the reaction.

Once dedicated microwave reactors were designed and made commercially available, one of the early design considerations was the ability of the reactor to accommodate a condenser. Indeed, several commercial microwave reactors are able to accommodate standard glassware for refluxing solutions. A number of reactions have been reported using this approach including the N-alkylation of primary and secondary amines by alkyl halides (Scheme 1.12) [47]. The reaction was operationally simple to set up and simply consisted of adding all the reagents/solvent to a flask, capping with a condenser, and irradiating for 20 min.

1.7.1 General Checklist for Performing a Microwave-Assisted Reaction

Is microwave chemistry an option? For reactions that need to be heated, the answer to this question is almost always yes. However, care must be taken when determining the conditions for a specific reaction. The following sections will aid in making an educated first attempt rather than simply blindly irradiating the sample to see what would happen.

Solvent selection. One of the most important considerations when designing a microwave-assisted reaction is whether or not a solvent is actually needed for the reaction. Some reactions will not be successful under solvent-free conditions; however, since the solvents are typically disposed of at the end of reactions, the elimination of solvents from chemical reactions is a step forward when designing sustainable chemical reactions. The vast majority of molecules containing functional groups will have a dipole moment and absorb microwave irradiation without the addition of a solvent. If a solvent is required for the success of the reaction, a minimal amount of solvent should be used. These "near-solvent-free" reactions still significantly reduce the amount of solvent used by the synthesis.

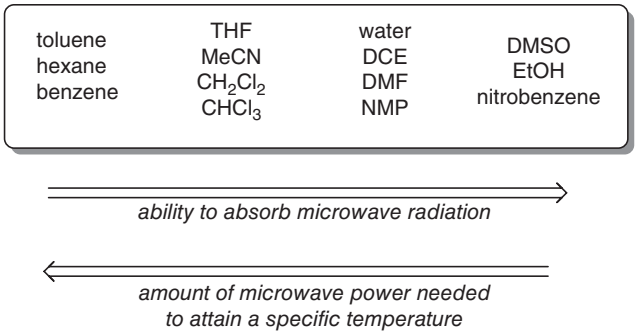


FIGURE 1.3 General relationship between the polarity of the solvent and the ability of the solvent to absorb microwave energy.

For microwave-assisted reactions, polar solvents such as alcohols and DMSO absorb microwave radiation well, while nonpolar solvents such as hexane and toluene are poor microwave absorbers and cannot be heated effectively (Figure 1.3). A number of different additives can be used to help heat reaction mixtures where both the reagents and solvents are nonpolar. Detailed information regarding the behavior of solvents in a microwave field as well as examples of reactions in various solvents has been summarized in several excellent reviews and texts [37,38,42,48,49].

Although commercial microwave reactors are able to accommodate condensers and other pieces of glassware, the vast majority of reported reactions are carried out using sealed reactor vessels. Using these sealed vessels, many organic solvents can be heated well above their boiling points. Some solvents can exhibit significantly different properties when heated above the boiling point of the solvent. For example, while water has a high dielectric constant at 25 °C, the dielectric constant is significantly lower when water is heated to 250 °C [50].

Many synthetic chemists are accustomed to designing reactions where a solvent is used to dissolve all of the reagents. If reagents or catalysts are not fully dissolved, this can lead to confusing conclusions when trying to interpret the results of subsequent runs. In some cases, heating the reactions will solubilize all of the reagents and create a homogeneous reaction. Given the precise control over the reaction time temperature and microwave power that commercial microwave reactors provide, reactions can routinely be carried out under neat conditions, near-solvent-free conditions, or diluted with solvent (Figure 1.4).

In order to gain insight into the physical state of the reaction mixture, it would be advantageous to be able to visually inspect the reaction mixture while it is being irradiated. While this might seem like a challenging task, CEM has been able to incorporate a camera into the microwave cavity that allows visual inspection of the reaction mixture before, during, and following irradiation. This camera provides insight into the physical state of the reaction mixture and facilitates the determination of whether all the materials are dissolved, the effectiveness of the stirring, and whether decomposition is occurring. Figure 1.5 shows an example of this approach. The reaction pictured is a rhodium-catalyzed addition of secondary phosphine oxides to a testosterone derivative [51]. The reaction solvent was THF and $(Ph_3P)_3RhCl$ was the catalyst used for the reaction. Without the camera, a heterogeneous reaction mixture was placed into the reactor, and a heterogeneous reaction mixture was removed from the reactor at the end. The chemist would be

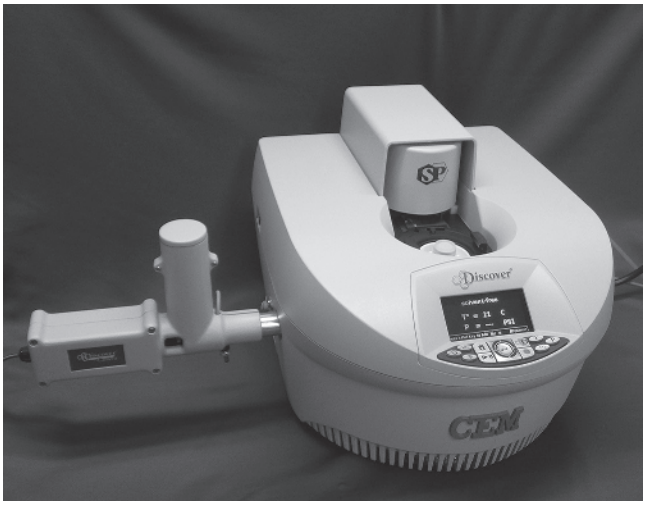
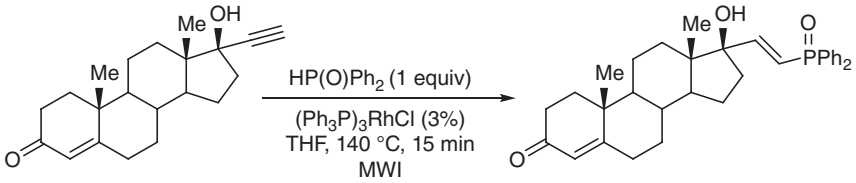
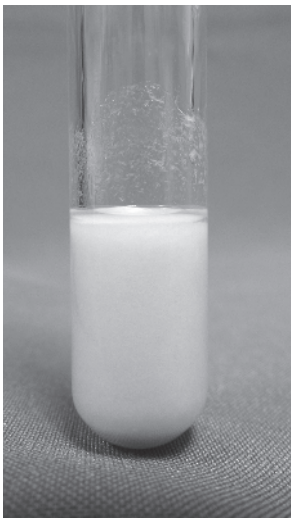


FIGURE 1.4 Example of a commercial microwave reactor with an integrated camera. *Source*: Acknowledgment is given to CEM Corporation for the generous loan of the microwave reactor for the construction of this text.



prior to irradiation
(heterogeneous)



following irradiation
(heterogeneous)

FIGURE 1.5 Before and after pictures of the reaction mixture. It should be noted that the picture of the final product has a slight yellow tint to the solution that is not shown in the B&W photo. *Source*: Images of the CEM microwave reactor vials were produced with permission from CEM Corporation.

