Organic Reaction Workup Formulas for Specific Reagents

Reactions with Triphenylphosphine oxide:

If your product is stable and relatively-non polar, a good way of removing triphenylphosphine oxide (produced in Wittig, Mitsunobu, bromination, and other reactions) is to concentrate the reaction mixture to a lower follow, suspend the residue in pentane (or hexane)/ether and filter over a silica plug. The compound can then be eluted with ether, leaving most of the phosphine oxide at the top of the column. Sometimes it is necessary to repeat this procedure 2-3 to remove most of the phosphine oxide.

Copper Salts:

 Quench rxn w/ sat NH₄Cl aq solution. stir up to a few hours at r.t. or until the solution becomes a dark blue (indicates complexation).
Remove aq layer and wash organic a few times with sat. NH₄Cl aq.
Isolate crude material as in step 4 above.

Boron Compounds: a number of boron compounds and residues (for example from hydroboration, allylation, reduction, Suzuki coupling, etc) can be removed by concentrating the reaction mixture repeatedly from MeOH. This process forms (MeO)₃B, which is volatile.

R₃Sn-X Byproducts:

1. Byproducts of tin based reactions such as Bu₃SnBr can be removed by treatment with AlMe₃ to create the nonpolar Bu₃SnMe or NaOH to create the polar Bu₃SnOH. See: P. Renaud, E. Lacote, L. Quaranta *Tetrahedron Lett.* **1998**, *39*, 2123. (partially taken from the Merlic Group at UCLA, <u>The Organic Companion</u>)

2. Filter through a mixture of KF/Celite

3.

- a) Dilute rxn with suitable organic solvent
- b) Add aqueous phase (water, sat. NH₄Cl, etc.)

c) Remove aq layer and wash organic phase 2-3 times with 1M KF aq solution. Shake in sep funnel for up to 1 minute for each wash. Solid Bu_3SnF precip may form at organic/aqueous interface. If a problem, filter through celite.

d) Wash aq 1 X brine, dry organic phase and remove solvent.

4. In many Stille reactions, the Bu₃SnX junk can be almost entirely removed by filtering through (or columning directly) on silica made up with ~2-5% triethylamine in the eleunt. Run in the same solvent. Quicker than stirring with aq, KF, and more fun than grinding a big bowl of toxic KF with silica or celite for a good dispersion. (contributed by <u>Graham Cumming</u>)

5. For Bu_3SnH : add I_2 to convert $Bu_3SnSnBu_3$ and unreacted Bu_3SnH to Bu_3SnI , KF treatment (see above) then converts this to Bu_3SnF , which is more easily removed. (contributed by <u>Thomas Pettus</u>)

Metal Salts

Many transition metals can be removed by precipitation of the sulfides. Wash with aqueous sodium sulfide. If necessary, adjust pH to create H_2S .

Some transition metals can be removed by aqueous extraction with tris(hydroxymethyl)phosphine. See: R. H. Grubs *Tetrahedron Lett.* **1999**, *40*, 4137.

Aluminum based Reductions:

A. To workup a reaction containing x g lithium aluminum hydride:

- 1. Dilute with ether and cool to 0° C
- 2. Slowly add x mL water
- 3. Add x mL 15 % aqueous sodium hydroxide
- 4. Add 3x mL water
- 5. Warm to RT and stir 15 min
- 6. Add some anhydrous magnesium sulfate
- 7. Stir 15 min and filter to remove salts
- B. To workup a reaction containing x mmol of an agent such as Diisobutyl aluminum hydride (Dibal):
 - 1. Dilute with ether and cool to 0° C
 - 2. Slowly add 0.04x mL water
 - 3. Add 0.04x mL 15 % aqueous sodium hydroxide
 - 4. Add 0.1x mL water
 - 5. Warm to RT and stir 15 min
 - 6. Add some anhydrous magnesium sulfate
 - 7. Stir 15 min and filter to remove salts

Titanium: Quench with Aqueous ammonium chloride, the titanium byproduct will partition into the aqueous layer during workup.

