

*Unconventional reaction media: A solvent-based discovery  
lab for first-year undergraduates*

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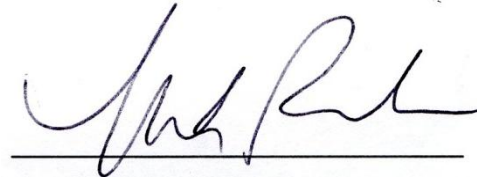


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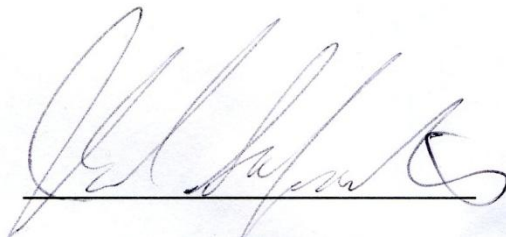


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**Abstract:**

A general chemistry laboratory that illustrates the effectiveness and benign nature of unconventional reaction media is outlined in a three step procedure: 1) a solventless condensation reaction between two solids, 2) an oxidative coupling reaction in the presence of a liquid carbon dioxide solvent, and 3) the synthesis of an organic-transition metal complex in aqueous solvent. This laboratory exercise is designed illustrate the advantages and utility of alternative solvents through a straightforward procedure with visually qualitative results while further exploring the function of solvents in the synthetic process. The laboratory experiments address waste prevention and the use of innocuous solvents, thus also providing students with an excellent introduction to several principles of green chemistry.

## **Introduction**

### *Solvents*

The use of solvents is seemingly inherent in many synthetic transformations. A well-chosen solvent aids in the manipulation of chemicals but is not an integral part of the molecules involved. The solvent allows high reactant mobility in a homogeneous environment and a medium for the exchange of mass and energy, while often modulating the reactivity of substrates<sup>1</sup>. Solvents are often the largest volumetric constituents in organic reactions, thus greatly contributing to the waste, cleanup, and hazards involved with those reactions.

### *Health and Environmental Implications*

The chemical industry remains a major contributor to environmental pollution largely due to the prevalence of hazardous solvents in chemical processes. Five out of the top ten chemicals disposed of by the chemical industry in the mid-1990s were the organic solvents: methanol, toluene, xylene, methyl ethyl ketone, and methylene chloride<sup>2</sup>. Organic solvents are often flammable and hazardous. Halogenated solvents such as methylene chloride, chloroform, perchloroethylene, and carbon tetrachloride have been identified as human carcinogens while benzene, many other aromatics, and hydrocarbons have been implicated<sup>3</sup>. With heightened regulations regarding the use and disposal of many organic solvents, the search for alternative solvents with desirable processing characteristics and fewer health and environmental hazards is of great significance<sup>1</sup>.

Green chemistry is chemical design that minimizes the use and generation of hazardous substances to avoid waste problems before they occur. Accordingly, the use of safe and environmentally benign substances, including solvents, whenever possible is an important aspect of greener chemical practice<sup>3</sup>.

#### *Instances of Alternative Solvents*

The most desirable alternative solvent is no solvent at all. Solventless reactions are especially advantageous for human health and the environment as the generation of solvent waste is nonexistent. Solventless reactions can reduce time spent under reflux conditions<sup>3</sup>. Although refluxing on a laboratory scale does not require great amounts of energy, the energy requirements for refluxing on an industrial scale can be very large. Many solventless reactions are thought to be solid-solid interactions; however, many possess a liquid melt-precondition for rapid chemical reaction<sup>4</sup>. Upon mixing or grinding a melt phase is observed. Through this phase the reactants have increased mobility of liquid phase conditions without the dilution effects of a solvent. Documented solventless reactions include aldol condensations, Michael addition, Diels-Alder, Baeyer Villiger oxidations, bromination of aromatics, and etherification of alcohols<sup>1,4-6</sup>, with new research continually expanding the scope of this technique.

When a solvent must be used, non-hazardous and inexpensive solvents that do not compromise reactivity and specificity are desired. One such example is carbon dioxide, which has become a widely used green solvent in industrial processes<sup>7-9</sup>. Carbon dioxide is a nonflammable, relatively non-toxic, and environmentally benign solvent when used in its liquid and supercritical phases.



The phase diagram in Figure 1 illustrates that carbon dioxide is a supercritical fluid above its critical point of 31.1 °C and 72.9 atm while the minimum temperature and pressure required for liquid carbon dioxide to exist are -56.6 °C and 5.1 atm, respectively<sup>10</sup>.

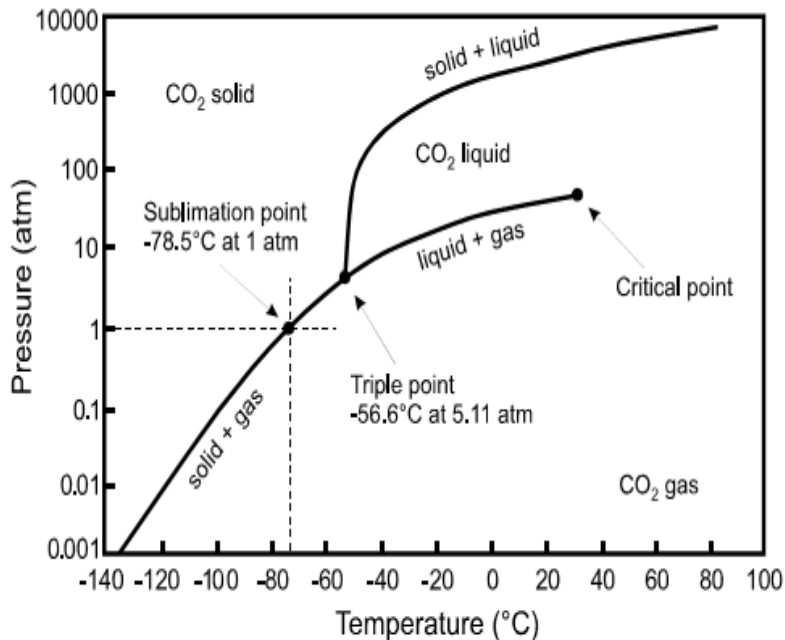


Figure 1: Carbon dioxide pressure-temperature phase diagram showing the triple point and critical point.

Although carbon dioxide is a greenhouse gas, liquid and supercritical carbon dioxide are obtained *from* and released *into* the atmosphere resulting in no net emission<sup>11</sup>. With tightened industrial regulations, supercritical fluid extraction technologies have become common replacements for conventional organic solvents and steam distillations. The tunable solvent properties, inert nature, resistance to oxidation, and low toxicity of supercritical carbon dioxide have led

to an increase of industrial processes that use supercritical carbon dioxide as a solvent<sup>11</sup>.

Although much attention has been directed towards supercritical carbon dioxide, liquid carbon dioxide has great utility as a benign solvent. The pressures and temperatures required for carbon dioxide to exist in the liquid state are much lower than the conditions necessary for the supercritical phase; consequently, any tendency toward unstable product degradation is reduced<sup>11</sup>. Like supercritical carbon dioxide, desired surface tension and viscosity values of liquid carbon dioxide can be attained through the manipulation of temperature and pressure<sup>11</sup>. Liquid carbon dioxide is used as a solvent in the industrial extraction of essential oils<sup>12,13</sup>, in dry cleaning as a replacement for perchloroethylene<sup>14</sup>, and in materials synthesis<sup>15</sup>. When extractions and reactions are complete, release of pressure causes the vaporization of the carbon dioxide solvent off of the products<sup>11</sup>, eliminating the need for solvent separation.

Water is also an instance of an alternative solvent for organic reactions. Water is an exceptionally benign substance due to its high heat capacity and unique reduction/oxidation stability<sup>16</sup>. This high heat capacity also allows for excellent control of reaction temperature as water readily facilitates heat exchange<sup>17</sup>.

In most organic reactions, water creates a separate phase and thus does not dilute like most traditional solvents. The separate solvent phase can result in higher thermodynamic activities and rate accelerations due to solvation without

dilution<sup>18</sup>. Although insoluble reactants deleteriously affect some organic reactions, insolubility of reactants has become a desired characteristic for other synthetic transformations. Certain Diels Alder reactions are accelerated when performed ‘on water’. The reaction between cyclopentadiene and butenone proceeds 730 fold faster in water than in isooctane<sup>18</sup>. The axiom from the days of alchemy, “corpora non agunt nisi soluta” (substances do not interact unless dissolved)<sup>16</sup> is apparently untrue for certain organic reactions that take place in an aqueous environment. The types of organic reactions employing water as a solvent are broad ranging and include pericyclic reactions, carbanion equivalents, carbocation equivalents, radicals, carbenes, transition metal catalysis, and oxidation/reductions<sup>16, 19</sup>.