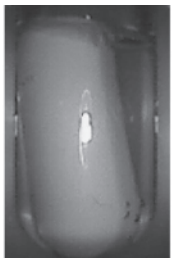
				
1	**2**	**3**	**4**	**5**
After placing the sample into the microwave reactor	After stirring for a few seconds and starting irradiation	After stirring and irradiating for a few minutes (THF is boiling)	End of irradiation and starting to cool	After cooling for a few moments-crystallization begins
heterogeneous	heterogeneous	homogeneous	homogeneous	heterogeneous

FIGURE 1.6 Pictures from inside the microwave cavity before, during, and following irradiation. It should be noted that the color of the reaction mixture is slightly yellow after a few minutes of irradiation. The color is not illustrated in this B&W photo. The bright spot in the middle of the frame is due to the LED light used to provide light in the otherwise dark cavity of the microwave reactor. *Source*: Acknowledgment is given to CEM Corporation for the generous loan of a microwave reactor with integrated camera for the construction of this text.

unable to determine whether or not the reaction was ever homogeneous during irradiation. Figure 1.6 shows the progression of the reaction using the integrated camera. Before irradiation, the reaction is clearly heterogeneous, and the red (dark) catalyst can be seen in the bottom right side of the reactor vial (picture 1). As the reaction begins, it is still clearly heterogeneous, and the stirring bar is barely visible (picture 2). After reaching 140 °C and boiling for a few minutes, the solution has become homogeneous (picture 3). At the end of the irradiation period, all of the materials are still dissolved (picture 4). After standing for a few moments and cooling to 50 °C, the product begins to precipitate from the reaction mixture (picture 5). It should be noted that the microwave reactor will be unlikely to homogenize truly heterogeneous reactions. Mineral bases, molecular sieves, supported catalysts, or silicon carbide disks would be cases when the microwave reactor would not be effective at bringing all of the reaction components into the same phase. The most valuable aspect of camera is the ability to evaluate the reaction in real time. Additionally, the reaction can be remotely monitored and evaluated by multiple people simultaneously. This can be particularly attractive when collaborators or research facilities are in different locations.

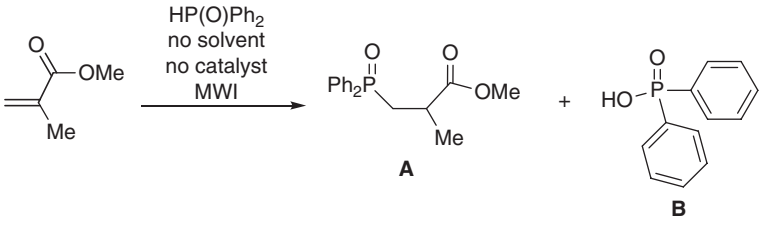
Time, temperature, and power. Modern microwave reactors are able to provide precise control over the amount of microwave energy that is used to heat the reaction mixture. Through careful selection of the reagents, catalysts, and solvents, many reactions can be designed to rapidly generate the target compounds in high yields. With a little experimentation, conventionally heated reactions can be readily converted into microwave-assisted versions.

Irradiating the sample with the highest available power for the shortest period of time in order to rapidly heat the reaction mixture to the highest possible temperature is a very popular method and has been used to generate countless compounds. While this might seem like a natural approach to microwave-assisted reactions, it could present problems for some systems. Unfortunately, this is often how chemists who are new to microwave chemistry approach their first reactions. They are often excited about the published results using microwave reactors and have read about how microwave reactors decrease reaction times, increase yields, and decrease secondary products. They take a reaction they are having trouble with and irradiate it at the maximum power level thinking that more power is better. This can result in the formation of an intractable mixture that is not salvageable. When working with a new reaction or catalyst, it often takes some experimentation to find the optimal conditions. For example, if the reaction is being carried out under solvent-free conditions, one of the reagents could preferentially absorb more of the applied microwaves and be preferentially heated. In the extreme case, this heated reagent could decompose before it ever has a chance to react with the other substrates. In some cases, the preferential heating leads to the formation of side reactions and secondary products. Additionally, metal-containing catalysts and additives could absorb more than the other reagents and become preferentially heated/destroyed. This leads to a significant amount of frustration on the part of the scientist trying to synthesize a desired compound. When a transition metal-catalyzed microwave-assisted reaction fails, the scientist is left to wonder if the catalyst was the problem, whether or not oxygen was introduced, or could the reagents be contaminated. While all of these reasons are entirely valid, it is also entirely possible that the failure of the reaction was simply due to using too much microwave power.

In some cases, only minimal amounts of microwave power are needed to promote a specific reaction. This is often the case when irradiating reactions carried out under solvent-free conditions with polar reagents or reactions carried out with polar solvents. Determining how much power is needed can often be the critical aspect of the synthetic design. The good news is that due to the operational simplicity of modern microwave reactors, finding a good set of conditions often takes less than a day. For high-absorbing materials such as DMF or ionic liquids, this power level could be quite low. Once the minimum power level has been determined, increasing/decreasing the power setting for subsequent screening reactions in 10–20% increments and analyzing the results will rapidly provide an experimental determination of how much microwave power is needed to achieve a desired result.

The microwave-assisted addition of secondary phosphine oxides to activated alkenes is an excellent example of how the power setting can significantly affect the outcome of a reaction (Table 1.1) [52]. This reaction was operationally trivial and consisted of adding the solid reagents to a reactor vial (in air), exchanging of the atmosphere for nitrogen, injecting the liquid reagents, and irradiating. For most of the examples, the neat reaction mixture absorbed microwaves well and heated to the desired temperature rapidly. When a high amount of microwave power (250 W) was applied to rapidly heat the sample to the desired temperature of 125 °C, the yield of the desired alkylphosphine oxide was low and a significant amount of diphenylphosphinic acid was observed. Using the optimization approach described in the preceding paragraph, the authors discovered that reducing the initial microwave power led to reduced amounts of the undesired phosphinic acid. Using this low power level, outstanding yields of the target alkylphosphine oxides were obtained after only 30 min of irradiation. While it might be tempting to irradiate reaction mixtures at

TABLE 1.1 Effect of Microwave Power on the Product Distribution of a *Phospha*-Michael Addition [52].