Chromium Oxidations:

1. PCC/PDC: Filter the reaction mixture through a pad of florisil.

2. Jones: Add isopropanol until the reaction turns from orange/red to green: this indicates that the oxidant has been consumed.

m-CPBA:

If reaction is done in refluxing DCE (for example), cool reaction mixture to 0°C to precipitate out all m-CPBA. Then add 10% aqueous solution of Na₂SO₄. Two layers form. Separate and extract with DCM. Repeat the addition of Na₂SO₄ several times then combine all organic layers, wash with saturated solution of NaHCO₃, then saturated aqueous solution of NaCl, then dry (MgSO₄) and evaporate under reduced pressure. If purifying product by FCC, any m-CPBA still present is easily separated as it is UV active, extremely polar and it ends to deposit on column tip during purification. This is easily taken care of as m-CPBA is soluable in EtOAc.

DCC:

Filter the reaction mixture through a medium frit, rinsing with a minimal amount of reaction solvent, then work up. Depending one runs reaction in dioxane, THF, DMF, dichloromethane, etc., but urea is mostly insoluble in most solvents and this is a good way to get rid of it (the rest can be flashed away pretty straightforwardly). If it is too soluble, one can concentrate the reaction mixture first and take it up in ether, then filter and rinse. (contributed by <u>Philippe Rabbat</u>)

Tricky Reaction Solvents:

When you have to mix solvents for an aqueous workup, complications can occur.

- Acetonitrile: Soluble in water. If convenient, remove solvent before workup to avoid losing polar products. If product is very nonpolar, partition between hexanes and water and carry out aqueous extraction. On small scale, you can dilute with a lot of the extraction solvent, and washed several times. Acetonitrile will partition into the aqueous layer
- Alcohols: Miscible with both water and organic solvents, alcohols do not cooperate during the typical aqueous workup. Remove the solvent by rotoevaporation first.
- THF and Dioxane: These ethers are water soluble. If diluted sufficiently with extraction solvent, and washed several times, they will partition into the aqueous layer. However, sometimes product goes along with them, and sometimes emulsions form. It is safer to remove THF by rotoevaporation before workup if practical, especially for large scale procedures. Dioxane is high boiling, usually making rotoevaporation impractical.
- Aromatic solvents: These are very nonpolar and will usually stay in the organic layer. Benzene is miscible with water and can lead to emulsion formation. It should be either removed by rotoevaporation before workup, or diluted well with the extraction solvent before washing with water.
- DMF or DMSO: Very polar and high-boiling solvents that are difficult to remove. If your product is not dangerously polar, dilute with lots and lots of water before extracting with a nonpolar solvent. Then thoroughly wash the organic layer with water.

Rule of Thumb (see all): For 5 mL of DMF or DMSO, use 5 X 10 mL of water during the aqueous wash. This should remove all of the DMF or DMSO.

Two aqueous washes to remove DMF: 1. 5% LiCl (aq) 2. 0.5 N HCl

Boc groups will survive the dilute HCl wash. TMS groups may not.

Amine solvents (pyridine, di- and trialkylamines): Amines will partition into the organic layer during a typical aqueous workup. However, they become water soluble if you

- 1. Wash the organic layer several times with dilute HCl solution. The protonated amine will partition into the aqueous layer. For use with acid stable target compounds only.
- 2. Wash the organic layer several times with 10% copper sulfate (aqueous and blue). The copper-complexed amine will partition into the aqueous solution, which turns purple. Continue to wash with the copper sulfate solution until no color change is observed.

Rule of Thumb (see all): For 5 mL of an amine solvent, use 5 X 10 mL of the 10% aq. $CuSO_4$ solution during the aqueous wash. This should remove all of the amine.

