1

Fundamental Techniques

1.1 Safety!

What we do in a modern organic chemistry laboratory is serious business. While it can provide social benefit, basic scientific discoveries, and intellectual satisfaction, chemical experiment is not just fun, it can also be very hazardous, some experiments inherently so. Complacency is often observed by veterans and novices alike. One often forgets that chemistry is a potentially dangerous enterprise; a cavalier attitude often results in disastrous consequences. Therefore, extreme caution should be exercised at all time, especially when one handles large-scale reactions that are exothermic or when dealing with toxic chemicals.

1.1.1 Personal Protection Equipment

1.1.1.1 Safety Glasses

If a chemical splashes into your eyes, it could do serious and sometimes permanent damage to your vision. The most common forms of eye protection include safety glasses (with sideshields), goggles, and face shields. Prescription eye glasses are acceptable provided that the lenses are impact resistant and they are equipped with side shields.

While at the Massachusetts Institute of Technology, Professor K. Barry Sharpless, the 2001 chemistry Nobel laureate, experienced an event that forever changed his life. Professor Sharpless normally wore his safety glasses, but one evening in 1970 he was examining a sealed nuclear magnetic resonance (NMR) tube without safety glasses. Unfortunately for Professor Sharpless, the tube exploded, spraying glass fragments into one of his eyes. The damage was so severe that he lost functional

vision in the injured eye. Professor Sharpless's own words summarize the importance of eye protection, "The lesson to be learned from my experience is straightforward: there's simply never an adequate excuse for not wearing safety glasses in the laboratory at all times" (Scripps Research Institutes' Environmental Health and Safety Department Safety Gram, 2000 (2nd quarter), www.scripps.edu/researchservices/ehs/News/safetygram/).

1.1.1.2 Gloves

Laboratory gloves are an essential part of safe laboratory practice and *must* be worn while handling chemicals. Despite practicing good safety techniques, tragedy may still strike. In 1997, Dr. Karen Wetterhahn, a world-renowned Dartmouth College chemistry professor, died of mercury poisoning 10 months after as little as a drop (0.1 mL) of dimethylmercury [$Hg(CH_3)_2$] seeped through her latex gloves [(a) Blayney, M. B.; Winn, J. S.; Nierenberg, D. W. *Chem. Eng. News* **1997**, *75(19)*, 7. (b) Nagal, M. C. *Chem Health Safety* **1997**, *4*, 14–18]. Although she was working in a ventilated hood and was gowned with personal protection equipment (PPE), independent tests showed that her latex gloves provided virtually no protection against dimethylmercury. This tragic event illustrates that gloves are not a perfect barrier to chemicals, care must still be taken to minimize exposure, and the *proper* gloves must be worn. When choosing the type of glove, the researcher should consider several factors, including degradation and permeation by the chemical, type of exposure, temperature, glove thickness, and physical resistance of the glove. Table 1.1 summarizes the types of gloves available and their recommended use. The manufacturer's description of the gloves should be consulted. In addition, glove selection references include (a) Mellstrom, G. A.; Wahlberg, J. E.; Maibach, H. I. *Protective Gloves for Occupational Use*; CRC: Boca Raton, FL, 1994. (b) http://www.bestglove.com (accessed 30 Jan 2007).

1.1.1.3 Laboratory Coats

Laboratory coats provide an important barrier for your clothes and, more important, your skin from chemicals. The laboratory coat should fit comfortably, have long sleeves, and should be clean.

Table 1.1 Types of gloves and recommended uses

Glove type	Recommended
Latex	Dilute acids and bases
Butyl	Acetone, CH_3CN, DMF, DMSO
Neoprene	Acids, bases, peroxides, hydrocarbons, alcohols, phenols
Nitrile	Acetic acid, acetonitrile, DMSO, ethanol, ether, hexane, dilute acids
Polyvinyl alcohol	Aromatic and chlorinated solvents
Polyvinyl chloride	Acids, bases, amines, peroxides
Viton	Chlorinated solvents, aromatic solvents
Silver shield	Wide variety of chemicals, provides the highest level of protection

DMF, dimethylformamide; DMSO, dimethylsulfoxide.

1.1.2 Material Safety Data Sheets

When dealing with chemicals, caution is warranted, especially with reactive chemicals, carcinogens, and toxic reagents. A useful resource is the Material Safety Data Sheets (MSDS). The MSDS can be considered the "identification card" for a given reagent. A researcher should exercise due diligence and read the MSDS to have a better understanding of the chemical. An MSDS provides a plethora of data, including chemical and physical properties, health hazards, first aid measures in case of exposure, fire fighting measures, handling/storage, stability/reactivity, recommended PPE, toxicological data, and other pertinent information specific to the given chemical. Nowadays, many chemicals come with MSDS sheets, enabling us to scrutinize them before use in our reactions. There are a variety of resources that can be accessed online, including the following: www.ilpi.com/msds (accessed Jan. 30, 2007), MSDS Solution [www.msds.com (accessed Jan. 30, 2007)], MSDS online [www.msdsonline.com (accessed Jan. 30, 2007)], Seton Compliance Research Center [www.setonresourcecenter.com (accessed Jan. 30, 2007)], Cornell University [msds.ehs.cornell.edu (accessed Jan. 30, 2007)], Vermont SIRI [hazard.com (accessed Jan. 30, 2007)], as well as chemical suppliers/manufactures such as Sigma-Aldrich (www.sigmaaldrich.com), VWR (www.vwrsp.com), and others.

Gone are the days when a chemist could smoke a cigarette in the laboratory. Arthur J. Birch was photographed smoking a cigar while demonstrating an ether extraction, which is unthinkable today.

1.1.3 Never Taste Chemicals

In the "good old days," chemists routinely tasted newly synthesized compounds and documented their taste as part of the scientific record. This practice may explain why so many prominent chemists suffered poor health during that time. In the 19th century, the German chemist Justus von Liebig once declared, "A chemist with good health must not be a good chemist" (Li, J. J. *Laughing Gas, Viagra, and Lipitor: The Human Stories behind the Drugs We Use*; Oxford University Press: New York; 2006, p. 79). In 1965, a chemist at G. D. Searle, Jim Schlatter, accidentally had a small amount of a compound on his hands without noticing it. Later that morning, he licked his finger as he reached for a piece of paper and noticed a sweet taste. After careful analysis, he discovered that the compound was the methyl ester of the dipeptide of *L*-aspartic acid and *L*-phenylalanine that was later marketed as the sugar substitute Nutrasweet® (aspartame), a multibillion dollar a year product. Schlatter was lucky. If the by-product had been an extremely toxic chemical, we would have lost a chemist rather than gaining a food additive.

1.2 Useful Preparations

Setting up the reaction is probably the most import job for an organic chemist. Once a reaction is initiated, there is little left that needs to be done to change the outcome. Individual reaction conditions are surveyed in the ensuing chapters. Herein, anhydrous solvents and a list of useful cooling baths for maintaining reaction temperatures below 0 ºC are provided. In addition, several important preparations of commonly

used organic reagents, including Grignard reagents, organolithium reagents, organozinc reagents, diazomethane, Dess-Martin reagent, preparation of lithium diisopropylamide (LDA), and Jones reagent, are described.

1.2.1 Anhydrous Solvents

Traditionally, anhydrous solvents are obtained from distilling the solvent from a drying agent under an inert atmosphere (i.e., nitrogen or argon). The distilled solvent is then collected in a reservoir and removed via a syringe or transferred directly to a round-bottomed flask (Figure 1.1). Table 1.2 lists typical solvents and the drying agents.