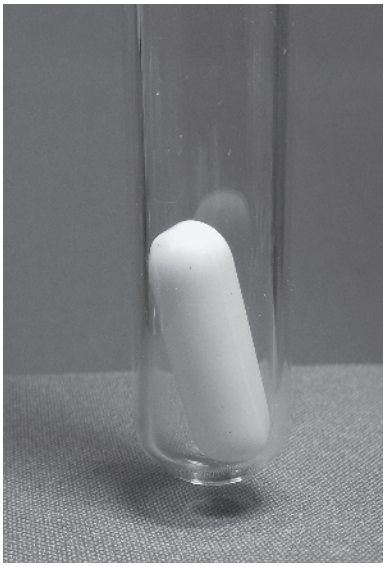
Run	Power (W)	Time (Min)	Temperature (°C)[a]	%A[b]	%B[b]
1	250	5	125	60	30
2	200	10	125	65	29
3	100	10	125	73	22
4	25	30	125	95	0

[a] Temperatures measured using an IR sensor at the bottom of the reaction vessel.
[b] The remaining compounds were not identified.

the highest available power for the shortest amount of time, it might be worth decreasing to lower power levels to obtain a cleaner product.

A solvent-free reaction using all solid reagents is another reaction that might tempt a researcher to increase the amount of microwave power. The researcher may believe that irradiating at a high power level will melt the sample rapidly. Typically, solid reagents need to "melt" or gel in order to absorb significant amounts of the microwave irradiation. While this does happen in some cases, it is also likely that the melted reagents will be exposed to high levels of microwave radiation for a few moments while the reactor lowers the power to prevent overheating. Even a few moments at high power could be enough to generate secondary products and decompose the sample. When working with a mixture of solids under solvent-free conditions, the obvious initial thought is to check the melting point of the solids to give an approximate temperature where melting will occur. However, when two or more solids are mixed, the melting point of the mixture is typically lowered, sometimes significantly. Researchers can take advantage of this observation and design a heating profile that might take advantage of this observation.

Another issue that could complicate the interpretation of results from microwave-assisted reactions involves syntheses that generate an ionic material or products that have a higher dipole than the starting materials/solvent. These products will absorb well and heat the sample rapidly. Common examples of this include the synthesis of ionic liquids and phosphonium salts. Consider the reaction of triphenylphosphine with benzyl chloride. It could be argued that these reagents might absorb some of the applied microwave radiation; however, neither will absorb as well as the ionic phosphonium salt generated in the reaction. Once even a small amount of this product was formed, it will be rapidly heated by even a small amount of applied microwave radiation. Even if the microwave reactor is programmed to decrease the microwave power in response to an increase in temperature, it may not be able to compensate if this ionic material is generated in the reaction. In such cases, a vessel failure is possible. These issues could be very important when trying to convert a conventionally heated reaction into a microwave-assisted reaction.



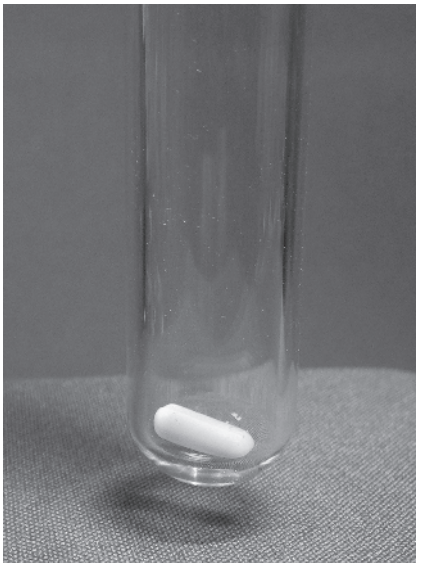
1 inch stirring bar

Advantages

- good with heterogeneous mixtures
- good with homogeneous mixtures
- excellent for triturating solids
- excellent for solvent free and near solvent free reactions

Disadvantages

- occupies a considerable volume



micro stirring bar

Advantages

- good with homogeneous reactions
- occupies a very small volume

Disadvantages

- ineffective with heterogeneous reactions
- poor for triturating solids
- poor for solvent free reactions unless all reactants, additives, and products are fluid

FIGURE 1.7 Stirring options when using small reactor vials. *Source*: Images of the CEM microwave reactor vials were produced with permission from CEM Corporation.

Stirred or not stirred. One of the considerations to address when designing a microwave-assisted synthesis is whether or not the reaction needs to be stirred. If all of the reagents and products are liquids or everything is fully dissolved in a solvent (homogeneous reaction), stirring may not be needed provided that the solution is well mixed prior to irradiation. If one or more of the reagents, catalysts, or additives are solids and not dissolved (heterogeneous reaction), best results will be obtained if the reaction is stirred. There are several options for effective stirring. In some cases, small stirring bars will provide effective stirring; however, the formation of gels or precipitation of products or reagents can inhibit the stirring process. In those cases, it is best to change to a larger stirring bar for effective stirring. Examples of the two scenarios are shown in Figure 1.7. For microwave-assisted reactions, make sure that the stirring bar is less than ¼ of the standing wave for the microwave reactor.

Safety considerations. This is dependent upon the type of synthesis that will be carried out in the microwave reactor. Arguably, one of the biggest concerns is the possibility for a pressure buildup that results in a vessel failure. This can happen when volatile compounds are used as reagents or solvents or when volatile compounds are generated from the

reaction. Most modern microwave reactors have safety protocols built into the system to vent the cavity in case of a vessel failure. In general, it is advisable to review all of the boiling points of the compounds that are added and generated from the reaction to ensure that a low-boiling compound will be minimized.

In addition to the use of volatile organic compounds, another possibility for a vessel failure occurs when small amounts of a transition metal catalyst become stuck to the side of the reactor vial. If the metal is reduced to its elemental state, arcing is possible. This is more commonly encountered in solvent-free reactions. The solution to this issue is to use a sleeve to make sure that all of the reagents are transferred to the bottom of the reaction vial.