As aqueous organic reactions become industrially prevalent, the need for water soluble/tolerant catalysts increases. In certain on water reactions with both aqueous and organic phases, water soluble catalysts can exhibit higher selectivities and activities that are usually only associated with homogeneous systems. Additionally, the isolation of insoluble organic products and the recovery of catalysts can be reduced to simple phase separations<sup>20,21</sup>.

## **Background**

### *Greener Chemistry for the Undergraduate Laboratory*

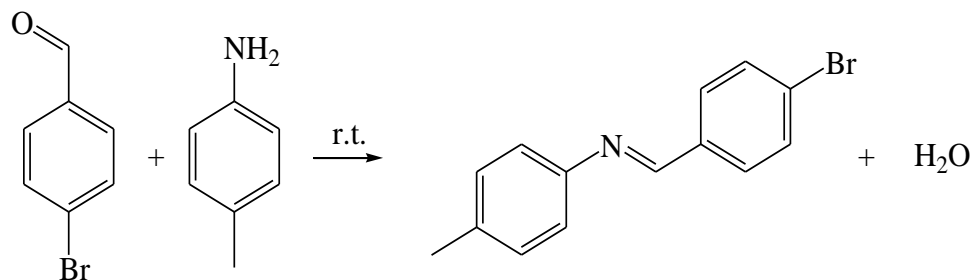
Greener chemical practice has seen advances in industry and research; however, introduction of green practice and strategy into the teaching environment is still limited. A growing collection of educational materials

concerning alternative solvents in the organic chemistry laboratory is available<sup>1,5,11</sup>, yet little material exists for first year undergraduate chemistry students. Accordingly, a laboratory exercise for the introductory chemistry course was designed to explore unconventional solvents with three reactions that display color change to indicate reaction: 1) the solventless condensation of 4-aminotoluene and 4-bromobenzene to form N-(4-bromobenzylidene)-p-toluidine, 2) the coupling of 2-naphthol in the presence of iron(III) chloride and a liquid carbon dioxide solvent, and 3) the formation of a Cu(I)Cl-tetramethylethylenediamine (TMEDA) complex on water. This laboratory introduction to alternative solvents demonstrates concepts of green chemistry while encouraging students to question optimality of conventional chemical processes. This laboratory is designed to reinforce concepts of solutions and solute/solvent interactions encountered in lecture/textual material while introducing students to greener practices that are currently employed in industry and academia early in their scientific training.

#### *Solventless Azomethine Condensation*

In the first experiment of the laboratory, a solventless azomethine condensation reaction is performed. Interest in azomethines pertains to their importance in cycloadditions, cyclizations, and enantioselective oxidations<sup>4</sup>. Azomethines are characterized by the presence of the imino group (R-CH=N-R'), which is vital to transamination and racemization<sup>22</sup> within biological systems. Consequently, azomethines are of great biological interest as antibacterial<sup>13,23,24</sup>, antifungal<sup>25,26</sup> and antiparasitic agents<sup>22,27</sup>.

In this reaction, 4-aminotoluene and 4-bromobenzaldehyde are both ground separately and then ground together. The stoichiometric mixture of these two white crystalline solids soon liquefies as indicated by a spectacular yellow melt phase observed within seconds of contact. As the reaction proceeds, water is lost and a cream colored solid (N-(4-bromobenzylidene)-p-toluidine) crystallizes from the melt phase (Scheme 1).



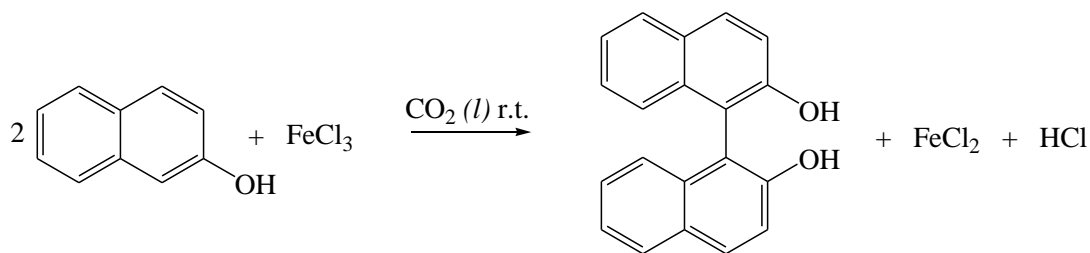
Scheme 1: Solventless condensation of 4-aminotoluene and 4-bromobenzaldehyde to form N-(4-bromobenzylidene)-p-toluidine.

### *Naphthol Coupling*

The second experiment uses liquid carbon dioxide in the coupling reaction of 2-naphthol with iron(III) chloride as the oxidant. Oxidative coupling products of naphthols are commonly used by agrochemical and pharmaceutical industries as building block for pesticides and pharmaceuticals. Coupled naphthols are also of great interest to natural product chemistry research<sup>4</sup>. The coupling product 1,1'-bi-2-naphthol or BINOL, is an important chiral ligand and precursor for the BINAP ligand. Both BINOL and BINAP are used industrially to catalyze asymmetric synthesis<sup>28</sup>. Coupling reactions under neat conditions with iron(III) chloride have

been well documented and iron salts are readily available, inexpensive, and environmentally friendly<sup>29</sup>.

In this experiment 2-naphthol and iron(III) chloride are both ground separately and then ground together. No reaction proceeds as the  $T_{fusion}$  for these two crystalline solids is around 50 °C. Rather than heat the mixture, a liquid carbon dioxide solvent is introduced to the reaction. The reaction proceeds to form the BINOL coupling product after solvation in liquid carbon dioxide (Scheme 2).



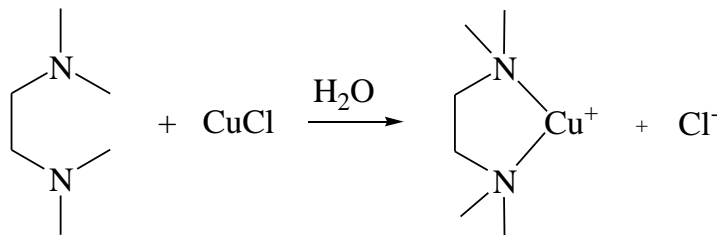
Scheme 2: Coupling reaction of 2-naphthol in the presence of FeCl<sub>3</sub>·6H<sub>2</sub>O and CO<sub>2</sub>(l)

Owing to the only slightly elevated pressures required to obtain liquid carbon dioxide, an inexpensive centrifuge tube can be used as a reaction vessel safely instead of expensive high-pressure vessels such as those used for supercritical carbon dioxide conditions. Not only is visibility of reaction enhanced in the clear tubes, but the slow escape of pressure from the tube-cap junction reduces the possibility of hazardous pressure failure. Moreover, centrifuge tubes as liquid carbon dioxide vessels have been demonstrated safe, with adherence to moderate precautions in the undergraduate laboratory<sup>11</sup>.

### *Cu-TMEDA Complex*

The third experiment of the laboratory exercise uses water as a solvent in the formation of a CuCl-TMEDA complex. Tetramethylethylenediamine or TMEDA is an organic molecule widely used as a bidentate ligand for metal ions. TMEDA forms stable complexes with many metal halides, e.g. zinc chloride and copper iodide, giving complexes that are soluble in organic and aqueous solvents<sup>30</sup>. Some of these metal-TMEDA complexes serve as catalysts for aqueous organic reactions such as arylation<sup>31,32</sup>, bis-carbene complex formation<sup>33</sup>, allylation/benzylation<sup>34</sup>, and ferrocene coupling reactions<sup>35</sup>.

In this experiment, sparingly soluble CuCl is mixed with water and allowed to settle out. With the addition of TMEDA, a blue, water-soluble CuCl-TMEDA complex forms in the aqueous solution (Scheme 3). Although the complex is not a documented catalyst itself, it is a precursor to the  $[\text{Cu}(\text{OH})\cdot\text{TMEDA}]_2\text{Cl}_2$  catalyst and an analog of the CuI-TMEDA catalyst, both of which are water soluble complexes used to promote ‘on’ and ‘in’ water organic reactions.