Aqueous Solutions for Workup

Mildly Acidic

- Ammonium chloride, pH 5-6 (to neutralize)
- 1N or 2N HCl, pH 1 (to neutralize or acidify)

Brine: Removes residual water from the organic layer. The last wash in every workup

For Special Purposes:

- Sodium thiosulfate (10%): to remove bromine or iodine
- Rochelle's salt (10%): to remove aluminum salts
- Copper sulfate (saturated): to remove amines
- Potassium fluoride: to remove trialkyltin byproducts
- Aqueous ammonium hydroxide/ ammonium chloride (pH 8): to remove copper (I) salts

Drying Methods

- Magnesium sulfate: Fast, always works, but kind of messy.
- Sodium Sulfate: convenient for small scale drying- it is very easy to filter. You should start with a clear organic layer (washed with brine, and not poured into a wet flask). Drying takes longer than for magnesium sulfate. Sit it over the drying agent ~15 minutes for dichloromethane, ~30 minutes for ethyl acetate. It does not work well for ether.
- Celite: Sometimes it is useful to filter small scale reactions through Celite to remove trace water.

Miscellaneous Tricks and Advice

- Azeotropes: Often traces of a high boiling solvent or other impurity can be removed from a product or reaction mixture by concentration of a solution of the compounds from an appropriate solvent. This works because higher boiling solvents often azeotrope with lower boiling solvents, forming an easy to remove binary distillate. For an extensive table of azeotropic mixtures, see The Chemists Companion.
 - 1. **Pyridine**: repeated (2-3 times) concentration of a reaction mixture containing pyridine from heptane, cyclohexane, or toluene.
 - 2. **Water**: organic compounds are conveniently dried by concentration (rotavap or on the vacuum pump) by concentrating the compound to be dried from benzene or especially tolunne. This technique is also useful for removal of water from organic hydrates (eg. NMO) by concentrating the compound from toluene 1-3 times followed by drying in a vacuum dessicator.
- To pull aqueous soluble organics out of the aqueous phase when CH₂Cl₂, EtOAc, Et₂O, etc. don't work. (submitted by <u>Bill Spencer</u>, Albany Molecular Research, Inc.)

Problem (Workup Nightmare #1): Upon combination of organic and aqueous solutions, a gooey or insoluble precipitate appears, which floats between the two layers and obscures the border.

Solution: Keep washing with water until most of the goo is removed. Then use copious drying agent, and with luck, the goo will be absorbed and you will be able to filter it away.

Problem (Workup Nightmare #2): When an aqueous solvent is added to the diluted reaction mixture, an emulsion forms. All efforts to resolve the layers fail, your solution has swollen to gargantuan proportions, and you can't find or can't lift a separatory funnel large enough to hold it

Solutions:

- If an emulsion forms during workup of a reaction, next time try evaporating the solvent first, then taking the residue up in the solvent for the extraction.
- Wait half an hour to see if separation will occur on its own. Then think twice before introducing more aqueous solution.
- Add solid NaCl to the emulsion- very briny solutions sometimes separate better.

- Last resort- especially when the solution is already dilute- Try diluting the organic layer significantly-5X or 10X.
- Filter the whole thing through Celite

Problem (Workup Nightmare #3): During Acid/Base Workup, the expected precipitate does not form.

Solution: See Acid/Base Workup.

Problem (Workup Nightmare #4): Upon addition of aqueous bicarbonate, the organic layer becomes a graceful fountain, coating the inside of your fume hood.

Solution: When you repeat the procedure, add aqueous bicarbonate carefully, shake gently, and vent the separatory funnel often.

Problem (Workup Nightmare #5): Addition of aqueous solution to your black organic reaction mixture leads to a uniform black mixture. The solution in the addition funnel is opaque, and you can't see the border between the organic and aqueous layers.

Solution: Try adding ice, which will float on the water, between the layers.

Problem (Workup Nightmare #6): The aqueous solution you use to wash the organic layer turns yellow, orange, brown or pink- the first ten times you try it.

Solution: If the color is caused by excess halogen reagent from your reaction mixture, try washing with sodium thiosulfate. The solution should become instantly clear- if it does not and you still suspect halide, try stirring vigorously in an Erlenmeyer for 10-15 minutes to complete the reduction of halogen molecules.

Problem: (Workup Nightmare #7): After workup, you can't find your product.

Explanations and Solutions:

• Your product may be soluble in the aqueous layer- check it (you still