Also, there is a misconception concerning solvents distilled from sodium/benzophenone. For example, tetrahydrofuran (THF) is distilled from sodium/benzophenone. Prior to obtaining "dry" THF, the solvent in the distillation pot is a characteristic blue or sometimes purple in color because of the thus afforded benzophenone ketyl radical. It has been assumed by many that the blue color is indicative of "water free" THF. In fact, this may not be the case. Mallinkrodt-Baker conducted a study that showed that the blue color was an indication of the absence

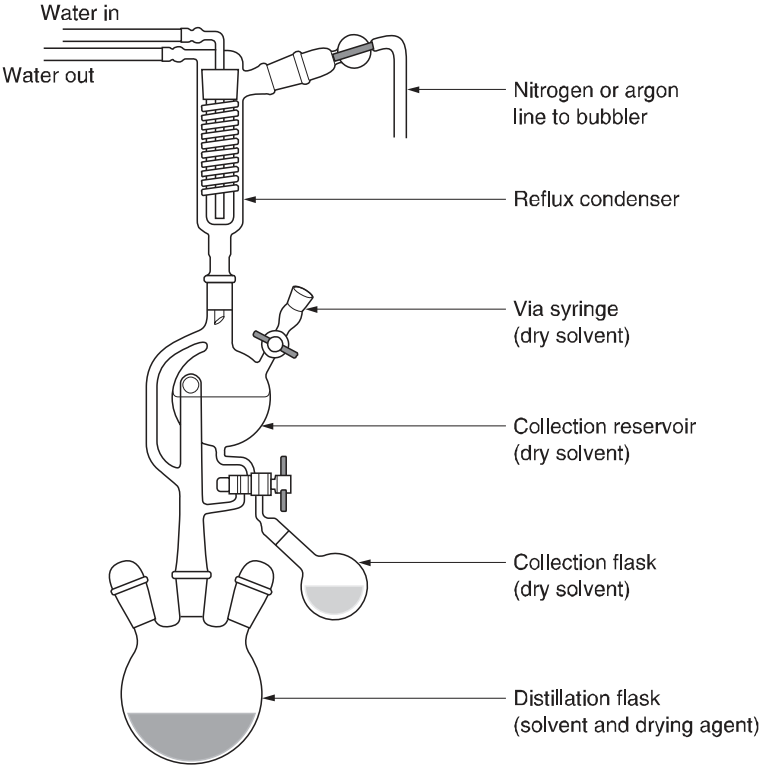


Figure 1.1 Solvent distillation setup.

Table 1.2 Anhydrous solvents from distillation

Solvent	Drying agent
Dichloromethane	Calcium hydride
Diethyl ether	Sodium/benzophenone
Tetrahydrofuran	Sodium/benzophenone
Acetonitrile	Calcium hydride
Ethanol or methanol	Magnesium/iodine
Toluene	Calcium hydride or sodium
Benzene	Calcium hydride or sodium
Triethylamine	Calcium hydride

of dissolved oxygen, not water (see "Benzophenonone Ketyl Study," www.mallbaker.com/techlib/). It required approximately 8 mol% oxygen to quench the benzophenone radical color; however, a full 100% mol of water was added before the blue color dissipated. In addition, the breakdown of the benzophenone radical delivered benzene as the major impurity (150 ppm), as well as other impurities, including triphenylmethanol, phenol, and diphenylmethane. Any one of these impurities could adversely affect a given reaction.

Although distillation is an effective drying technique, it is laden with serious safety issues. They include fire hazards, the handling of large quantities of reactive metals or metal hydrides, quenching of the metals or metal hydrides, and waste disposal.

Instead of using solvent stills there are other options. Perhaps the least expensive method is to dry the solvent over activated 4 Å molecular sieves. This is a particularly effective method when small quantities of solvent are required (<100 mL). Also, there are now commercial sources of a variety of anhydrous solvents. Some solvents include acetonitrile, chloroform, dichloromethane, dimethylsulfoxide (DMSO), 1,4-dioxane, dimethylformamide (DMF), diethyl ether, hexane, ethyl acetate, ethanol, isopropanol, methanol, 1-methyl-2-pyrrolidinone, 2-methylTHF, THF, and toluene. Although there is a cost disadvantage, these solvents are usually suitable for most reactions requiring an anhydrous solvent. Finally, a method that many institutions have adapted is solvent purification systems. This method was popularized after the ground-breaking paper by Grubbs and coworkers in 1996 (Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). Although homemade units can be constructed, commercial instruments are available (Figure 1.2). In a typical set up, ultra dry solvent in a flammable proof solvent cabinet is pushed through two columns, typically alumina and copper catalyst columns, with nitrogen or argon. The anhydrous and oxygen free solvent is now ready for removal via a flask or syringe. These are far safer than solvent stills; however, they too have disadvantages, including the initial cost and a pressurized system.

In the future, anhydrous solvents will more than likely be obtained from all of the methods described but one should always choose wisely. If a safer alternative is available, one should opt for it.

In the past 15 years, the organic chemistry community has been very cognizant of the environmental impact of organic solvents and thus green solvents are growing in importance. Green solvents are defined as solvents that have minimal toxicity to

Figure 1.2 Commercial solvent purification unit: Pure-Solv 400 Solvent Purification System (reprinted with permission from Innovative Technology).

humans and the environment where their toxicities are well understood (Nelson, W. M. *Green Solvents for Chemistry Perspectives and Practice*; Oxford University Press: Oxford; 2003, pp. 91–92). Green solvents that are growing in importance include ionic liquids, fluorous solvents, supercritical carbon dioxide, water, ethanol, and aqueous miscelles and polymers (Mikami, K., ed. *Green Reaction Media in Organic Synthesis*: Blackwell: Oxford, 2005). Although green solvents are nontraditional, there are traditional solvents that are considered green, including acetic acid, benzyl benzoate, diethyl glycol dimethyl ether, DMSO, ethyl acetate, glycerol, hexane, methanol, *t*-butanol, and THF (Nelson, W. M. *Green Solvents for Chemistry Perspectives and Practice*; Oxford University Press: Oxford; 2003, p. 213). In addition to green solvents, organic chemists have identified alternatives (or drop-in) solvents which are considered safer alternatives for a variety of reasons. Table 1.3 illustrates some of these alternatives.

Table 1.3 Alternative solvents

Traditional solvent	Issue with solvent	Drop-in solvent
Benzene	Carcinogen	Toluene
Carbon tetrachloride	Carcinogen; depletion of ozone	Cyclohexane
Chloroform	Toxicity; stability	Dimethoxyethane
Dichloromethane	Volatile; possible carcinogen	Benzotrifluoride
Diethyl ether	Low flash point	Methyl *t*-butyl ether
Hexane, pentane	Volatility	Heptane
THF	Miscibility with H_2O	2-MeTHF
Dioxane, dimethoxyethane	Toxicity	2-MeTHF
HMPA	Carcinogen	DMPU

DMPU, *N*,*N*-Dimethylpropylene urea or 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; HMPA, hexamethylphosphoric triamide; THF, tetrahydrofuran.

1.2.2 Cooling Baths

Often it is necessary to use cooling baths to chill a reaction below 0 ºC (Table 1.4). The low temperature could be important for a variety of reasons, including stereoselectivity dependence, decomposition of reagents, and decomposition of products. Thus, a simple and inexpensive method for maintaining the reaction is with a cooling bath. A cooling bath can be produced by creating a slush with solvent and ice, solid CO_2 (dry ice), or liquid nitrogen in a Dewar flask. To maintain the temperature, additional amounts of ice, dry ice, or liquid nitrogen must added. *However, an internal thermometer should be used to determine the actual temperature of the reaction mixture*.

Reference: Phillips, A. M.; Hume, D. N. *J. Chem. Edu*. **1968**, *54*, 664; Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heineman: Oxford, 1996; p. 36.