Additives. As mentioned previously, some reaction mixtures may be poor absorbers and heat very slowly in the microwave. In those cases, it is possible to include an additive to promote heating. The two main types of additives are ionic materials and silicon carbide disks. When considering ionic materials, a wide variety of versions to choose from are commercially available. The best choice for the specific reaction under investigation will vary from reaction to reaction and can range from mineral salts to ionic liquids. Ionic liquids are attractive since their polarity can be manipulated so they are immiscible with the main reaction solvent and serve only to transfer heat to the nonpolar reaction medium. This is a very effective method since ionic liquids absorb microwave energy very efficiently. They also have the advantage that they do not interfere with the stirring. Detailed investigations by Leadbeater have shown this to be an effective means of heating a poorly absorbing mixture [53]. Once the reaction is complete, simply spinning the reactor in a centrifuge will concentrate the ionic liquid and the reaction mixture can be decanted or removed with a pipette. The second type of additive is a silicon carbide disk [54]. These solid materials have an extremely high absorption of microwaves and will heat very rapidly. Since the disks are insoluble in the reaction medium, they are readily removed from once the reaction is over. It should be noted that in many cases, the disks will interfere with the stirring of the reaction mixture. Both approaches have advantages and disadvantages, and the approach that will work best will depend upon your specific reaction.

The use of ultrasound to promote organic reactions has also proven to be effective [55–59]. While several theories were initially proposed to explain the observations, the generally accepted explanation for the accelerating effect of ultrasound on chemical reactions is due to the formation of “hot spots” resulting from collapse of microbubbles in the reaction mixture. The local temperatures and pressures of these hot spots have been calculated to be extremely high (>4000 K and >400 atm) [56]. An excellent review by Thompson and Doraiswamy summarizes the critical parameters that should be consulted when designing an ultrasound-assisted reaction [56]. It is also noteworthy to mention that several groups have been working to combine ultrasound and microwave chemistry [57,58]. While only a few reports have been published, combining the two techniques is an interesting approach. Despite the potential advantages to ultrasound-assisted reactions, it has not been as widely adopted as microwave chemistry.

1.8 SUSTAINABILITY

There are a range of areas that need to be addressed when designing sustainable organic syntheses. Essentially, sustainable processes will be easier to adopt if they are operationally simple and convenient to implement. It is easy to think about trying to take the philosophical

high road and try to force scientists to adapt. Practically, this will be nearly impossible. If the new techniques/approaches are overly time intensive, cumbersome, or low yielding, widespread adoption will be less likely. The following sections will highlight a number of areas for further development.

Designing catalysts and reactions that are compatible with water. Organic solvents often need to be anhydrous and deoxygenated; thus, one of the most time-intensive components of a synthesis involves the drying and deoxygenating of reaction solvents. While some of this is mitigated through the use of solvent purification systems, the system must be constantly maintained and the solvent checked for trace amounts of moisture. If a solvent purification system is not available, solvents can be distilled from reactive metals. In addition to the safety hazard this introduces to the laboratory, the stills must be maintained and checked daily. As an alternative, organic solvents can also be dried using activated molecular sieves. A recent report compared the effectiveness of molecular sieves and reactive metals and concluded that molecular sieves were just as successful at removing water from common organic solvents as the reactive metals [1]. While using molecular sieves is easier, it creates additional waste since the molecular sieves are rarely recycled and reused. A significant reduction in the preparation time and amount of waste generated would be achieved through the development of reactions that will tolerate small to large amounts of water. While a number of reactions have been reported that are successful in the presence of small amounts of water, a vast number of syntheses are not. Thus, the challenge for the synthetic community is to develop a substantial number of water-tolerant reactions that would enable researchers to prepare a vast array of functional groups. The need to dry and deoxygenate organic solvents would then become the exception rather than the rule.

A reduction in the amount of solvents needed to isolate target compounds is one of the top priorities when designing sustainable practices. While the conversion to solvent-free reactions or near-solvent-free reactions will eliminate the solvent from the carbon–heteroelement bond-forming step, a significant amount of solvent will often be used to isolate the target compound by column chromatography. There are a couple of general strategies that are often used to address the use of hazardous solvents in column chromatography. The first approach entails simply exchanging commonly used solvents such as hexane for less hazardous versions such as heptane. Blends of ethyl acetate and ethanol have been used as replacements for dichloromethane. While this is not ideal, it allows researchers to continue to use the equipment already in place in their laboratories. A number of excellent reviews on green solvents have appeared [49,60–67]. The use of automated chromatography systems is attractive since they provide more precise control of the separation. The second option entails changing to supercritical CO_2 as the mobile phase. This requires a substantial economic commitment since new equipment will be needed. A significant amount of time will be required to understand the strengths and limitations of the new system.

Strategies to overcome functional group intolerance. Historically, the most common approach to dealing with functional group intolerance entailed the conversion of sensitive groups into more stable derivatives for the course of the reaction (Figure 1.8). Later in the synthesis, removal of the protecting group generated the target compound. While this appears straightforward, the removal of protecting groups can be quite cumbersome and result in significant reductions of the isolated yields. Thus, the development of high-yielding protection/deprotection strategies continues to be a challenge for the synthetic community.

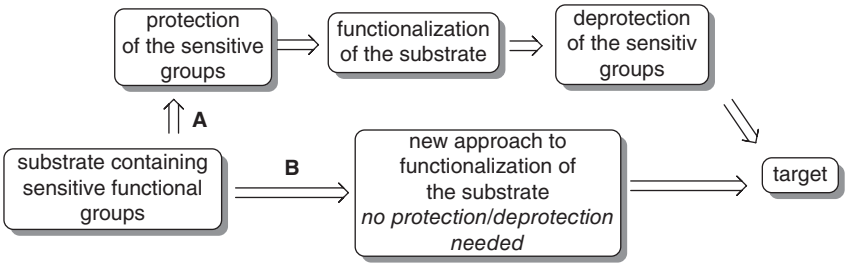


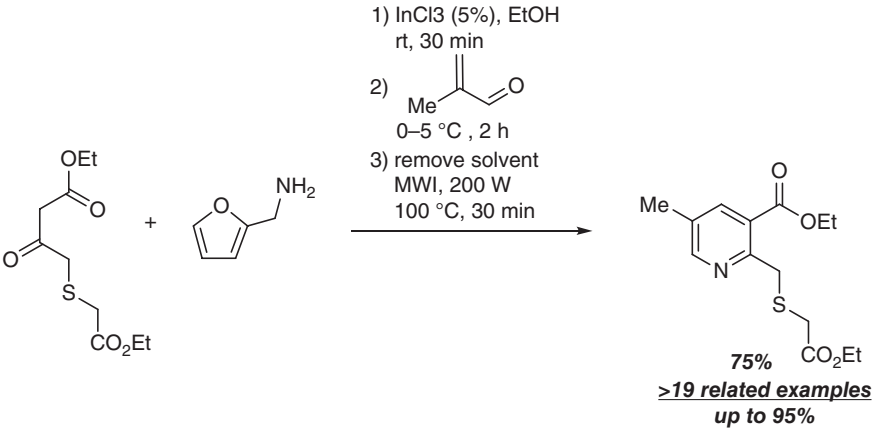
FIGURE 1.8 Development of new approaches versus protection/deprotection strategies.