Scheme 3: Formation of aqueous Cu-TMEDA complex

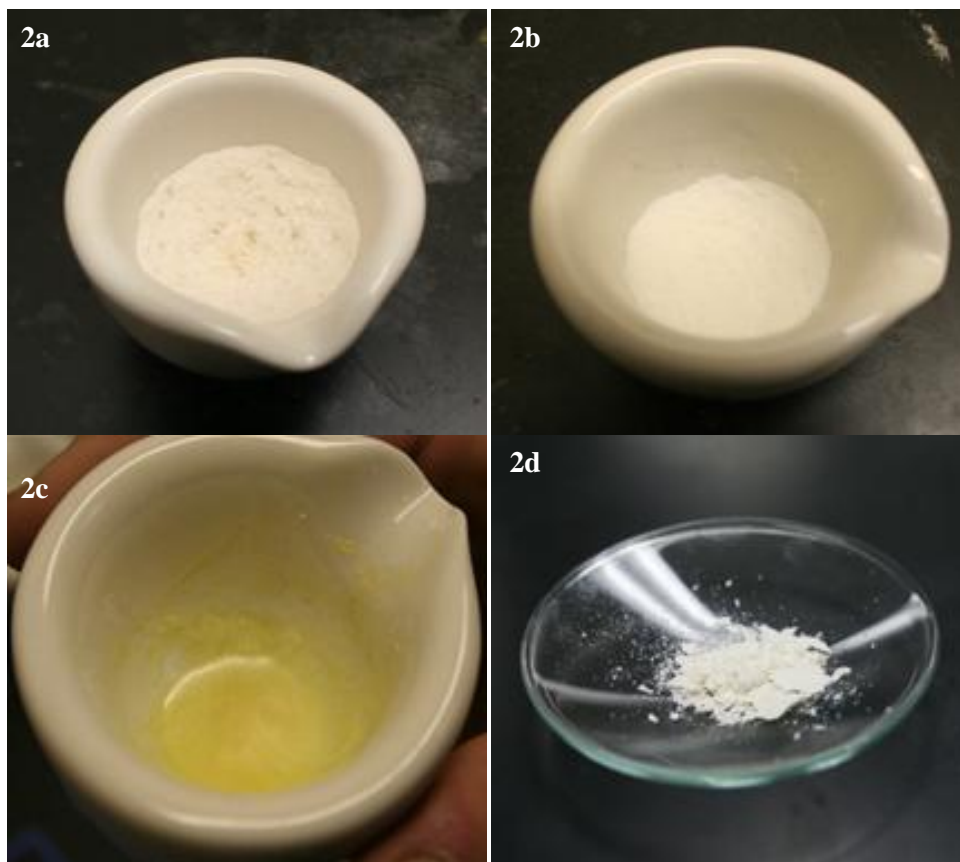
## Experimental

Commercial-grade dry ice was purchased through local grocers and welding supply retailers. The water used was purified using reverse osmosis. All other chemicals used for this laboratory are available through Sigma Aldrich and may be used without any additional purification. All reactions were performed in a laboratory hood. See Appendix I for the necessary safety precautions for each experiment

### *Azomethine Condensation*

4-aminotoluene, 300 mg (2.8 mmol) and 510 mg (2.8 mmol) of 4-bromobenzaldehyde were ground separately using mortar and pestle. Figures 2a and b show that upon grinding, neither 4-aminotoluene nor 4-bromobenzaldehyde melted. The 4-aminotoluene and 4-bromobenzaldehyde were then ground together in a new mortar. Figure 2c shows the bright yellow liquid melt-phase that was observed upon combination and grinding of the two white solids. The melt solidified within two minutes to yield N-(4-bromobenzylidene)-p-toluidine as a white solid as seen in Figure 2d.



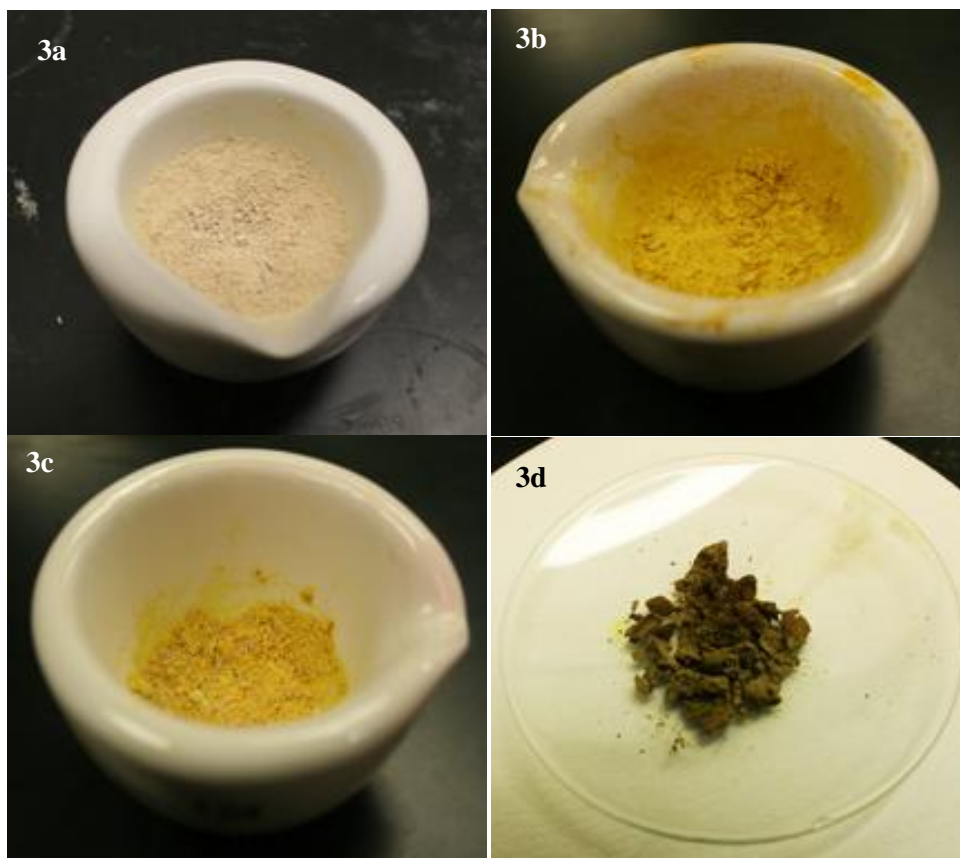


**Figure 2:** a- ground 4-aminotoluene b- ground 4-bromobenzaldehyde c- mixture of 4-aminotoluene and 4-bromobenzaldehyde after 5 sec. of grinding d- Solid N-(4-bromobenzylidene)-p-toluidine collected 2 min.

#### *Coupling of 2-naphthol*

2-naphthol, 1.00 g (7.0 mmol) and 3.80 g (14.0 mmol) of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  were ground separately with mortar and pestle. Neither the  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  nor the 2-naphthol melted when ground as shown in Figures 3a,b. The  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and 2-naphthol were then combined in one mortar and ground together for 2 min. as seen in Figure 3c with no visible melt occurring. The ground mixture was transferred to a plastic 15 ml centrifuge tube. Approximately 1.00 g of finely crushed dry ice was added to the reactants in the centrifuge tube. The reaction

centrifuge tube was capped tightly, and submerged in a plastic beaker of warm tap water. The solid carbon dioxide melted into a clear colorless liquid followed by the appearance of small dark brown regions throughout the mixture indicative of the product, BINOL. The liquid carbon dioxide vented slowly, but continuously from the centrifuge tube where the cap and tube meet. After about 5 min. all liquid carbon dioxide was gone, and the remaining pressure was released by slowly uncapping the centrifuge tube. To the tube another 1 gram of ground dry ice was added. The centrifuge tube was then re-capped and re-submerged in the beaker of warm tap water. This process was repeated 5-7 times in a 30 min. time interval to yield a uniform dark brown melt inside the centrifuge tube. The product 2, 2'-dihydroxybinaphthalene (BINOL) and iron(II) chloride byproduct were scraped from the reaction centrifuge tube to a watch glass as shown in Figure 3d.