Table 1.4 Cooling Baths

Mixture	Temperature (ºC)
Crushed ice	0
Ice/sodium chloride	−5 to −20
Ethylene glycol/CO_2(s)	−11
Carbon tetrachloride/CO_2(s)	−23
Heptan-3-one/CO_2(s)	−38
Acetonitrile/CO_2(s)	−41
Chloroform/CO_2(s)	−61
Ethanol/CO_2(s)	−72
Acetone/CO_2(s)	−78
Ethyl acetate/N_2(l)	−84
Methanol/N_2(l)	−98
Ethanol/N_2(l)	−116
Pentane/N_2(l)	−131

Table 1.5 Common commercially available Grignard reagents

Organomagnesium reagent	Solvent (concentration in M)
Methylmagnesium chloride	THF (3.0)
Methylmagnesium bromide	butyl ether (1.0), ether (3.0), PhMe/THF (75/25, 1.4)
Methylmagnesium iodide	ether (1.0)
Ethylmagnesium bromide	TBME (1.0), ether (3.0), THF (1.0)
Propylmagnesium chloride	Ether (2.0)
Isopropylmagnesium	Butyl diglyme (1.4), ether (2.0), THF (2.0)
tert-Butylmagnesium chloride	Ether (2.0), THF (1.0)
Vinylmagnesium chloride	THF (1.0, 1.6)
Allylmagnesium bromide	Ether (1.0)
Allylmagnesium chloride	THF (2.0)
Phenylmagnesium bromide	Ether (3.0), THF (1.0)
Phenylmagnesium chloride	THF (2.0)

TBME, *tert*-butylmethyl ether; THF, tetrahydrofuran.

Source: Sigma-Aldrich. See Sigma-Aldrich ChemFiles 2002, Vol. 2, No.5, for more organomagnesium reagents.

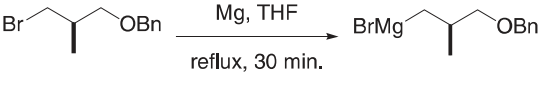
1.2.3 Preparation and Titration of Grignard Reagents

A. Preparation of Grignard Reagents

Tricks to initiate the Grignard reagent formation

Typically, dibromoethane or iodine is added to the reaction flask containing the magnesium metal in the solvent. Dibromoethane ($BrCH_2CH_2Br$) reacts with the oxidized magnesium surface, giving $MgBr_2$ and ethylene gas. As a result, fresh magnesium metal is exposed to the organohalide which leads to Grignard reagent formation. Likewise, I_2 reacts with the oxidized surface layer, giving MgI_2 and exposing fresh magnesium metal to the organohalide. Also, Grignard reagents must be generated in ethereal solvents such as diethyl ether or THF because the reagents form stable chelates with these solvents.

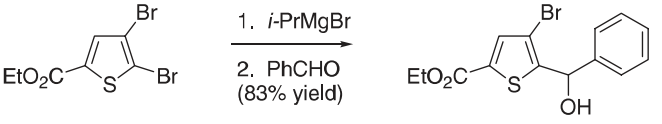
1. Preparation by reaction with magnesium metal



Magnesium turnings (3.5 g, 146 mmol, flamed dried, and cooled under argon) were immersed in THF (10 mL). Two drops of dibromoethane was added to remove the magnesium oxide on the surface of the magnesium turnings. (2*R*)-(–)-Benzyloxy-2-methylpropylbromide (10.4 g, 43 mmol) in THF (70 mL) was added at a rate to keep a gentle reflux (not more than approximately 25% of the bromide should be added before the reaction begins). The reaction mixture was then stirred at reflux for 30 min, cooled to room temperature, and additional THF (40 mL) was added to give a solution of 0.5 M Grignard reagent solution.

Reference: Li, J. *Total Synthesis of Myxovirescin A and Approaches Toward the Synthesis of the A/B Ring System of Zoanthamine*. Ph.D. Thesis, Indiana Univiversity: Bloomington, Indiana; 1996.

2. Preparation by reaction with commercially available Grignard reagents



A solution of *i*-PrMgBr (1.05 mmol) in THF (0.8 M, 1.31 mL) was added dropwise over 5 min to a stirred solution of the starting material (314 mg, 1 mmol) in THF (10 mL) at –40 ºC under argon. The resulting solution was then stirred for 30 min, and benzaldehyde (122 μL, 1.20 mmol) was added. The reaction mixture was allowed to warm to room temperature, brine (20 mL) was added, and the reaction was worked up asnormal. The crude residue was purified by column chromatography on silica (pentane/Et_2O, 4:1) to give the alcohol product (283 mg, 83%) as a colorless oil.

Reference: Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem*. **2000**, *65*, 4618–4634.

Also see Chapter 5 for additional examples of organomagnesium generation. For more on the preparation of organomagnesium reagents see Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: San Diego, CA, 1996, pp. 21–71.

B. Titration of Grignard Reagents

An effective method for the titration of Grignard reagents is with menthol in the presence of 1,10-phenanthroline in THF. The endpoint of the titration is reached when a violet or burgundy color persists, which is indicative of a charge transfer complex formed beween the organomagnesium reagent and 1,10-phenanthroline.

A 50-mL, flame-dried, one-necked, round-bottomed flask fitted with a magnetic stirring bar was rapidly charged with menthol (312 mg, 2 mmol) and 1,10-phenanthroline (4 mg, 0.02 mmol) before being capped with a rubber septum and flushed with dry nitrogen via a syringe needle. Dry THF (15 mL, distilled from CaH_2) was introduced, and the resulting solution was stirred at room temperature under the nitrogen atmosphere. The Grignard solution was then added dropwise by the syringe technique until a distinct violet or burgundy color persisted for longer than a minute.

[RMgX] in M = mmol of menthol/volume of RMgX in mL

Note: *the volume of RMgX solution required to generate the charge-transfer complex with 1,10-phenanthroline, after formation of the magnesium alkoxide, is negligible and not included in the titer calculation.*

Reference: Lin, H.-S.; Paquette, L. A. *Synthetic Communications* **1994**, *24*, 2503–2506. See also, Watson, S. C.; Eastham, J. F. *J. Organometal. Chem*. **1967**, *9*, 165–168.

1.2.4 Preparation and Titration of Common Organolithium Reagents

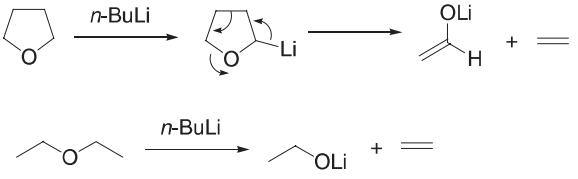
Typical solvents used for organolithium reactions include THF, diethyl ether (ether), dimethoxyethane, toluene, and hexane. Although THF and diethyl ether are the most common solvents involving organolithium reagents, one should be aware that both

Table 1.6 Common commercially available organolithium reagents

Organolithium reagent	Solvent (concentration)
n-Butyllithium	Cyclohexane (2.0 M); hexanes (1.6, 2.5, 10 M); pentane (2.0 M)
sec-Butyllithium	Cyclohexane (1.4 M)
tert-Butyllithium	Pentane (1.7 M)
Methylithium	Diethoxymethane (3.0 M); diethylether (1.6 M)
Ethyllithium	Benzene/cyclohexane (90/10, 0.5 M)
Phenyllithium	di-*n*-Butylether (2.0 M)

Source: Sigma-Aldrich.

solvents are susceptible to decomposition. THF can undergo metallation at the α-position; the anion can then breakdown through a fragmentation process to deliver the enolate of ethanal and ethylene gas (Wakefield, B. J. *Organolithium Methods*; Academic Press: San Diego, CA, 1988, p. 178). In addition, diethyl ether can decompose to form lithium ethoxide and ethylene gas.



To help understand the stability of some common alkyllithium reagents, Table 1.7 lists the half-lives of *n*-BuLi, *s*-BuLi, and *t*-BuLi in ether and THF.