From another perspective, the design of new reactions that would enable the substrate to be functionalized without protection of the sensitive groups would remove both the protection and deprotection steps from the synthesis entirely.

An example of this entails the synthesis of air-sensitive phosphines. Exposing many phosphines to oxygen results in the formation of phosphine oxides. These compounds can be quite difficult to separate from the desired phosphines. While researchers are often quite adept at removing the oxygen from reaction mixtures, it is often much more challenging to remove all traces of oxygen from every step in the isolation and purification process. As a result, several strategies have been developed to circumvent the formation of unwanted phosphine oxides. One of the most promising ways to accomplish this is through the formation of borane-protected phosphines [68]. The formation of these masked phosphines is trivial and typically consists of simply injecting a solution of $Me_2S\text{-}BH_3$ to the reaction mixture. Once isolated, the free phosphine can be generated from the borane-protected species through several approaches. Arguably, the simplest of which entails simply refluxing the phosphine-borane in ethanol [69]. Thus, the protection of the sensitive phosphine is straightforward, and removal of the protecting group can be trivial.

Developing one-pot reactions or multicomponent reactions. Syntheses that are able to combine several sequential reactions into a single vessel without purification of the intermediates are quite valuable [70–74]. These reactions often save time as well as eliminate the solvents that would have normally been used for chromatographic separation of the intermediates. These processes are often referred to as "telescoping" or "one-pot" reactions and have been steadily growing in popularity. The trick with these reactions is to design the syntheses so that the steps are chemoselective for the desired transformation and are not affected by any of the catalysts and additives from the previous reactions.

An elegant one-pot approach to the synthesis of functionalized pyridines has recently been provided by Menendez (Scheme 1.13) [75]. His approach started with a Lewis acid-promoted coupling reaction to generate an intermediate enamine. Microwave heating followed by air oxidation generated the heterocycle. A key reagent in the mechanism was 2-furylmethylamine. Once it was incorporated in the initial step, it underwent an elimination reaction upon heating in the absence of solvent to generate a cyclic imine followed by air oxidation to generate the functionalized pyridine. It was also noteworthy that the chemistry was successful using air as the sole oxidant. No additional oxidizing agents were required. A range of fused ring systems including quinolones, isoquinolines, and phenanthridines were successfully prepared in moderate to excellent yields (up to 93%) following this procedure.

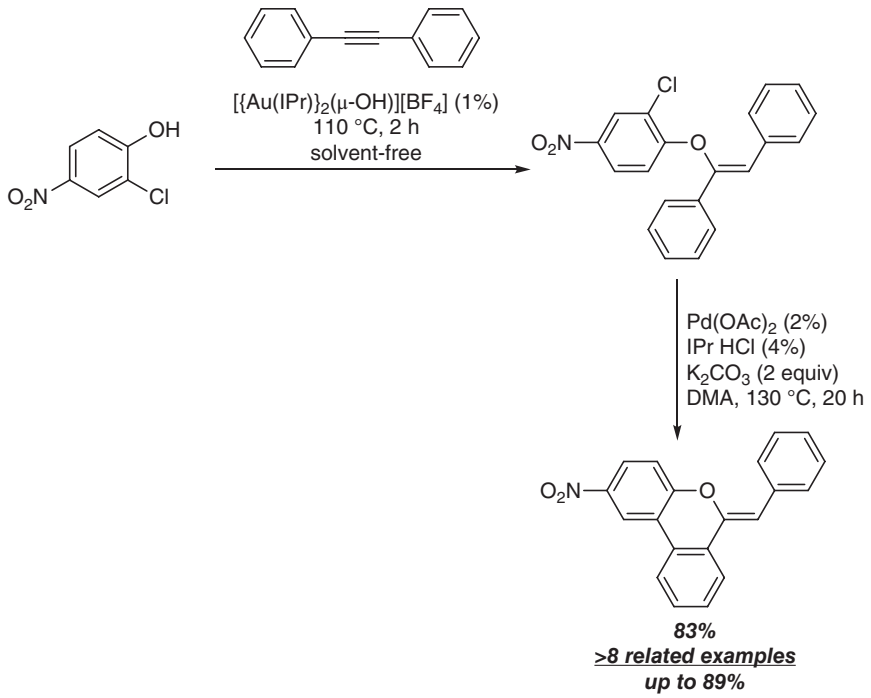


SCHEME 1.13 Lewis acid-catalyzed sequential synthesis of a pyridine [75].

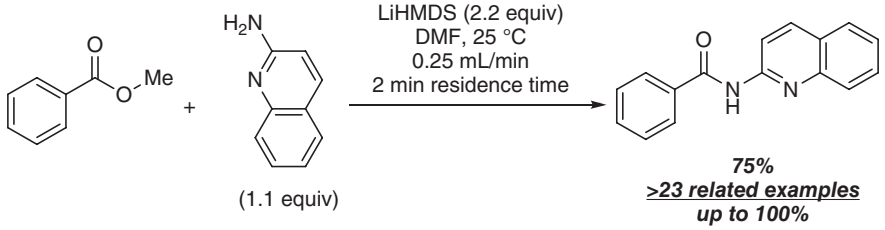
While a number of organic reactions can be linked together in a sequential fashion, it is often challenging to link several metal-catalyzed reactions into a one-pot reaction. A successful example of this was recently reported by Nolan [76]. He was able to combine a gold-catalyzed hydrophenoxylation reaction with a palladium-catalyzed C–H activation (Scheme 1.14) or Mizoroki–Heck coupling in a tandem one-pot reaction. Furthermore, he was able to accomplish the initial hydrophenoxylation reaction under solvent-free conditions. The chemistry was quite tolerant to a range of electron-donating and electron-withdrawing groups on the phenol, and moderate to excellent yields of the benzo[c]chromenes were obtained. This remarkable tolerance of the palladium-catalyzed reaction to the presence of gold provides the synthetic community with a proof of concept for the development of a myriad of sequential reactions given the wide range of gold-catalyzed reactions combined with the staggering number of palladium-catalyzed processes.