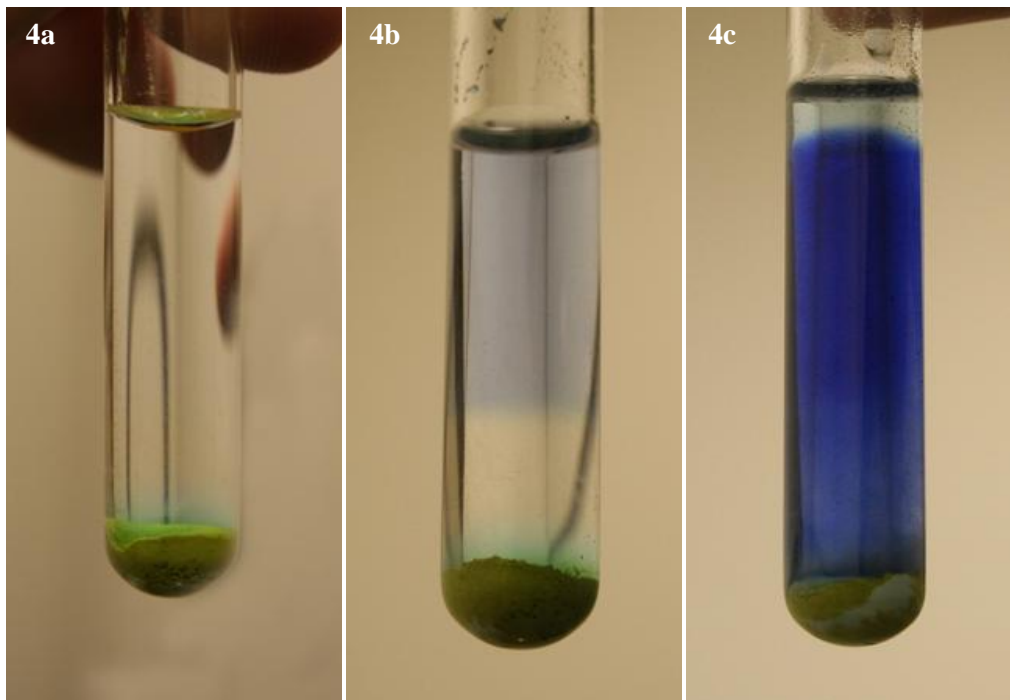


**Figure 3:** **a-** ground 2-naphthol **b-** ground  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  **c-** mixture of 2-naphthol and  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  with no apparent reaction **d-** precipitated BINOL and  $\text{FeCl}_2$  after 30 min. of solvation in carbon dioxide (*l*)

#### *Cu-TMEDA Catalyst*

Approximately 0.1 g (1.01 mmol) of copper(I) chloride was added to a three inch glass test tube. Purified water was then added to the test tube drop-wise so as not to disturb the solid. The test tube was filled with water to about one third of its total volume as seen in Figure 4a. TMEDA was added drop wise using a glass Pasteur pipet. The resulting  $\text{CuCl} \cdot \text{TMEDA}$  complex formed as indicated by a color change from colorless to deep blue in the aqueous phase. Figures 4b,c

illustrate the color change with respect to increasing concentration of TMEDA in solution.



**Figure 4:** a- Water with approximately 0.1 g of CuCl b- addition of three drops TMEDA to aqueous layer c- addition of 1 ml TMEDA to the aqueous layer.

### Results and Discussion

The experimental procedures and introductory information above were synthesized into a general chemistry laboratory experience designed explore solvents. The three part exercise introduces a number of green benefits for the undergraduate student regardless of major. The laboratory experimental procedure and accompanying supplementary materials can be found in Appendix I. The laboratory can be performed within a three hour laboratory period.

### *Azomethine Condensation*

The solventless azomethine condensation exercise demonstrates that some reactions do not require solvents at all. Students are introduced to the possibility of a solventless transformation- a lesson designed to accompany students through the chemistry curriculum as more synthetic freedom and responsibility are granted. The bright yellow melt phase illustrates the importance of solute mobility as a factor in reaction kinetics even when the medium for mobility is made up solely of reactants. The reaction occurs rapidly under ambient conditions and isolation of product from the water byproduct requires no additional heating or workup. In this exercise the hazards of traditional organic solvents are absent, and the only byproduct of the reaction is water. This condensation approaches an ideal reaction where the product is synthesized in one efficient step that proceeds quickly and produces high yields<sup>36</sup>. Although no solvent hazards are present, 4-aminotoluene and 4-bromobenzaldehyde are both toxic when contacted with skin/eyes, inhaled, or ingested. Consequently, this experiment is to be performed under ventilation and with appropriate personal protective equipment (nitrile gloves, lab coat, and eye protection).

### *Naphthol Coupling*

The naphthol coupling reaction reinforces the importance of reactant mobility. No melt phase is observed at ambient temperatures when grinding the 2-naphthol and iron(III) chloride oxidant together; as a result, no reaction occurs. The solid-solid interface is not conducive to fast reactions as mass mobility is limited to stirring or agitation. Such a solid/solid interaction without the mobility

of a liquid phase would display diffusion controlled kinetics with accompanying very slow reaction velocities. Contrastingly, the presence of a solvent that facilitates mass transfer and molecular mobility allows for increased rates of collisions<sup>4</sup>. Upon addition of liquid carbon dioxide the reaction is able to proceed quickly.

Regarding safety, liquid carbon dioxide possesses a few important advantages over supercritical carbon dioxide for the undergraduate laboratory. For liquid carbon dioxide only 5.1 atm of pressure are required; therefore, a less expensive reaction vessel, as exemplified by the plastic centrifuge tubes, can be used in this experiment. Furthermore, reactions can be performed at ambient temperatures and the concentration of reagent in the reaction phase is higher than with typical supercritical carbon dioxide conditions<sup>37</sup>.

The carbon dioxide in this portion of the exercise undergoes sublimation (when the dry ice is crushed), melting (when submersed in a capped centrifuge tube), and evaporation (when the cap is removed from the pressurized centrifuge tube). Phase transitions with respect to temperature and pressure are regularly discussed in the general chemistry curriculum. Accordingly, this experiment allows the student to visualize these phases and transitions as an additional benefit without dangerous temperatures or pressures required to view phase transitions of many other substances. Students are most likely familiar with dry ice and gaseous carbon dioxide; however, liquid carbon dioxide is a phase that few may have experienced, adding to the novelty and interest generated by this experiment.

The carbon dioxide in this experiment poses no risk to human health as long as the safety precautions outlined in the procedure are followed. The use of liquid carbon dioxide introduces an important tool of green chemistry to the laboratory, further emphasizing strategies now employed to reduce the footprint of chemical processes. There is no generation of solvent waste with this reaction, and the energy requirements are considerably lower than typical reflux conditions. Iron(III) chloride and 2-naphthol are both toxic when contacted with skin/eyes, inhaled, or ingested. Consequently, this experiment is to be performed under ventilation and with appropriate personal protective equipment (nitrile gloves, lab coat, and eye protection).

#### *Cu-TMEDA Complex*

The CuCl-TMEDA complex experiment provides an excellent introduction to water as a benign solvent. The reaction exemplifies an 'on water' reaction as the copper(I) chloride reactant is only slightly soluble; whereas the resulting CuCl-TMEDA complex is soluble in water. The sparingly soluble copper(I) chloride rests at the bottom of the test tube leaving the aqueous solvent colorless. Upon addition of the TMEDA, students are afforded a brilliant color change in the aqueous layer as the CuCl-TMEDA complex is formed. This experiment provides an excellent introduction to complex formation and catalysis; both of which may be discussed in as much detail as is desired by the instructor. As interest in organic reactions in and on water increases and finds advancement in industry, it is beneficial for the young undergraduates to learn about the value of this unconventional approach. Copper(I) chloride and TMEDA are both toxic

when contacted with skin/eyes, inhaled, or ingested. This experiment is to be performed under ventilation and with appropriate personal protective equipment (nitrile gloves, lab coat, and eye protection). TMEDA is flammable and should never be stored around heat sources.

*A Note on 'Greenness'*

Although the solvents presented within this laboratory exercise are indeed “greener” than many traditional organic solvents, the green metrics for each reaction (the measure of overall greenness<sup>5</sup>) remains uninvestigated. Alternative solvents do not reduce the toxicity and hazards associated with reactants and products of a given reaction, but rather reduce any further toxicity and hazards that would be incurred from the use of traditional solvents. The environmental impact of a chemical process is determined by many other factors such as atom economy, energy requirements, reagent/product toxicity, and the cost reaction cleanup/disposal. The finding that a process performs as well in low cost, relatively abundant, and benign solvent just as well as it does in an organic solvent tells little about potential environmental impact<sup>38</sup>. The use of green solvents can sometimes lead to increased waste, inefficiency, and energy usage<sup>39</sup>, negating many of the benefits of the chosen benign solvents. Although supercritical carbon dioxide is relatively inexpensive and benign, reaction vessels and equipment needed to perform extractions and synthesis in supercritical dioxide are expensive, while the energy requirements of the high temperatures and pressures to attain this phase are also high.