A. Preparation of Organolithium Reagent

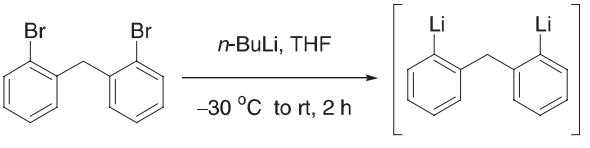


Table 1.7 Half-lives ($t_{1/2}$) of common alkyllithium reagents in ether and THF at various temperatures

Alkyllithium/solvent	–40 °C	–20 °C	0 °C	20 °C
n-BuLi/ether	—	—	—	153 h
n-BuLi/THF	—	—	17.3 h	1.78 h
s-BuLi/ether	—	19.8 h	2.32 h	—
s-BuLi/THF	Stabilization at 0.4 $[s\text{-BuLi}]_o$	1.30 h	—	—
t-BuLi/ether	—	8.05 h	1.02 h	—
t-BuLi/THF	5.63 h	0.70 h	—	—

THF, tetrahydrofuran.

Source: Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514–1515.

A halogen/metal exchange reaction is exemplified here for the preparation of organilithium reagent:

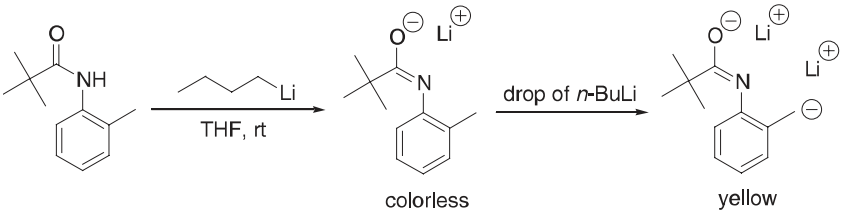
A solution of bis(2-bromophenyl)methane (1.63 g, 5 mmol) in THF (300 mL) was cooled to −30 ºC and *n*-BuLi (2.5 M, 4 mL, 10 mmol) was added dropwise. After completion, the yellow solution was allowed to warm to room temperature and stirred for 2 h. The resulting dilithio reagent was then ready for further reaction.

Reference: Lee, W. Y.; Park, C. H.; Kim, Y. D. *J. Org. Chem*. **1992**, *57*, 4074.

Also see Chapter 5 for additional examples of organolithium generation via halogen/metal exchange. For more on the preparation of organolithium reagents see Wakefield, B. J. *Organolithium Methods*; Academic Press: San Diego, CA, 1988, pp. 21–5.

B. Titration of Organolithium Reagent

A reliable method for titrating commercial alkyllithium reagents such *n*-BuLi, *sec*-BuLi, and *t*-BuLi is with pivolyl-*o*-toluidine in THF. The first equivalent of the alkyllithium reacts with pivolyl-*o*-toluidine to generate a colorless monoanion. The endpoint of the titration is achieved with the next drop of the alkyllithium solution which metallates the benzylic position of the aryl species to form a yellow to yellow/orange dianion.



A 25-mL round-bottomed flask fitted with a septum and containing a magnetic stirring bar was evacuated and flushed with argon or nitrogen. Approximately 250–380 mg (0.9–2.0 mmol) of *N*-pivaloyl-*o*-toluidine charged into the flask. Anhydrous THF (5–10 mL) was added, and a white sheet of paper was placed behind the flask. The organolithium solution was added from a 1-mL Hamilton gas-tight syringe. The solution was rapidly stirred under argon. When the titration was completed, the dianion gave an intense yellow color.

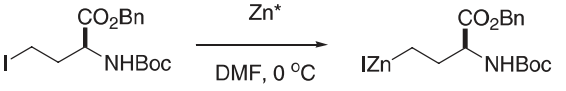
[RLi] in M = mmol of *N*-pivaloyl-*o*-toluidine/volume of RLi in mL

Note: *the volume of n-BuLi solution required to generate the dianion, after formation of the monoanion, is negligible and not included in the titer calculation.*

Reference: Suffert, J. *J. Org. Chem*. **1989**, *54*, 509.

1.2.5 Generation of Zinc Reagent

Organozinc reagents have emerged as a versatile group of organometallic reagents; consequently, the number of reagents available has increased dramatically in recent years. Table 1.8 is a representative subset, but a large number of alkyl- aryl-, and heteroarylorgano zinc reagents are available. For a review of functionalized zinc reagents see Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React*. **2001**, *58*, 417–731.



Zinc dust (325 mesh, 0.147 g, 2.25 mmol, 3 equiv.) was weighed into a 50-mL round-bottomed flask with side arm, which was repeatedly evacuated, heated using a hot air gun, and flushed with nitrogen. Dry DMF (0.5 mL) and trimethylsilyl chloride (6 μL, 0.046 mmol) were added, and the resultant mixture was stirred for 30 min at room temperature. Iodide (0.75 mmol) was dissolved in dry DMF (0.5 mL) under nitrogen. The iodide solution was transferred via a syringe to the zinc suspension at 0 ºC, and the mixture was then stirred. Thin layer chromatography (TLC) analysis (petroleum ether–ethyl acetate, 2:1) showed complete consumption of the iodide within 5–60 min.

Reference: Deboves, H. J. C.; Hunter, C. F. W; Jackson, R. F. W. *J. Chem. Soc. Perkin Trans*. *1*, **2002**, 733–736.

1.2.6 Preparation of Diazomethane

Diazomethane, especially when pure and in large quantities, has been known to be explosive. *Thus, extraordinary caution must be taken to prevent diazomethane from coming into contact with sharp objects. Care must be taken not to allow contact between diazomethane and any metal, ground glass joints, or scratched glassware. In addition, diazomethane solution should not be exposed to direct sunlight or allowed to sit under artificial light for an extended period of time*. For safety concerns see Moore, J. A.; Reed, D. E. *Org. Synth.* **1973**, *Coll. Vol. 5*, 351–354. Diazomethane is never isolated neat, and is typically used in excess (it is a bright yellow solution), and the excess can be quenched with acetic acid to form the easily removed methyl acetate. A safer alternative to diazomethane is the commercially available trimethylsilyldiazomethane ($TMSCHN_2$). $TMSCHN_2$ is sold as a solution in hexanes. See Chapter 2 for this reagent.

EXAMPLE 1

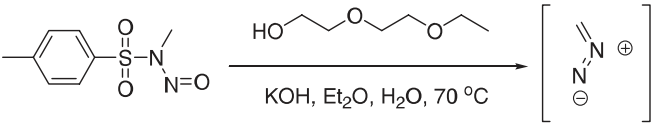


Table 1.8 Some common commercially available zinc reagents

Organozinc reagents (0.5 M in THF)
Propylzinc bromide
Butylzinc bromide
Cyclohexylzinc bromide
3-Ethoxy-3-oxopropylzinc bromide
Phenylzinc bromide
2-Pyridylzinc bromide
2-Thienylzinc bromide

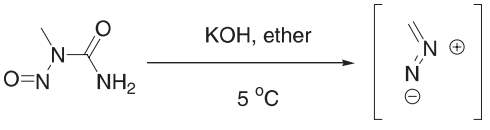
THF, tetrahydrofuran.

See Sigma-Aldrich ChemFiles 2002, Vol. 2, No.5.

Diazomethane was generated with a diazomethane-generating glassware kit (Aldrich). A solution of *N*-methyl-*N*-nitroso-4-toluenesulfonamide (Diazald, 2.23 g, 10.4 mmol) in ether (24 mL) was added dropwise to a mixture of KOH (1.75 g, 31.2 mmol) in H_2O (18 mL), ether (4 mL), and 2-(2-ethoxyethoxy)ethanol (18 mL) kept at 70 ºC. The ethereal solution of diazomethane was continuously distilled into a flask that was ready to use for the next reaction.

Reference: Tchilibon, S.; Kim, S.-K.; Gao, Z.-G.; Harris, B. A.; Blaustein, J. B.; Gross, A. S.; Duong, H. T.; Melman, N.; Jacobson, K.A. *Bioorg. Med. Chem*. **2004**, *12*, 2021–2034.