Flow chemistry. There has been a growing interest in the development of continuous flow reactors for the preparation of organic compounds [77–84]. Performing the reaction under flow conditions typically uses considerably less solvent than a typical batch reaction and can afford higher yields of target compounds. The ability to generate moderate to large amounts of material as needed is a significant benefit to using continuous flow reactions. The conversion of amines into amides using esters as substrates serves as a representative example of this chemistry (Scheme 1.15) [85]. The reaction was carried out under mild conditions (25 °C) using THF or DMF as the solvent, and the base used in this chemistry was a bulky amide ($LiN(SiMe_3)_2$) in order to mitigate potential secondary reactions resulting from nucleophilic behavior of the base.

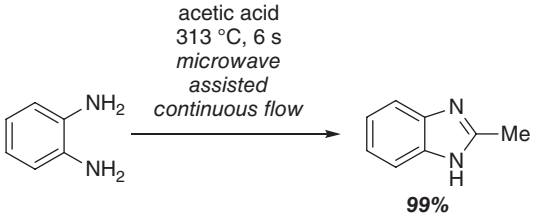
In addition to flow systems that use conventional heating, microwave-assisted flow chemistry has also been reported [78,86–88]. Organ reported the synthesis of benzimidazole through microwave-assisted flow chemistry (Scheme 1.16) [86]. One of the critical components of the flow system was a silicon carbide reactor tube. As mentioned previously, these materials have a very high absorption of microwave radiation and heat very rapidly upon irradiation. The ability of the silicon carbide to transfer heat is also very high; thus, this material is ideally suited for the construction of a reactor tube that will be used



SCHEME 1.14 One-pot sequential gold- and palladium-catalyzed reactions [76].



SCHEME 1.15 Amide synthesis at 25 °C using a continuous flow reactor [85].



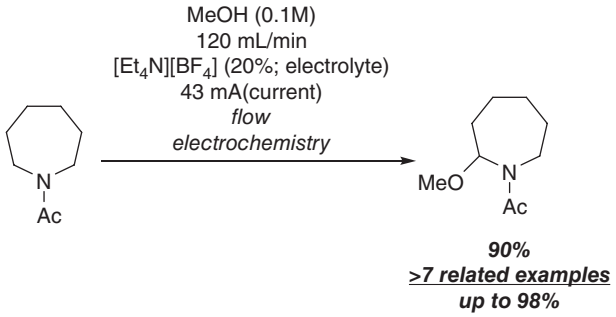
SCHEME 1.16 Benzimidazole synthesis through microwave-assisted flow chemistry [86].

in a microwave-assisted experiment. Historically, one of the limitations with focused microwave reactors was the requirement that all the reactions needed to be run in batches and the scales were relatively small. While this is appropriate for most small synthetic laboratories, the small batches are a limitation when larger amounts are needed. The microwave-assisted flow approach directly addresses this issue.

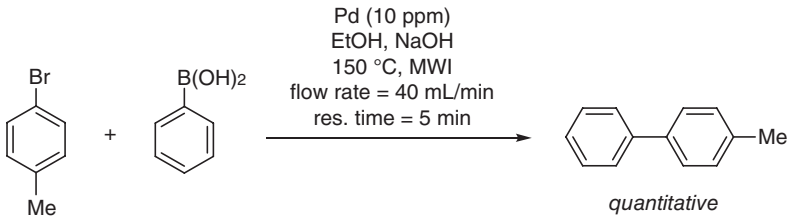
Given the potential advantages to performing reactions under continuous flow, a variety of chemistries have been modified for flow conditions. A recent example of this was reported by Ley and combined flow and electrochemistry for the methoxylation of cyclic amines (Scheme 1.17) [89]. The chemistry was carried out in a microfluidic electrolytic cell using a substoichiometric amount of $[Et_4N][BF_4]$ as an electrolyte. The authors used a steel cathode and screened a range of materials for the anode and determined that carbon was the most effective for the methoxylation reaction. The chemistry was selective for the α-position, and a range of cyclic amines were successfully functionalized using this approach.

The generation of solids that can clog a flow reactor remains one of the most significant issues that must be circumvented when designing a reaction that will be performed in a flow reactor. As a result of this, not every reaction will be amenable to this approach. It should be noted that this is a very active area of research and new developments that address the current difficulties are being published with increasing frequency. For example, Organ has recently reported the use of a pressure control device that is able to provide very high back pressures (1100 psi) [86]. Such pressures will aid in preventing tube clogging.

Transition metal-catalyzed reactions that use ultralow catalyst loadings have also been adapted for continuous flow. Leadbeater reported an elegant example of this chemistry and was able to decrease the palladium loading to 10 ppm and still achieve a quantitative conversion in the desired biaryl (Scheme 1.18) [90]. This was a microwave-assisted



SCHEME 1.17 Methoxylation reactions using flow electrochemistry [89].



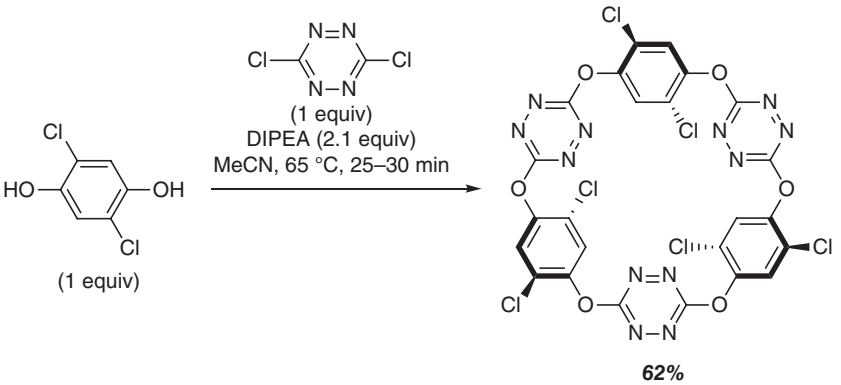
SCHEME 1.18 Microwave-assisted flow chemistry using ultralow catalyst loading [90].

reaction and used a residence time of 5 min in the reactor. As with many of the continuous flow approaches described previously, the authors noted that the buildup of solids in the tubing could inhibit the processing of large amount of material. Ideally, the synthesis would be designed such that the precipitation of the products or reagents does not occur. However, this is not always possible, and alternative strategies such as the use of systems that provide high back pressures as described in the previous paragraph might be successful.