Discussing the benefits and difficulties present in the use of alternative solvents exposes students to the challenges inherent in traditional solvent replacement. Emphasis should be placed on a holistic approach as the key to making informed solvent-choice decisions for every reaction. The role of the solvent must be fundamentally understood before its use in any reaction is encouraged. The goal of this laboratory investigation is not to encourage the use of alternative solvents in every synthetic process, but rather to expand the options available to the emerging chemist. The laboratory exercise only aims to introduce certain instances of unconventional and benign reaction solvents.

## **Conclusion**

A chemistry laboratory for first year undergraduates was created to introduce unconventional reaction solvents. The lab contains three experiments: 1) a solventless azomethine condensation between 4-aminotoluene and 4-bromobenzaldehyde 2) the oxidative coupling of 2-naphthol in the presence of iron(III) chloride and liquid carbon dioxide as the solvent, and 3) the formation of a CuCl-TMEDA complex in an aqueous solvent. The laboratory procedure is visual and interactive; designed to reinforce the importance of waste prevention and safer solvents. In the first two experiments students experience the importance of reactant mobility in reactions while experiencing both sublimation and fusion of carbon dioxide with slight alterations of pressure and temperature. In the second exercise the use of liquid carbon dioxide as a green solvent for synthetic transformations is presented. The formation of the CuCl-TMEDA complex in water shows the application of water as a benign and effective

alternative for organic reactions. The Cu-TMEDA complex has potential as a water soluble catalyst of biphasic organic reactions, thus affording the instructor an opportunity to introduce catalysis in any desired depth.

Extensions of this work may include the transformation of the current laboratory procedure into a longer, more in-depth student project. More laboratory periods can be used to further develop extensions of this work. For example, melting points would be taken of the N-(4-bromobenzylidene)-p-toluidine product of the azomethine condensation to confirm product identity. The crude BINOL/iron(II) chloride mixture present after the 2-naphthol coupling reaction would be recrystallized using ethanol in water to yield only the BINOL product. Melting point determination would then also be performed on this purified product. This addition would introduce melting point determination as a valuable tool in the determination of chemical identity and purity.

Another exciting possibility for further enhancement of the laboratory procedure is the exploration of aqueous *o*-arylation reactions using the CuCl-TMEDA complex, rather than the documented CuI-TMEDA complex<sup>30</sup> as a possible catalyst. If the CuCl-TMEDA was a viable catalytic alternative, incorporation of an *o*-arylation reaction into this laboratory exercise would further reinforce the use of water as a benign and effective solvent.

The work presented here demonstrates instances of greener solvents as alternatives to traditional solvents. The laboratory exercises are designed to

communicate certain notions of greener chemical practice while reinforcing concepts concerning solvents and their roles in synthetic transformations.

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# APPENDIX I

*Unconventional reaction media: A solvent-based discovery lab for first-year undergraduates*

## Supplementary Materials

## Notes to Instructors:

This chemistry laboratory for first year undergraduates was created to introduce unconventional reaction solvents. The lab contains three experiments: 1) a solventless azomethine condensation between 4-aminotoluene and 4-bromobenzaldehyde 2) the oxidative coupling of 2-naphthol in the presence of iron(III) chloride and a liquid carbon dioxide solvent, and 3) the formation of a CuCl-TMEDA complex in an aqueous solvent. The laboratory procedure is visual and interactive; designed to reinforce the importance of waste prevention and safer solvents.

### *Experiment 1: Azomethine Condensation*

The solventless azomethine condensation exercise demonstrates that some reactions do not require solvents at all. Students are introduced to the possibility of a solventless transformation; a lesson designed to accompany students through the chemistry curriculum as more synthetic freedom and responsibility are granted. The bright yellow melt phase illustrates the importance of solute mobility as a factor in reaction kinetics even if the medium through which mobility is enhanced is made up solely of reactants. The reaction occurs rapidly under ambient conditions and isolation of product from the water byproduct requires no additional heating or workup. In this exercise the hazards of traditional organic solvents are absent, and the only byproduct of the reaction is water. This condensation approaches an ideal reaction where the product is synthesized in one efficient step that proceeds quickly and produces high yields<sup>1</sup>. Although no solvent hazards are present, 4-aminotoluene and 4-bromobenzaldehyde are both toxic when contacted with skin/eyes, inhaled, or ingested. Consequently, this experiment is to be performed under ventilation and with appropriate personal protective equipment (nitrile gloves, lab coat, and eye protection).

### *Experiment 2: Naphthol Coupling*

The naphthol coupling reaction reinforces the importance of reactant mobility. No melt phase is observed at ambient temperatures when grinding the 2-naphthol and iron(III) chloride oxidant together; consequently, no reaction occurs. The solid-solid interface is not conducive to fast reactions, as mass mobility is limited to stirring or agitation. Such a solid/solid interaction without a mobile reaction phase would display diffusion controlled kinetics with accompanying very slow reaction velocities. Contrastingly, the presence of a liquid phase that facilitates mass transfer and molecular mobility allows for increased rates of collisions<sup>2</sup>. Upon addition of liquid carbon dioxide, the reaction is able to proceed quickly.

Regarding safety, liquid carbon dioxide possesses a few important advantages over supercritical carbon dioxide for the undergraduate laboratory. For liquid carbon dioxide only 5.1 atm of pressure are required; therefore, a less expensive reaction vessel can be used as exemplified by the plastic centrifuge tubes employed in this experiment. Furthermore, reactions can be performed at



ambient temperatures and the concentration of reagent in the reaction phase is higher than with typical supercritical carbon dioxide conditions<sup>3</sup>.

The carbon dioxide in this portion of the exercise undergoes sublimation (when the dry ice is crushed), melting (when submersed in a capped centrifuge tube), and evaporation (when the cap is removed from the pressurized centrifuge tube). Phase transitions with respect to temperature and pressure are regularly discussed in the general chemistry curriculum. Accordingly, this experiment allows the student to visualize these phases and transitions as an additional benefit without dangerous temperatures or pressures required to view phase transitions of many other substances. Students are most likely familiar with dry ice and gaseous carbon dioxide; however, liquid carbon dioxide is a phase that few may have experienced, adding to the novelty and interest generated by this experiment.

The carbon dioxide in this experiment poses no risk to human health as long as the safety precautions outlined in the procedure are followed. The use of liquid carbon dioxide introduces an important tool of green chemistry to the laboratory, further emphasizing strategies now employed to reduce the footprint of chemical processes. There is no generation of solvent waste with this reaction, and the energy requirements are considerably lower than typical reflux conditions. Iron(III) chloride and 2-naphthol are both toxic when contacted with skin/eyes, inhaled, or ingested. Consequently, this experiment is to be performed under ventilation and with appropriate personal protective equipment (nitrile gloves, lab coat, and eye protection).

### *Experiment 3: Cu-TMEDA Complex*

The CuCl-TMEDA complex experiment provides an excellent introduction to water as a benign solvent. The reaction exemplifies an ‘on water’ reaction as the copper(I) chloride reactant is only slightly soluble; whereas the resulting CuCl-TMEDA complex is soluble in water. The sparingly soluble copper(I) chloride rests at the bottom of the test tube leaving the aqueous solvent colorless. Upon addition of the TMEDA, students are afforded a brilliant color change in the aqueous layer as the CuCl complex is formed. This experiment provides an excellent introduction to complex formation and catalysis; both of which may be discussed in as much detail as is desired by the instructor. As interest in organic reactions in and on water increases and finds advancement in industry, it is beneficial for the young undergraduates to learn about the value of this unconventional approach. Copper(I) chloride and TMEDA are both toxic when contacted with skin/eyes, inhaled, or ingested. This experiment is to be performed under ventilation and with appropriate personal protective equipment (nitrile gloves, lab coat, and eye protection). TMEDA is flammable and should never be stored around heat sources.

### *A Note on ‘Greenness’*

Although the solvents presented within this laboratory exercise are indeed “greener” than many traditional organic solvents, the measure of overall

greenness for each reaction remains uninvestigated. Alternative solvents do not reduce the toxicity and hazards associated with reactants and products of a given reaction, but rather reduce any further toxicity and hazards that would be incurred from the use of traditional solvents. The finding that a process performs as well in low cost, relatively abundant, and benign solvent just as well as it does in an organic solvent tells little about potential environmental impact<sup>4</sup>. Emphasis should be placed on a holistic approach as the key to making informed solvent-choice decisions for every reaction. The role of the solvent must be fundamentally understood before its use in any organic or organocatalytic reaction is encouraged. The goal of this laboratory investigation is not to encourage the use of alternative solvents in every synthetic process, but rather to expand the options available to the emerging chemist. The laboratory exercise only aims to introduce certain instances of unconventional and benign reaction solvents.