EXAMPLE 2

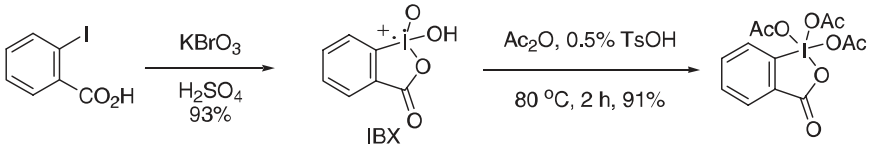


An aqueous solution of potassium hydroxide (40%, 30 mL) was added to diethylether (100 mL), and the mixture was cooled to 5 ºC. Finely powdered *N*-nitroso-*N*-methylurea (10 g) was added in small portions over a period of 1–2 min. The deep yellow ether layer can be decanted readily; it contains about 2.8 g of diazomethane together with some dissolved impurities and water. *Note*: *DO NOT use a glass container with a ground glass joint; however, an Erlenmeyer flask or a test tube is usually suitable. In addition, the vessel should be free of any interior scratches. The ethereal layer may be removed using a flame-polished pipette*.

Reference: Arndt, F. *Org. Synth*. **1943**, *Coll. Vol. II*, 165–167.

1.2.7 Preparation of the Dess–Martin Reagent

The Dess–Martin oxidation is the method of choice for the oxidation of alcohols bearing sensitive functional groups.



CAUTION! The Dess–Martin precursor [1-hydroxy-l,2-benziodoxol-3(1*H*)-one (IBX)] was reported to be explosive under excessive heating (> 200 ºC) or impact. Sporadically, IBX did not decompose explosively at 233 ºC, but melted with browning. However, this *cannot be taken as an indication of absence of explosivity as the same batch showed inconsistent results*. An analytically pure sample (≥ 99%) was subjected to explosibility tests.

A. 1-Hydroxy-l,2-benziodoxol-3(1*H*)-one (IBX). (≥ 95% Purity)

2-Iodobenzoic acid (50.0 g, 0.20 mol) was added all at once to a solution of Oxone (181.0 g, 0.29 mol, 1.3 equiv.) in deionized water (650 mL, 0.45 M) in a 2 L flask. The reaction mixture was warmed to 70–73 ºC over 20 min and mechanically stirred

at this temperature for 3 h. The aspect of the mixture varies consistently during the reaction. The initial thick slurry coating the walls of the flask eventually becomes a finely dispersed, easy to stir suspension of a small amount of solid that sediments easily on stopping the stirring. The suspension was then cooled to 5 ºC and left at this temperature for 1.5 h with slow stirring. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with water (6 × 100 mL) and acetone (2 × 100 mL). The white crystalline solid was left to dry at room temperature for 16 h and weighed 44.8–45.7 g (79–81%).

Mother and washing liquors were oxidizing and acidic. They were treated with solid Na_2SO_3 (70 g, 0.55 mol) and neutralized with NaOH (1 M) before disposal. The internal temperature rose to 30 ºC.

Reference: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem*. **1999**, *64*, 4537–4538.

B. 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (the Dess–Martin reagent)

IBX 100 g was added to a 1-L round-bottomed flask containing Ac_2O (400 mL), $TsOH{\cdot}H_2O$ (0.5 g), and a magnetic stirring bar. The flask was equipped with a drying tube and was immersed in an oil bath at ca. 80 ºC. The mixture was stirred for 2 h and then cooled in an ice-water bath. The cold mixture was filtered through a fritted glass funnel followed by rinsing with anhydrous ether (5 × 50 mL). The resulting white crystalline solid (138 g, 91% for two steps) was quickly transferred to an argon flushed amber-glass bottle and stored in a freezer: mp 134 ºC.

Reference: Ireland, R. E.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899. See also, Meyer, S. D.; Schreiber, S. L. *J. Org. Chem*. **1994**, *59*, 7549–7552.

1.2.8 Preparation of Lithium Diisopropylamide

Lithium diisopropylamide (LDA) is a strong, non-nucleophilic base that is widely used. Because of its reactivity with many solvents, it has historically been generated in the laboratory by reaction of *n*-butyllithium and diisopropyl amine. Recently, LDA has become commercially available as a solution in THF/heptane/ethyl benzene. The commercially available material is frequently colored, making titration difficult.

Freshly prepared LDA has varying stability, being most stable in alkanes and 1:1 alkanes:THF. Homemade LDA should be stored cold to extend its shelf-life. The preparation of LDA is representative of other lithium amide bases, such as lithium tetramethylpiperidide and lithium hexamethyl disilylamide.

To a solution of diisopropylamine (3.44 g, 4.76 ml, 0.0341 mole) in THF (25 mL) at −78 ºC (methanol–dry ice bath) is added a solution of *n*-butyllithium (1.61 M in hexane, 21.1 mL, 0.0340 mol) with stirring under argon. The solution is warmed to 0 ºC in 15 min to provide an approximately 0.7 M solution of LDA.

Reference: Enders, D.; Pieter, R.; Renger, B.; Seebach, D. *Org. Synth*. **1978**, *58*, 113 or Enders, D.; Pieter, R.; Renger, B.; Seebach, D. *Org. Synth*. **1988**, *Coll. Vol. 6*, 542.

1.2.9 Jones Reagent

The Jones reagent is prepared by first dissolving chromium trioxide (70 g, 0.70 mol) in water (100 mL) in a 500 mL beaker. The beaker is then immersed in an ice bath,

18 M sulfuric acid (61 mL, 1.10 mol), and water (200 mL) is added cautiously with manual stirring. The solution is cooled to 0–5 ºC.

Reference: Meinwald, J.; Crandall, J.; Hymans, W. E. *Org. Syn.* **1973**, *Coll. Vol. 5*, 866.

1.3 Chromatography

In this section, two types of chromatography are presented: TLC and flash chromatography.

1.3.1 Thin Layer Chromatography

Reference: Wall, P. E. *Thin Layer Chromatography*; Royal Society of Chemistry: Cambridge (UK), 2005.

The thin layer chromatography (TLC) plates that we buy are slide glasses coated with silica gel. In order to visualize UV-active organic compounds, the silica gel is coated with a layer of fluorescent dye "Flur." Therefore, UV-active compounds can be detected under UV light. Occasionally, non-UV-active compounds are also seen. One case is iodides, which are UV-light quenchers, while another case is inorganic salts, often seen on the baseline; the salts are visualized under UV simply because they cover the fluorescent dye "Flur."

The TLC plates that we buy are somewhat too large. It is a good idea to cut the plates with a diamond-type or carbide roller into smaller plates. Not only does this save costs, it is also faster to develop a smaller TLC plate than a larger one.

Retention factor, R_f, is a measurement of how far up a plate the compound travels. R_f is calculated by *the distance of the center of the spot from the baseline (P or SM)* divided by *the distance of the solvent front from the baseline (S)*. Column volume (CV) is $1/R_f$ (Figure 1.3). These values will be referenced in the discussion of column chromatography.

In general, the eluting strength of commonly used solvents for normal phase chromatography is: stationary phase = silica gel neutral alumina; increasing order proceeds as follows: petroleum ethers < hexanes < cyclohexane < toluene < diethyl ether < dichloromethane < chloroform < ethyl acetate < acetone < ethanol < methanol < acetic acid.

Another useful technique is two-dimensional TLC (Figure 1.4). This method is a simple way of determining if decomposition of a desired product or products will occur on the stationary phase (typically silica gel or alumina). After spotting your compound on the TLC plate and developing the plate, the plate is turned 90º and then developed again. For a single component, one spot should be visible with the same R_f as the spot from the first development. If streaking is observed in the second development and/or new spots arise, decomposition has occurred. For compound mixtures, the final developed spots will fall in a straight line if no decomposition has occurred; however, if the spots do not fall in a straight line or additional spots appear within a lane, decomposition occurred during TLC development. Decomposition is usually an indication that a chemical interaction occurred with the stationary phase.