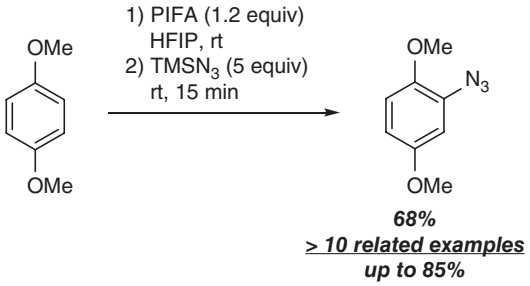
For those reactions that are well suited to this style of chemistry, performing the reaction under flow is a very practical approach to the synthesis of new compounds. There are start-up costs to consider when setting up a flow system, as well as time lost in order to understand how the system operates. Given the potential advantages, this is likely to be time well spent.

Transition metal-free addition and coupling reactions. Due to the high toxicity and high cost of many transition metal catalysts, the conversion of what are typically thought of as metal-catalyzed reactions into metal-free processes is of current interest to the synthetic community. The example shown in Scheme 1.19 shows the formation of an interesting tetrazine through metal-free S_NAr substitutions [91]. While most aryl halides are unreactive in classic nucleophilic substitution reactions and need to be generated through metal-catalyzed cross-coupling reactions, a number of highly activated systems are susceptible to S_NAr chemistry.

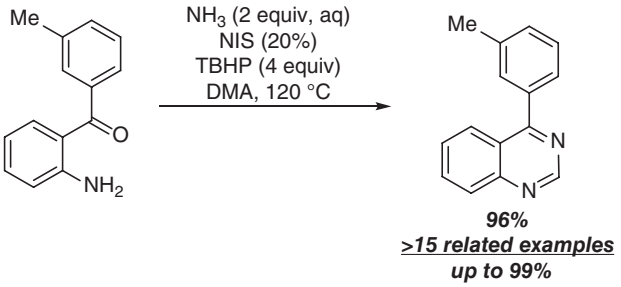
There is considerable interest in the development of metal-free C–H activation reactions that lead to the formation of carbon–heteroelement bonds [31,92]. The potential to transform unfunctionalized hydrocarbons into useful precursors and products remains the driving force in this area. This area of research is quite challenging, and significant hurdles have slowed the progress in this area. Many of the reactions exhibit a high degree of substrate specificity, and general procedures are rare. For the formation of nitrogen–carbon bonds, oxidative amination has shown some promise for the construction of azides, amides, and related compounds [92]. The conversion of unfunctionalized aryl ethers into azides through C–H activation (Scheme 1.20) serves as a representative example of this transformation [93]. The synthesis was achieved through the use of a hypervalent iodine reagent (PIFA) and $TMSN_3$ as the azide precursor. While many similar reactions proceed through the formation of diaryliodonium salts, the authors proposed that this chemistry



SCHEME 1.19 Metal-free synthesis of a tetrazine using S_NAr chemistry [91].



SCHEME 1.20 Metal-free C–H azidation of electron-rich arenes [93].



SCHEME 1.21 C–H oxidative amination reaction [94].

generated the functionalized materials through the formation of radical cations. The resulting aryl azides are valuable precursors for a range of nitrogen-rich compounds such as triazoles.

The development of effective methods for the functionalization of primary amines and ammonia remains a standing goal for the synthetic community. Although ammonia is readily available and inexpensive, it has been very challenging to involve in nitrogen–carbon bond-forming reactions. Combing such a transformation with a metal-free C–H activation reaction would be a valuable methodology. Recently, Wang has reported the synthesis of heterocycles through such a reaction (Scheme 1.21) [94]. He used aqueous ammonia as the nitrogen source and a substoichiometric amount of NIS along with an excess of TBHP to promote the reaction. While it was tempting to propose the involvement of a hypervalent iodine species in this chemistry, the authors discounted that possibility through carefully designed control reactions. This chemistry is specific for ortho-substituted anilines, tolerant of electron-donating and electron-withdrawing groups, and generated outstanding yields of the quinazolines.

1.9 ASYMMETRIC SYNTHESIS

The manipulation of the stereochemical outcome of a specific reaction is commonly achieved through the use of transition metal catalysts bearing a chiral ligand or through the use of a resolved organocatalyst. This requirement adds considerable challenges to the synthesis, and in some cases, the selective preparation of a target substrate with the desired

stereochemistry is not possible. Both transition metal and organocatalyzed approaches have their merits, and the most successful system will depend upon the reaction as well as the nature of the substrates. One of the consistent issues with asymmetric synthesis remains the substrate specificity inherent to many catalysts. It is quite common for the enantioselectivity of a new reaction to be extremely high for only three to four substrates. Furthermore, reports that list the selectivity for only one to two substrates are of limited value unless those specific substrates are known to be troublesome.

To this end, the burden is on the synthetic community to continue to develop active catalysts with greater selectivity and increased substrate scope. The following chapters will highlight asymmetric reactions for the formation of functional groups through the formation of carbon–heteroelement bonds with special attention paid to reactions that are highly selective but also to those that show the largest substrate scope.

REFERENCES

[1] Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351–8354.

[2] Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–854.

[3] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470.

[4] Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.

[5] Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976.

[6] Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.

[7] Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381–1384.

[8] Manbeck, G. F.; Lipman, A. J.; Stockland, R. A., Jr.; Freidl, A. L.; Hasler, A. F.; Stone, J. J.; Guzei, I. A. *J. Org. Chem.* **2005**, *70*, 244–250.

[9] Kamitani, M.; Itazaki, M.; Tamiya, C.; Nakazawa, H. *J. Am. Chem. Soc.* **2012**, *134*, 11932–11935.

[10] Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789–794.

[11] Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.

[12] Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 5351–5358.

[13] Friis, S. D.; Skrydstrup, T.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 4296–4299.

[14] Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007.

[15] Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

[16] Kendall, A. J.; Salazar, C. A.; Martino, P. F.; Tyler, D. R. *Organometallics* **2014**, *33*, 6171–6178.

[17] Burns, D. J.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 9931–9935.

[18] Banerjee, D.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 13049–13053.

[19] Abbas, S.; Bertram, R. D.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3365–3367.

[20] Li, X.; Yang, F.; Wu, Y.; Wu, Y. *Org. Lett.* **2014**, *16*, 992–995.

[21] Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 3792–3795.

[22] Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302–2309.

[23] Buchwald, S. L.; Bolm, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5586–5587.

[24] Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774–793.

[25] Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8–27.

[26] Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010.

[27] Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K.N. *Acc. Chem. Res.* **2004**, *37*, 558–569.