#### **CAS Registry Numbers of Chemicals Used in This Project**

*Para*-toluidine [106-49-0]

4-bromobenzaldehyde [1122-91-4]

2-naphthol [135-19-3]

Anhydrous iron(III) chloride [7705-08-0]

Tetramethylethylenediamine (TMEDA) [110-18-9]

Copper(I) chloride [7758-89-6]

#### **Estimated Lab Time**

2-3 hours

#### **Waste Collection and Disposal**

All waste from the three experiments should be treated as halogenated waste and disposed of accordingly. The azomethine from the first reaction can be washed out of mortar with acetone. All mortars used for grinding in the three experiments can be cleaned out with acetone and the resulting acetone-product mixtures can be contained as halogenated waste. The test tubes used in the third experiment may be dumped into a halogenated waste container, cleaned with acetone and stored for later use.

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## **Laboratory Exercise:** Unconventional reaction media: A solvent-based discovery lab for first year undergraduates

### **Introduction:**

The use of solvents is seemingly inherent in many synthetic transformations. A well-chosen solvent aids in the manipulation of chemicals, but is not an integral part of the molecules involved. The solvent allows high reactant mobility in a homogeneous environment and a medium for the exchange of mass and energy, while often modulating the reactivity of substrates<sup>1</sup>. Solvents are often the largest volumetric constituents in organic reactions; and thus greatly contribute to the waste, cleanup, and hazards involved with those reactions. Five out of the top ten chemicals disposed of by the chemical industry in the mid-1990s were the organic solvents: methanol, toluene, xylene, methyl ethyl ketone, and methylene chloride<sup>2</sup>. Organic solvents are often flammable and hazardous. Halogenated solvents such as methylene chloride, chloroform, perchloroethylene, and carbon tetrachloride have been identified as human carcinogens while benzene and many other aromatics and hydrocarbons have been implicated<sup>3</sup>. With heightened regulations regarding the use and disposal of many organic solvents, the search for alternative solvents with desirable processing characteristics and fewer health and environmental hazards<sup>1</sup> is of great significance.

In this lab, we will explore benign alternative solvents through three experiments. In the first experiment of the laboratory, a solventless reaction is performed, generating no solvent waste. The second experiment explores the use of a less hazardous, non-flammable solvent, liquid carbon dioxide. The third experiment of the laboratory exercise was designed to explore water as an alternative to organic solvents through the formation of a colored complex in an aqueous environment.

### **Experiment 1:** Solventless reaction of two solids

#### **Safety Notes:**

**Wear Goggles, Gloves, and Apron/Lab coat** when working with reagents to avoid skin and eye irritation.

**Perform all mortar/pestle grinding under ventilation** of a fume hood to avoid inhalation of toxic reagents.

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<sup>1</sup> McKenzie, L.C.; Huffman, L.M.; Hutchison, J.E.; Rogers, C.E.; Goodwin, T.E.; Spessard, G.O. Greener Solutions for the Organic Chemistry Teaching Lab: Exploring the Advantages of Alternative Reaction Media. *J. Chem. Educ.* [Online] **2009**, 86, 488-493. <http://pubs.acs.org/doi/pdf/10.1021/ed086p488> (accessed Jan 12, 2011).

<sup>2</sup> Anastas, P. T.; Heine, L. G.; Williamson, T. C. *Green Chemical Syntheses and Processes*; American Chemical Society: Washington, D.C., 2000.

<sup>3</sup> Anastas, P.T.; Warner, J.C.. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 1998.

**Disposal:** All unreacted starting material and product can be disposed of as halogenated organic waste in a crock or appropriate container.

**Materials:**

Chemicals	Equipment
paratoluene	3 mortars
4-bromobenzaldehyde	3 pestles
	2 weigh boats

**Procedure**

1. Weigh out 0.20 g of *para*-toluidine on the balance using a weigh boat.
2. Transfer the *para*-toluidine to a mortar and grind with pestle using a circular motion. Frequently tap the mortar on a hard surface two or three times to bring larger crystals to the top and continue grinding.
3. Weigh out 0.34 g of 4-bromobenzene on the balance using a new weigh boat.
4. Transfer the 4-bromobenzene to a mortar and grind with pestle using a circular motion. To bring larger crystals to the top for grinding, occasionally tap the mortar two to three times on a hard surface.
5. Combine the ground *para*-toluidine and ground 4-bromobenzaldehyde into a new mortar and begin grinding with a new pestle.
6. After about a minute, a yellow liquid should form, cease grinding and observe the reaction until the yellow liquid solidifies.

**Questions for Discussion**

Did a color change or melt occur when grinding *para*-toluidine?

Did a color change or melt occur when grinding bromobenzaldehyde?

Did a color change or melt occur when grinding the *para*-toluidine and bromobenzaldehyde together?

Although no solvent was present, do you think the liquid mobility of reagents allowed for more molecular collisions?

What does this tell you about the importance of a mobile phase for reaction rates?

After reaction, what is the appearance of the final product?

What does this tell you about the melting temperature for the final product vs. the mixture of reactants?

## Experiment 2: Solid-solid reaction with liquid carbon dioxide solvent

### Safety Notes:

**No Glassware** during this experiment: glass centrifuge tubes or beakers could result in serious injuries if shattering should occur.

**Wear Goggles, Gloves, and Apron/Lab coat** when working with reagents to avoid skin and eye irritation. Due to the pressure involved with this experiment, foreign material could become lodged in the eye if not covered. Iron(III) chloride stains skin and clothing.

**Use insulated gloves** when working with dry ice. Contact with dry ice can damage skin tissues.

**Disposal:** All unreacted starting material and product can be disposed of as halogenated organic waste in a crock or appropriate container. The centrifuge tubes are to be rinsed once with acetone and disposed of as garbage after rinsing.

### Materials:

Chemicals	Equipment
2-naphthol	3 mortars
Iron(III) chloride	3 pestles
commercial grade dry ice	2 weigh boats
warm tap water	15 ml centrifuge tube and cap
	plastic beaker (250 ml minimum)
	Metal Spatula

### Procedure

1. Weigh out 0.10 g of 2-naphthol on the balance using a weigh boat.
2. Transfer the 2-naphthol to a mortar and grind with pestle using a circular motion. Frequently tap the mortar on a hard surface two or three times to bring larger crystals to the top and continue grinding.

3. Weigh out 0.38 g of iron(III) chloride on the balance using a new weigh boat.
4. Transfer the iron(III) chloride to a mortar and grind with pestle using a circular motion. To bring larger crystals to the top for grinding, occasionally tap the mortar two to three times on a hard surface.
5. Combine the ground 2-naphthol and ground iron(III) chloride into a new mortar and begin grinding with a new pestle.
6. Transfer the ground mixture to a 15 ml plastic centrifuge tube, cap and set aside
7. Wearing insulated hand wear, crush dry ice into fine powder using a hammer.
8. Transfer the dry ice to the centrifuge tube, filling the centrifuge tube to about half its volume.
9. Twist the centrifuge tube cap on tightly until it stops turning. **If cap does not stop turning when tightened, remove the cap before proceeding.** Without a complete seal, the cap is likely to shoot off. Replace the cap with a new one before placing in water.
10. Place the centrifuge into a plastic beaker of warm tap water so that the portion of the centrifuge tube containing the reactants is submerged.
11. Pressure will begin to build in the tube and gas will escape slowly from the region where the tube and the cap meet. The plastic beaker protects you from possible injury if the tube shatters or the cap shoots off. Any projectiles will be directed straight up, so monitor the reaction from the side, and not the top.
12. The CO<sub>2</sub> should liquefy within 15 seconds. If this does not occur, a there is not a sufficient seal between the cap and the tube. Ask your instructor for a new cap. If the carbon dioxide still does not liquefy, ask your instructor for a new centrifuge tube and cap and start the experiment over.
13. The liquid CO<sub>2</sub> will boil off and gas will escape for 3-5 minutes. When all of the liquid CO<sub>2</sub> has left the centrifuge tube, repeat steps 7-12 until the reaction is complete and a uniform brown paste is at the bottom of the centrifuge tube.
14. When the reaction is complete, slowly unscrew the centrifuge tube cap pointing it away from the eyes.
15. Scrape out some of the brown product with a metal spatula and make observations

### Questions for Discussion

Did a color change or melt occur when grinding 2-naphthol?