1.3.2 Recipes of Common Thin Layer Chromatography Stains

For compounds that do not visualize well under UV, TLC stains are necessary to visualize the spots. Listed herein are some popular TLC stains often used in an

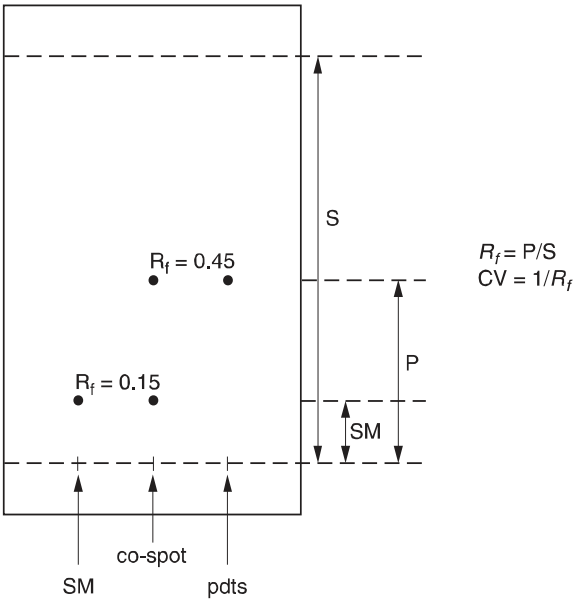


Figure 1.3 One-dimensional TLC.

organic chemistry laboratory. Most of these visualization stains require the submersion of the TLC plate in a solution of stain, carefully blotting excess stain, and then heating the stained TLC plate on a hot plate or with a heat gun. *All of these manipulations should be performed in a well ventilated hood, particularly the heating step, because many of these stains are toxic!*

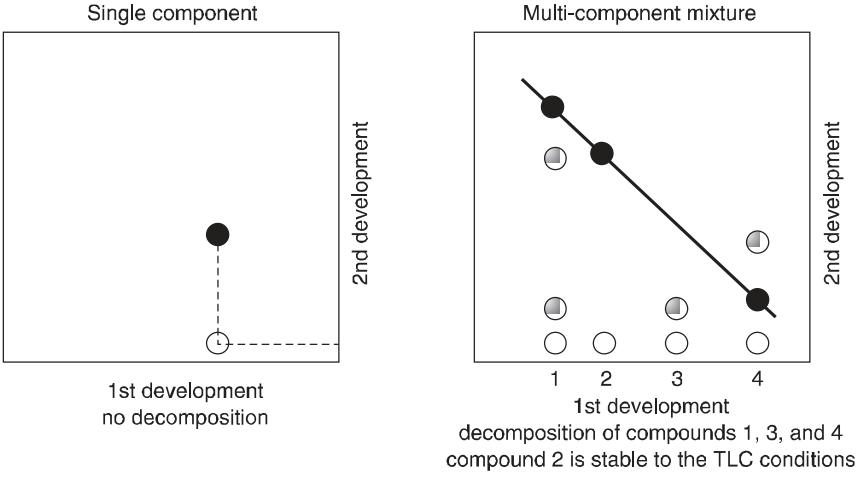


Figure 1.4 Two-dimensional TLC.

p-Anisaldehyde Stain

The greatest advantage of this stain is that different colors are manifested on TLC on heating for different molecules. Therefore, molecules can be differentiated even if they have the same R_f values. The disadvantage is its strong but pleasant odor release during heating (*toxic, in the hood!*).

p-Anisaldehyde	12 g (11 mL)
Ethanol	500 mL
Concentrated H_2SO_4	5 mL

Cerium Sulfate Stain

General stain. Most compounds are stained brown or yellow.

Cerium Sulfate (8 g)

15% sulfuric acid (100 mL)

Hanessian Stain (cerium molybdate stain)

One of the most sensitive stains which detects most functional groups. The disadvantage is that everything stains blue.

$Ce(SO_4)_2$	5g
$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$	25 g
Concentrated H_2SO_4	50 mL
H_2O	450 mL

I_2 or I_2 in Silica Gel

Everything stains yellow. Solid I_2 can be added to a developing chamber and the TLC plate developed by placing the plate in the chamber. Alternatively, the I_2 can be dispersed on silica gel in a developing chamber, and the TLC plate immersed in the silica gel; the silica gel development tends to be faster. The spots will fade, but the plate can be redeveloped by placing the plate back into the I_2 chamber.

$KMnO_4$

Detects molecules with an "oxidizable" functional group. Relatively insensitive, everything stains yellow, frequently even without heating. Eventually, the entire plate will turn yellow and the spots will be indistinguishable from the background.

$KMnO_4$	6 g
K_2CO_3	40 g
5% aqueous NaOH	10 mL
H_2O	600 mL

Ninhydrin Stain

Especially sensitive to amino acids, as well as amines and anilines. Avoid contact with skin, or all of your friends will know that you have had an affair with nihydrin.

0.25% of nihydrin in water

Phosphomolybdic Acid (PMA)

Everything stains blue–green. A very sensitive stain, possibly used most often. A 20% PMA in ethanol is commercially available; this should be diluted to 5% with ethanol.

Phosphomolybdic acid	12 g
Ethanol	500 mL

Vanillin Stain

Different colors are manifested on heating for different molecules. Smells great, too (*do not inhale intentionally!*).

Vanillin	12 g
Ethanol	250 mL
Concentrated H_2SO_4	50 mL

1.3.3 Flash Chromatography

Reference: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

One of the most versatile methods of purifying reaction mixtures is flash chromatography using silica gel. Surprisingly, silica gel is one of the most hazardous chemicals in an organic chemistry laboratory. Inhalation of the fine powder of silica gel could cause lung diseases, even lung cancer. Therefore, flash chromatography using silica gel should be carried out in a fume hood. Glass chromatography columns must be inspected routinely for cracks to ensure that the glass is strong enough to withstand the pressure that will be applied. Care must be taken not to apply too much pressure to the column.

Before setting up a column for the separation of the reaction mixture, the type of silica gel to use must be decided. The two most common grades of silica gel are gravity silica gel and silica gel for a flash column. Gravity silica gel, more suitable for easy separations, is composed of larger sized silica gel, 0.062–0.200 mm (70–230 mesh ASTM). In contrast, silica gel for the flash column, more suitable for more difficult separations, is finer, 0.040–0.063 mm (230–400 mesh ASTM). Regarding flash chromatography, Still's flash chromatography technique is the standard procedure. A typical flash chromatography setup is shown in Figure 1.5.

According to Still's 1978 *Journal of Organic Chemistry* paper (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923), the size of the glass column depends on the scale of the separation. First, a solvent system is chosen based on its polarity so that the desired product has an R_f of 0.3. For a mixture of 1 g of compounds, 25 g of silica gel is used, on average.

The greatest advantage of Still's flash chromatography technique is its expediency. On average, a column should not take more than 10–15 min. The rule of thumb is, if it takes more than 30 min for a routine chromatographic separation, it is likely to be unsucessful or the flow rate is too slow. The trick is to select a column of appropriate diameter. The height of the silica gel should not be taller than 6 inches, changing the diameter to accommodate the endpoint, where 25 g of silica gel is loaded for each 1 g of the reaction mixture to be separated. For more difficult separations, a ratio of 100:1 to 200:1 silica gel to mass of mixture is not unusual. As a consequence, run times are extended.

In the example in Figure 1.3, the product will come out after 2.2 (1/0.45) column volumes, while the starting material will come out after 6.7 column volumes (1/0.15). The column volume is approximately 1.25 times the mass of silica gel used (e.g., a column with 2 g of silica gel has a column volume of approximately 2.5 mL). In this case, a more polar solvent system could be developed to make the compounds come off the silica gel more quickly, or a silica gel:compound ratio of less than the 25:1 could be used. The fraction size should be approximately twice the column volume; if ΔCV is < 1, this will obviously have to be smaller.