[28] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

[29] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.

[30] Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114*, 10829–10868.

[31] Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219–9280.

[32] Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807–8864.

[33] Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199–8256.

[34] Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390–2431.

[35] Meninno, S.; Croce, G.; Lattanzi, A. *Org. Lett.* **2013**, *15*, 3436–3439.

[36] Jiang, X.; Wu, L.; Xing, Y.; Wang, L.; Wang, S.; Chen, Z.; Wang, R. *Chem. Commun.* **2012**, *48*, 446–448.

[37] Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.

[38] Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127–1139.

[39] Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325–3355.

[40] Antonio, C.; Deam, R. T. *Phys. Chem. Chem. Phys.* **2007**, *9*, 2976–2982.

[41] Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.

[42] Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–224.

[43] Strauss, C. R.; Rooney, D. W. *Green Chem.* **2010**, *12*, 1340–1344.

[44] Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284.

[45] Nilsson, P.; Olofsson, K.; Larhed, M. *Top. Curr. Chem.* **2006**, *266*, 103–144.

[46] Pillai, U. R.; Sahle-Demessie, E.; Varma, R. S. *J. Mater. Chem.* **2002**, *12*, 3199–3207.

[47] Ju, Y.; Varma, R. S. *Green Chem.* **2004**, *6*, 219–221.

[48] Hayes, B. L. *In Microwave synthesis: chemistry at the speed of light;* CEM Publishing: Matthews, NC, **2002**.

[49] Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629–639.

[50] Patrick, H. R.; Griffith, K.; Liotta, C. L.; Eckert, C. A.; Glaser, R. *Ind. Eng. Chem. Res.* **2001**, *40*, 6063–6067.

[51] Stockland, R. A., Jr.; Lipman, A. J.; Bawiec, J. A., III; Morrison, P. E.; Guzei, I. A.; Findeis, P. M.; Tamblin, J. F. *J. Organomet. Chem.* **2006**, *691*, 4042–4053.

[52] Stockland, R. A. Jr.; Taylor, R. I.; Thompson, L. E.; Patel, P. B. *Org. Lett.* **2005**, *7*, 851–853.

[53] Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145–3148.

[54] Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651–4658.

[55] Cravotto, G.; Gaudino, E. C.; Cintas, P. *Chem. Soc. Rev.* **2013**, *42*, 7521–7534.

[56] Thompson, L. H.; Doraiswamy, L. K. *Ind. Eng. Chem. Res.* **1999**, *38*, 1215–1249.

[57] Barge, A.; Tagliapietra, S.; Tei, L.; Cintas, P.; Cravotto, G. *Curr. Org. Chem.* **2008**, *12*, 1588–1612.

[58] Cravotto, G.; Cintas, P. *Chem. Eur. J.* **2007**, *13*, 1902–1909.

[59] Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131–1141.

[60] Sheldon, R. A. *Green Chem.* **2005**, *7*, 267–278.

[61] Li, C.-J. *Chem. Rev.*. **2005**, *105*, 3095–3166.

[62] Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546–1557.

[63] Liu, S.; Xiao, J. *J. Mol. Catal. A Chem.* **2007**, *270*, 1–43.

[64] Dunn, J. B.; Savage, P. E. *Green Chem.* **2003**, *5*, 649–655.

[65] Hoffmann, J.; Nuchter, M.; Ondruschka, B.; Wasserscheid, P. *Green Chem.* **2003**, *5*, 296–299.

[66] Nolen, S. A.; Liotta, C. L.; Eckert, C. A.; Glaser, R. *Green Chem.* **2003**, *5*, 663–669.

[67] Miao, W.; Chan, T. H. *Acc. Chem. Res.* **2006**, *39*, 897–908.

[68] Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023–4078.

[69] Moulin, D.; Bago, S.; Bauduin, C.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3939–3956.

[70] Zeng, X. *Chem. Rev.* **2013**, *113*, 6864–6900.

[71] Yang, Z.-P.; Zhang, W.; You, S.-L. *J. Org. Chem.* **2014**, *79*, 7785–7798.

[72] Cantillo, D.; Damm, M.; Dallinger, D.; Bauser, M.; Berger, M.; Kappe, C. O. *Org. Process Res. Dev.* **2014**, *18*, 1360–1366.

[73] Kuethe, J. T.; Tellers, D. M.; Weissman, S. A.; Yasuda, N. *Org. Process Res. Dev.* **2009**, *13*, 471–477.

[74] Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484–491.

[75] Raja, V. P. A.; Tenti, G.; Perumal, S.; Menendez, J. C. *Chem. Commun.* **2014**, *50*, 12270–12272.

[76] Oonishi, Y.; Gómez-Suárez, A.; Martin, A. R.; Makida, Y.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Eur. J.* **2014**, *20*, 13507–13510.

[77] Noel, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010–5029.

[78] Baxendale, I. R.; Hayward, J. J.; Ley, S. V. *Comb. Chem. High Throughput Screen.* **2007**, *10*, 802–836.

[79] Ley, S. V. *Chem. Rec.* **2012**, *12*, 378–390.

[80] Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318.

[81] Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.

[82] Frost, C. G.; Mutton, L. *Green Chem.* **2010**, *12*, 1687–1703.

[83] Ley, S.; Baxendale, I. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 573–586.

[84] Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502–7519.

[85] Vrijdag, J. L.; Delgado, F.; Alonso, N.; De Borggraeve, W. M.; Perez-Macias, N.; Alcazar, J. *Chem. Commun.* **2014**, *50*, 15094–15097.

[86] Sauks, J. M.; Mallik, D.; Lawryshyn, Y.; Bender, T.; Organ, M. *Org. Process Res. Dev.* **2014**, *18*, 1310–1314.

[87] Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160–8167.

[88] Zang, Q.; Javed, S.; Porubsky, P.; Ullah, F.; Neuenswander, B.; Lushington, G. H.; Basha, F. Z.; Organ, M. G.; Hanson, P. R. *ACS Comb. Sci.* **2012**, *14*, 211–217.

[89] Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. *Org. Lett.* **2014**, *16*, 4618–4621.

[90] Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process Res. Dev.* **2008**, *12*, 41–57.

[91] Guo, Q.-H.; Fu, Z.-D.; Zhao, L.; Wang, M.-X. *Angew. Chem. Int. Ed.* **2014**, *53*, 13548–13552.

[92] Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, *2013*, 5769–5804.

[93] Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691.

[94] Yan, Y.; Zhang, Y.; Feng, C.; Zha, Z.; Wang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 8077–8081.