Did a color change or melt occur when grinding iron(III) chloride?

Did a color change or melt occur when grinding the 2-naphthol and iron(III) chloride together?

Did a color change or melt occur when the ground 2-naphthol and iron(III) chloride mixture was combined with liquid CO<sub>2</sub>? Describe what you saw?

Does this support your conclusions earlier about the importance of a mobile phase for reaction rates?

After reaction, what is the appearance of the final product?

What happened to the CO<sub>2</sub> liquid after the reaction?

How is the product easier to purify under these conditions than if it was dissolved in a liquid solvent such as hexane?

### Experiment 3: Aqueous formation of the CuCl-TMEDA complex

#### *Safety Notes:*

**Wear Goggles, Gloves, and Apron/Lab coat** when working with reagents to avoid skin and eye irritation.

**Perform all mortar/pestle grinding under ventilation** of a fume hood to avoid inhalation of toxic reagents.

**Disposal:** All unreacted starting material and product can be disposed of as halogenated organic waste in a crock or appropriate container. The centrifuge tubes are to be rinsed once with acetone and disposed of as garbage after rinsing.

#### **Materials:**

<b>Chemicals</b>	<b>Equipment</b>
distilled water	3-inch glass test tube
TMEDA (tetramethylethylenediamine)	glass Pasteur pipet
copper(I) chloride	rubber pipet bulb
	10 ml beaker

#### **Procedure**

1. Weigh out 0.10 g of copper(I) chloride on the balance using a weigh boat.

2. Transfer the 2-naphthol to a mortar and grind with pestle using a circular motion. Frequently tap the mortar on a hard surface two or three times to bring larger crystals to the top and continue grinding.
3. Transfer the ground copper(I) chloride to a 3-inch glass test tube.
4. So as not to disturb the copper(I) chloride at the bottom of the test tube, add distilled water to the tube drop wise so it runs down the side of the container.
5. Add distilled water in this manner until the water fills approximately 1/3 of the test tube volume.
6. Pour about 1 ml of TMEDA into a small beaker or graduated cylinder.
7. Fit a glass Pasteur pipet with a rubber suction bulb and draw up the TMEDA into the pipet.
8. To the test tube containing water and copper(I) chloride, add three drops of TMEDA and record your observations.
9. Repeat step 8.
10. Add the rest of the TMEDA to the test tube containing water and copper(I) chloride and record your observations

### **Questions for Discussion**

Does the copper(I) chloride appear to be soluble in water?

What is the color of the copper(I) chloride?

What happens when you added three drops of TMEDA?

What about the next three drops?

What about when all of the TMEDA was added?

If the CuCl-TMEDA complex is blue, is the product soluble in water?

How is this different from the copper(I) chloride reactant you started with?



## Optional Pre-Lab Introduction Handout

### *Solvents*

The use of solvents is seemingly inherent in many synthetic transformations. A well-chosen solvent aids in the manipulation of chemicals, but is not an integral part of the molecules involved. The solvent allows high reactant mobility and a medium for the exchange of mass and energy, while often modulating the reactivity of substrates<sup>1</sup>. Solvents are often the largest volumetric constituents in organic reactions; and thus greatly contribute to the waste, cleanup, and hazards involved with those reactions.

### *Health and Environmental Implications*

The chemical industry remains a major contributor to environmental pollution, largely due to the prevalence of hazardous solvents in chemical processes. Five out of the top ten chemicals disposed of by the chemical industry in the mid-1990s were the organic solvents: methanol, toluene, xylene, methyl ethyl ketone, and methylene chloride<sup>2</sup>. Organic solvents are often flammable and hazardous. Halogenated solvents such as methylene chloride, chloroform, perchloroethylene, and carbon tetrachloride have long been identified as human carcinogens while benzene and many other aromatics and hydrocarbons have been implicated<sup>3</sup>. With heightened regulations regarding the use and disposal of many organic solvents, the search for alternative solvents with desirable processing characteristics and fewer health and environmental hazards<sup>1</sup> is of great significance.

### *Solvents and Green Chemistry*

Green chemistry is chemical design that minimizes the use and generation of hazardous substances to avoid waste problems before they occur. Accordingly, the use of safe and environmentally benign substances, including solvents, whenever possible is an important aspect of greener chemical practice<sup>3</sup>. Several guidelines have been proposed to evaluate green chemical synthesis which have been summarized in the twelve principles of green chemistry<sup>3</sup>:

1. **Prevent Wastes:** It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy:** Synthetic methods should be designed to maximize the incorporation of all materials used during the process into the final product.
3. **Less Hazardous Chemical Syntheses:** Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals:** Chemical products should be designed to preserve efficacy of function while minimizing their toxicity.

5. **Safer Solvents and Auxiliaries:** The use of auxiliary substances (solvents, separation agents, etc) should be made unnecessary whenever possible and innocuous when used.
6. **Design for Energy Efficiency:** Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives:** Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical properties) should be avoided if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation:** Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. **Real-Time Analysis for Pollution Prevention:** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention:** Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

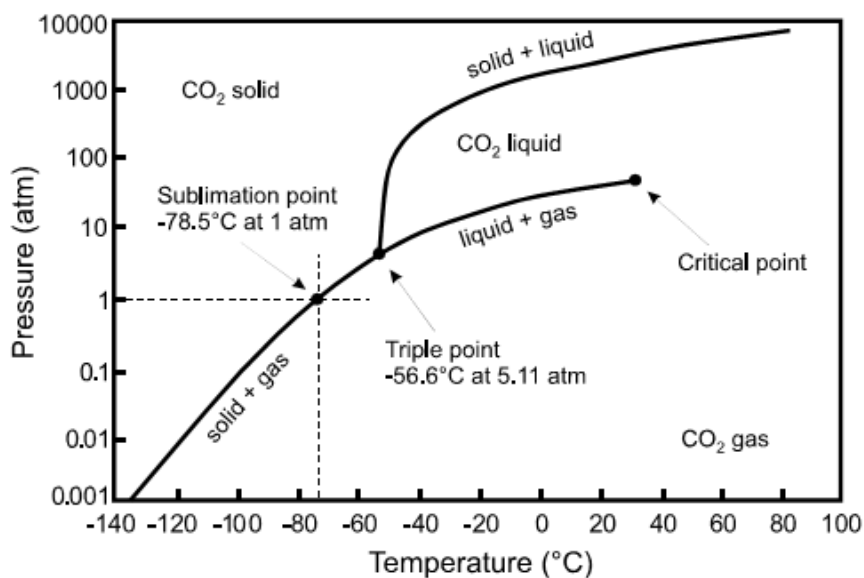
The use of alternative reaction solvents addresses the first and fifth principles of green chemistry in the prevention of waste, and the use of safer solvents and auxiliaries, respectively.

#### *Instances of Alternative Solvents*

The most desirable alternative solvent is no solvent at all. Solventless reactions are especially advantageous for human health and the environment as the generation of solvent waste is nonexistent. Solventless reactions can reduce time spent under reflux conditions. Although refluxing on a laboratory scale does not require great amounts of energy, the energy requirements for refluxing on an industrial scale can be very large. Though many solventless reactions are thought to be solid-solid interactions, many possess a liquid melt-precondition for rapid chemical reaction<sup>4</sup>. Upon mixing or grinding of two solids a melt phase is observed through which the reactants have enhanced mobility and collisions without the dilution of a solvent.

When a solvent must be used, non-hazardous and inexpensive solvents that do not compromise reactivity and specificity are desired. One such example is carbon dioxide which has become a widely used green solvent in industrial

processes<sup>5-7</sup>. Carbon dioxide is a nonflammable, relatively non-toxic, and environmentally benign solvent when used in its liquid and supercritical phases. The phase diagram in Figure 1 illustrates that carbon dioxide is a supercritical fluid above its critical point of 31.1 °C and 72.9 atm while the minimum temperature and pressure required for liquid carbon dioxide to exist are -56.6 °C and 5.1 atm, respectively<sup>8</sup>.



Pressure-Temperature phase diagram for CO<sub>2</sub>.

Figure 1: carbon dioxide pressure-temperature phase diagram showing the triple point and critical point

Although carbon dioxide is a greenhouse gas, liquid and supercritical carbon dioxide are obtained *from*, and released *into* the atmosphere resulting in no net emission<sup>9</sup>. With tightened industrial regulations, supercritical fluid extraction technologies have become common replacements for conventional organic solvents and steam distillations. The tunable solvent properties, inert nature, resistance to oxidation, and low toxicity of supercritical carbon dioxide have led to an increase of industrial processes that use supercritical carbon dioxide as a solvent<sup>9</sup>.