On the other hand, although it is a good idea to start the solvent system to ensure the R_f values range from 0.2 to 0.3, it is even better to apply a gradient solvent system by increasing the polarity. For instance, gradually changing the solvent system from 10% EtOAc/hexane to 50% EtOAc/hexane will afford a much faster separation than running the column at a constant 10% EtOAc/hexane solvent system. For very polar compounds, small quantities of aqueous ammonium hydroxide or triethyl amine (usually < 5% by volume) are added to a binary eluent such as CH_2Cl_2/MeOH to decrease "streaking" of amines down the column. The same argument holds true when purifying acids, although small quantities of acetic acid are used in the binary solvent mixture.

In addition to traditional flash column chromatography, there are now commercially available low and medium pressure chromatography systems. Manufacturers

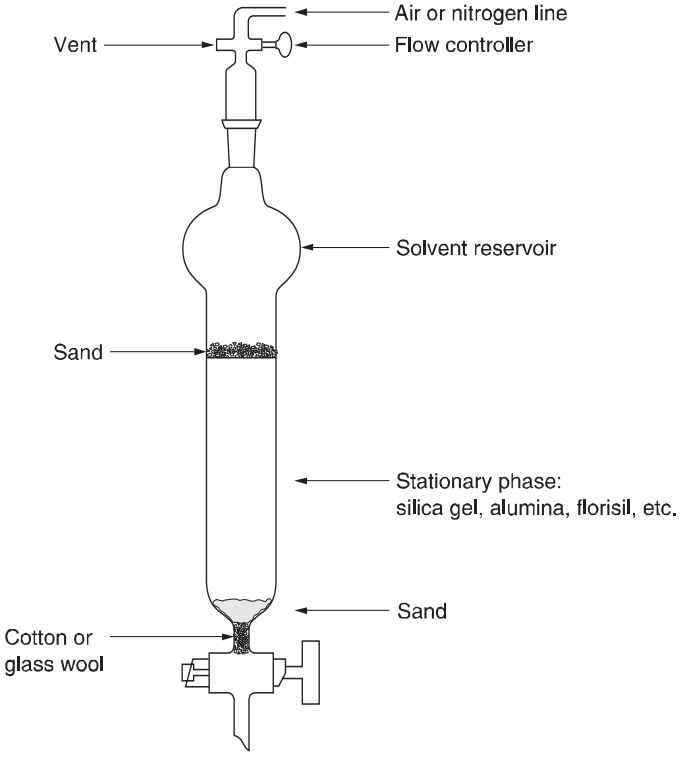


Figure 1.5 Typical flash chromatography setup.

include Analogix, Biotage, Teledyne ISCO, and many others (see Figure 1.6). The sophistication of these commercially available instruments varies and this is reflected in cost. An effective yet relatively inexpensive setup involves a solvent reservoir made of stainless steel and a commercial silica gel column housed in a metal chamber (i.e., Analogix F12/40 System™). The solvent is pushed from the reservoir via air or nitrogen through the column. The eluent is then collected in test tubes, as seen in Figure 1.6b. More elaborate systems are computer-driven which include interactive software, an electric pump/solvent mixer, UV detector, and automated fraction collector. These systems allow for tremendous flexibility and advantages over the traditional flash chromatography (i.e., Teledyne-Isco CombiFlash®Companion®). They include prepacked columns, high flow rates with good to excellent resolution of solutes, shorter run times, "true" solvent gradients, fraction monitoring by UV, and manipulation of the chromatographic conditions during the purification run. In addition, prepacked reverse phase columns (C18) are available. These instruments can separate samples in the milligram to kilogram range. Larger scale purification systems are also available that purify kilograms of material (i.e., Biotage Flash 400™).

1.4 Crystallization

Crystallization is the most desirable method of purification on a large scale for solids. Crystallizations require less solvent, time, and resource once they have been developed. Even above a 10 g scale, a little time invested on crystallization can save hours in front of a rotary evaporator.

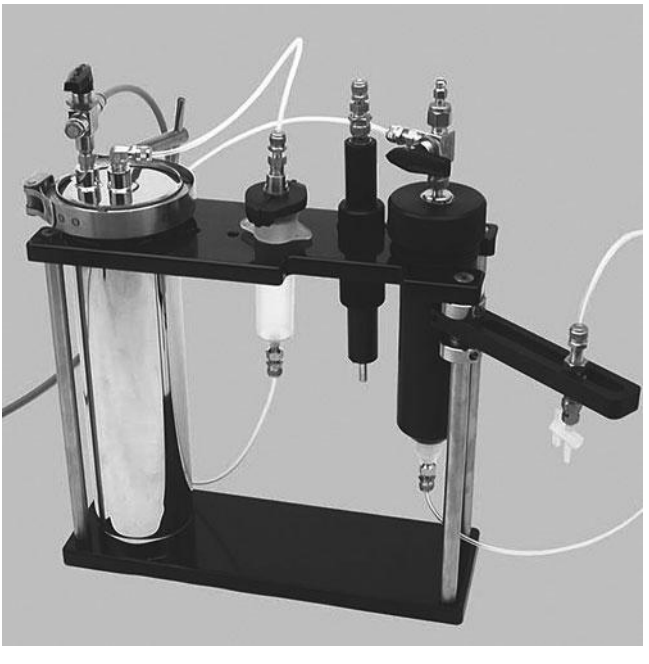


Figure 1.6 Commercial flash chromatography setups. (A) Flash 12/40 System™ (reprinted with permission from Analogix).

The ideal situation is a single solvent crystallization (Table 1.9). The compound of interest is not soluble in a solvent at low temperatures but very soluble at higher temperatures. In cases such as these, the material should be dissolved in a minimum amount of hot solvent and the solution allowed to cool slowly with stirring.

A good first pass approach in cases where a compound will not crystallize from a single solvent is to find a solvent in which the compound of interest is relatively soluble and a solvent miscible in the first in which the compound is not soluble (Table 1.10). Dissolve the compound in a minimum amount of the first solvent near the lower of the two boiling points, and then slowly add a second solvent, in which the compound is not soluble, until the solution becomes cloudy. If the antisolvent has a much lower boiling point than the solvent, allow the solution to cool slowly with stirring and add seeds periodically until the solids persist.

Very impure compounds typically do not crystallize well. Additionally, the target compound can oil out of solution if the solution reaches saturation above the melting point. Crystallizations for purification should be stirred. Crystallizations benefit by seeding with crystalline material; therefore, it may be beneficial to purify a small amount of material by column chromatography to determine the melting point, and to have seeds before proceeding with a crystallization.

Growing crystals for structure determination relies on similar principles, but requires slower crystal growth. If the crystals grown as described above are not sufficiently large for X-ray analysis, they have grown too fast. To slow the growth, slow evaporation can be attempted, where the compound is dissolved in an excess of

Figure 1.6 (*cont.*) (B) CombiFlash®Companion® (reprinted with permission from Teledyne-ISCO).