Although much attention has been directed towards supercritical carbon dioxide, liquid carbon dioxide has great utility as a benign solvent. The pressures and temperatures required for carbon dioxide to exist in the liquid state are much lower than the conditions necessary for the supercritical phase, consequently limited degradation of unstable products occurs<sup>9</sup>. Liquid carbon dioxide is used as a solvent in the industrial extraction of essential oils like soy bean oils, and hop oils used in beer<sup>10</sup>. Liquid Carbon dioxide is also used as a replacement for

perchloroethylene in dry cleaning<sup>11</sup>, and in materials synthesis<sup>12</sup>. When extractions and reactions are complete, release of pressure causes the vaporization of the solvent off of the products<sup>9</sup>, eliminating the need for solvent separation.

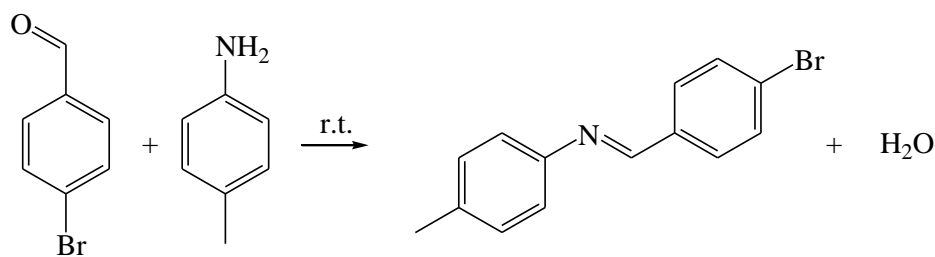
Water is also an instance of a benign alternative solvent in organic reactions. Water is an exceptionally safe and benign substance due to its high heat capacity and unique reduction/oxidation stability<sup>13</sup>. This high heat capacity also allows for excellent control of reaction temperature as water readily facilitates heat exchange<sup>14</sup>.

In most organic reaction, water creates a separate phase and thus does not dilute like most traditional solvents. The separate solvent phase can result in higher thermodynamic activities and rate accelerations due to solvation without dilution<sup>15</sup>. Although insoluble reactants can inhibit some organic reactions, insoluble reactants are desirable for other reactions. Certain organic reactions are accelerated by water itself. A reaction between cyclopentadiene and butenone proceeds 730 fold faster in water than in isooctane<sup>16</sup>. The axiom from the days of alchemy, “*corpora non agunt nisi soluta*” (substances do not interact unless dissolved)<sup>13</sup> is apparently untrue for certain organic reactions that take place in an aqueous environment.

#### *Solventless Azomethine Condensation*

In the first experiment of the laboratory, a solventless reaction between two solids is performed to yield an azomethine. Azomethines are characterized by the presence of the imino group (CH=N), which is vital to cellular processes within biological systems. Consequently, azomethines are of great biological interest as antibacterial<sup>10, 16, 17</sup>, antifungal<sup>18, 19</sup> and antil-parasitic agents<sup>20</sup>.

In this reaction, 4-aminotoluene and 4-bromobenzaldehyde are both ground separately and then ground together. The stoichiometric mixture of these two white crystalline solids soon liquefies as indicated by a spectacular yellow melt phase observed within seconds of contact. As the reaction proceeds, water is lost and a cream colored solid (N-(4-bromobenzylidene)-p-toluidine) crystallizes from the melt phase (Scheme 1).

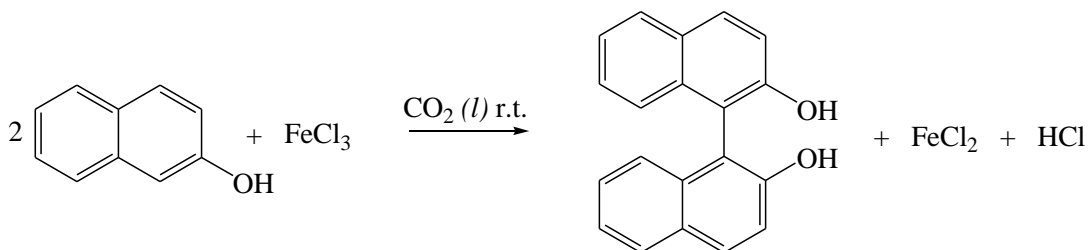


**Scheme 1:** Solventless condensation of 4-aminotoluene and 4-bromobenzaldehyde to form N-(4-Bromobenzylidene)-p-toluidine

### Naphthol Coupling

The second experiment uses a liquid carbon dioxide solvent in the coupling reaction of 2-naphthol with iron(III) chloride as the oxidant. Oxidative coupling products of naphthols are commonly used by agrochemical and pharmaceutical industries as building block for pesticides and pharmaceuticals. Coupled naphthols are also of great interest to natural product chemistry research<sup>4</sup>. The coupling product 1,1'-Bi-2-naphthol or BINOL is used as an industrial catalyst<sup>21</sup>.

In this experiment 2-naphthol and iron(III) chloride are both ground separately and then ground together. No reaction proceeds as the  $T_{fusion}$  for these two crystalline solids is around 50 °C. Rather than heat the mixture, a liquid carbon dioxide solvent is introduced to the reaction. The reaction proceeds to form the BINOL coupling product after solvation in the carbon dioxide (Scheme 2).



**Scheme 2:** Coupling reaction of 2-naphthol in the presence of FeCl<sub>3</sub>·6H<sub>2</sub>O and CO<sub>2</sub>(l)

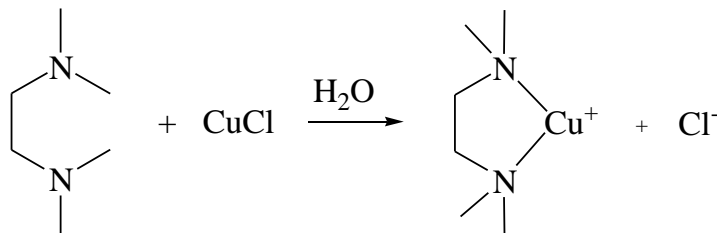
Owing to the only slightly elevated pressures required to obtain liquid carbon dioxide, an inexpensive centrifuge tube can be used as a reaction vessel safely instead of expensive high-pressure containing vessels such as those used for supercritical carbon dioxide conditions. Not only is visibility of reaction enhanced in the clear tubes, but the slow escape of pressure from the tube-cap junction reduces the possibility of hazardous pressure failure.

### Cu-TMEDA Complex

The third experiment of the laboratory exercise uses water as a solvent through the formation of a CuCl-TMEDA complex in an aqueous environment. Tetramethylethylenediamine or TMEDA is an organic molecule widely used as a ligand for metal ions. TMEDA forms stable complexes with many metal halides like zinc chloride and copper iodide, giving complexes that are soluble in organic and aqueous solvents<sup>22</sup>. Some of these metal-TMEDA complexes serve as catalysts for aqueous organic reactions.

In this experiment, sparingly soluble CuCl is mixed with water and allowed to settle out. With the addition of TMEDA, a bright blue, water-soluble CuCl-TMEDA complex forms in the aqueous solution (Scheme 3). Although the

complex is not a documented catalyst itself, it is a precursor to the  $[\text{Cu}(\text{OH})\cdot\text{TMEDA}]_2\text{Cl}_2$  catalyst and an analog of the CuI-TMEDA catalyst, both of which are water soluble complexes used to promote ‘on’ and ‘in’ water organic reactions.



**Scheme 3:** Formation of aqueous Cu-TMEDA complex

#### *A Note on ‘Greenness’*

Although the solvents presented within this laboratory exercise are indeed “greener” than many traditional organic solvents, the measure of overall greenness<sup>23</sup> of the reactions remains uninvestigated. Alternative solvents do not reduce the toxicity and hazards associated with reactants and products of a given reaction, but rather reduce any further toxicity and hazards that would be incurred from the use of traditional solvents. The finding that a process performs as well in low cost, relatively abundant, and benign solvent just as well as it does in an organic solvent tells little about potential environmental impact<sup>24</sup>. For instance, supercritical carbon dioxide is relatively inexpensive and benign; however, reaction vessels and equipment needed to perform extractions and synthesis in supercritical dioxide are expensive, while the energy requirements of the high temperatures and pressures to attain this phase are high. The role of the solvent must be fundamentally understood before its use in any organic reaction. These experiments only aim to introduce certain instances of unconventional and benign reaction solvents.

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