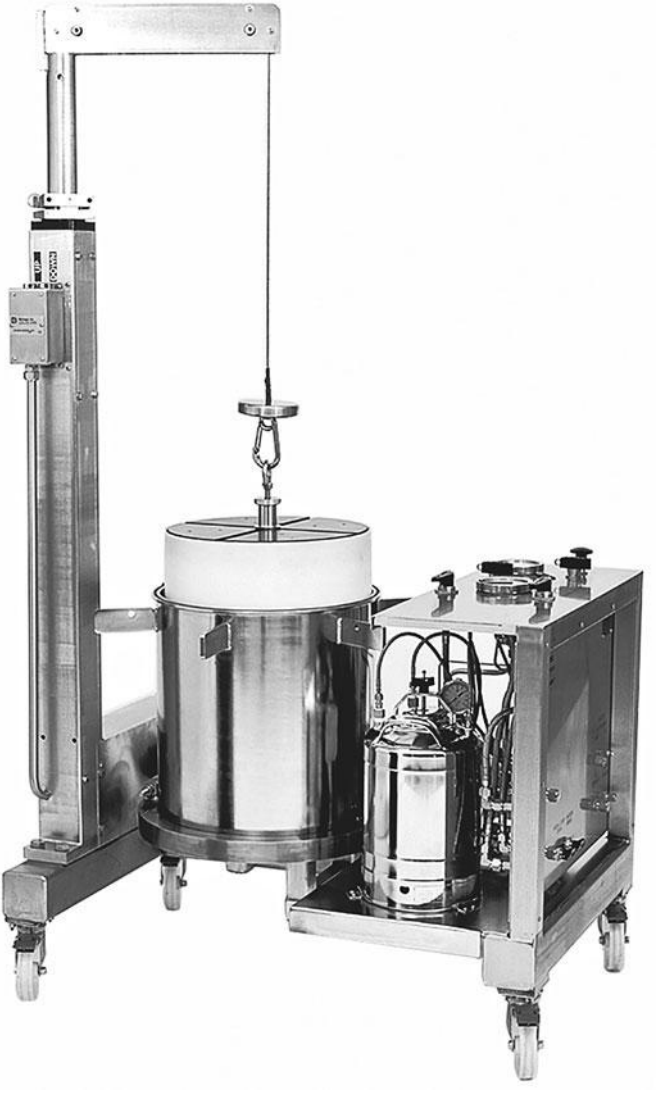


Figure 1.6 (*cont.*) (C) Flash 400™ (reprinted with permission from Biotage).

solvent (either single solvent or mixture) and that solvent is allowed to slowly evaporate. Alternatively, a solution of the compound in a vial can be placed in a larger flask containing an antisolvent and capped (Figure 1.7). The solvents will slowly exchange, resulting in crystallization.

1.5 Residual Solvent Peaks in Nuclear Magnetic Resonance

One of the daily nuisances of an organic chemist is interpreting residual solvent peaks in NMR spectra. One trick is to dissolve the compound with the solvent whose deuterated solvent one is going to use for taking the NMR spectrum. For instance, if $CDCl_3$ is the solvent being used for taking the NMR spectrum, $CHCl_3$ can be employed to

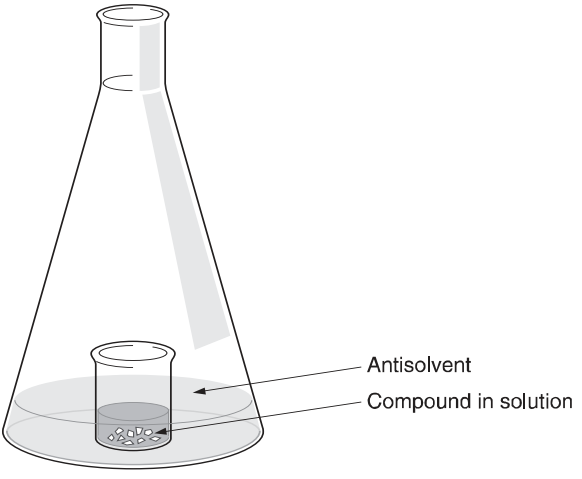


Figure 1.7 Crystallization setup.

dissolve the product and remove it in vacuo. After repeating the process a few times, most volatile residual solvents will be gone and a clean spectrum can be obtained.

As $CDCl_3$ is one of the most popular deuterated solvents used in the organic laboratory, the chemical shifts in ^1H NMR spectra of the most common laboratory solvents as trace impurities are in Table 1.11.

It is often the case that the chemical shifts of the same compounds are not the same in different deuterated solvents. To that end, d_6-DMSO ^1H NMR data are listed in Table 1.12.

Table 1.9 Common crystallization solvents

Solvent	Boiling point (°C)†	Dielectric constant†
Diethyl ether	34.5	4.27
Dichloromethane	40	8.93
Acetone	56	21.01
Chloroform	61	4.81
Methanol	64.6	33.0
Tetrahydrofuran	65	7.52
Hexane	68.7	1.89
Ethyl acetate	77.1	6.08
Ethanol	78.2	25.3
Benzene*	80.0	2.28
Acetonitrile	81.6	36.64
Isopropyl alcohol	82.3	20.18
Heptane	98.5	1.92
Water	100	80.10
1,4-Dioxane	101.5	2.22
Toluene	110.6	2.38
Acetic acid	117.9	6.20
Butyl acetate	126.1	5.07
N,N-dimethylformamide	153	38.25

†Lide, D. R., Ed. *Handbook of Chemistry and Physics*, 84th ed.; CRC Press LLC: Boca Raton, FL, 2003, pp. 8–129.
*Toluene is an excellent substitute for benzene.

Table 1.10 Miscible solvents

Diethyl ether	Acetone, ethyl acetate, ethanol, methanol, acetonitrile, hexanes
Dichloromethane	Acetic acid, acetone, toluene, ethyl acetate, methanol, isopropyl alcohol
Acetone	Toluene, dichloromethane, ethanol, ethyl acetate, acetonitrile, chloroform, hexanes, water
Chloroform	Acetic acid, acetone, toluene, ethanol, ethyl acetate, hexanes, methanol
Methanol	Dichloromethane, chloroform, ethyl ether, water
Hexanes	Toluene, dichloromethane, chloroform, ethanol
Ethyl acetate	Acetic acid, methanol, acetone, chloroform, dichloromethane
Ethanol	Acetic acid, acetone, chloroform, dichloromethane, diethyl ether, hexanes, toluene, water
Toluene	Acetone, diethyl ether, chloroform, dichloromethane, ethanol, acetonitrile
Water	Acetic acid, acetone, ethanol, methanol, acetonitrile

Adapted from Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals,* 4th ed.; Butterworth-Heinemann: Oxford, **1996**, p.35.

Table 1.11 ^{1}H NMR data of the most common laboratory solvents as trace impurities in $CDCl_3$ (in ppm)

Solvent	Pattern, chemical shift (δ)	Pattern, chemical shift (δ)	Pattern, chemical shift (δ)
Chloroform	s, 7.26	—	—
Acetic acid	s, 2.10	—	—
Acetone	s, 2.10	—	—
t-Butyl methyl ether	s, 1.19	s, 3.22	—
Dichloromethane	s, 5.30	—	—
Diethyl ether	t, 1.21	q, 3.48	—
Dimethylformaldehyde	s, 8.02	s, 2.96	s, 2.88
Dimethylsulfoxide	s, 2.62	—	—
et alhyl acetate	q, 4.12	s, 2.05	t, 1.26
Grease	br s, 1.26	m, 0.86	—
n-Hexane	m, 1.26	t, 0.88	—
Methanol	s, 3.49	s, 1.09	—
Pyridine	m, 8.63	m, 7.68	m, 7.29
Silicon grease	s, 0.07	—	—
Tetrahydrofuran	m, 3.76	m, 1.85	—
Toluene	s, 7.19	s, 2.34	—
Triethylamine	t, 2.53	t, 1.03	—
Water	s, 1.60	—	—

Reference: Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.

Table 1.12 ^{1}H NMR data of the most common laboratory solvents as trace impurities in d_6-DMSO (in ppm)

Solvent	Pattern, chemical shift (δ)	Pattern, chemical shift (δ)	Pattern, chemical shift (δ)
Acetic acid	s, 1.91	—	—
Acetone	s, 2.09	—	—
t-Butyl methyl ether	s, 1.11	s, 3.08	—
Chloroform	s, 8.32	—	—
Dichloromethane	s, 5.76	—	—
Diethyl ether	t, 1.09	q, 3.38	—
Dimethylformaldehyde	s, 7.95	s, 2.89	s, 2.73
Dimethylsulfoxide	s, 2.54	—	—
Ethyl acetate	q, 4.03	s, 1.99	t, 1.17
Grease	—	—	—
n-Hexane	m, 1.25	t, 0.86	—
Methanol	s, 4.01	s, 3.16	—
Pyridine	m, 8.58	m, 7.79	m, 7.39
Silicon grease	—	—	—
Tetrahydrofuran	m, 3.60	m, 1.76	—
Toluene	s, 7.18	s, 2.30	—
Triethylamine	t, 2.43	t, 0.93	—
Water	s, 3.33	—	—

Reference: Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.