

Applying the Principles of Green Chemistry to Selected Traditional Organic Chemistry
Reactions

By

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ABSTRACT

The primary objective of this project was to apply the principles of green chemistry to selected traditional synthetic organic chemistry reactions. The reactions studied in the lab were: amide formation, oxidation of alcohols with KMnO_4 and $\text{LiCl}/\text{H}_2\text{O}_2$, oxidation of alkylarenes with KMnO_4 , reduction of β -ketoesters with yeast, and formation of esters by phase transfer catalysis. Microwave irradiation, biocatalysis, phase transfer catalysis, solvent-free conditions, and/or alternate solvents were used to accomplish these syntheses. Results were analyzed by the traditionally used percent yield calculations and selected green chemistry metrics. The main limitation of the results was that most products were not completely purified due to time constraints.

For amidification it was found that results obtained using a commercial oven were better than results obtained using a domestic oven. Oxidation with KMnO_4 gave higher yields at one week reaction time under solvent-free conditions than under reflux in dichloromethane for 1.5 h. The catalytic oxidation procedure using $\text{LiCl}/\text{H}_2\text{O}_2$ was found to be more wasteful than the stoichiometric procedure using KMnO_4 . Both methods showed preference for oxidation at benzylic as opposed to aliphatic positions. For the oxidation of alkylarenes it was found that dimethylcarbonate is not a suitable replacement for dichloromethane as an extraction solvent in this procedure. Also, higher yields were obtained at one week reaction time under solvent-free conditions than under reflux in dichloromethane for 1.5 h. Product analysis for reduction of β -ketoesters with yeast tend to suggest that steric factors may play a large role in the reaction with more sterically hindered substrates giving lower yields. Further work in this area is required to elucidate this hypothesis. Only a few esterification reactions were carried out but two of

three results gave decent E-factors. Finally, it was shown that the majority of waste from each reaction was from the use of solvent. Therefore, recycling the solvent can have the biggest impact on reducing waste.

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1 GREEN CHEMISTRY

Sustainable chemistry, design for environment, clean chemistry, environmentally-benign synthesis, benign by design, and inherently safe are all synonymous with green chemistry. Green Chemistry is defined as the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products.¹⁻³ The guiding objective is the design of environmentally-benign products and processes, which is embodied in the *Twelve Principles of Green Chemistry* (see Section 1.1).

There is a subtle difference between environmental chemistry and green chemistry even though they both deal with environmental problems. Environmental chemistry often involves site monitoring and remediation, and so environmental chemists monitor problems at the “end of pipe”.⁴ By contrast, green chemistry seeks to change the intrinsic nature of the substances themselves so as to reduce or eliminate the hazards and wastes posed by the substances.^{2,4,5} Thus, green chemistry deals with pollution at the source and therefore green-focused synthetic chemists can have a positive impact on dealing with environmental problems. For instance, the best way to make a product “green” is to consider what needs to be done during the design phase to ensure that the product being produced has as few adverse impacts as possible while maximizing the benefits it brings to society.

In the green chemistry context, an ideal synthesis can be considered as one which produces complex molecules in just a few atom economical synthetic steps, using non-hazardous reagents and intermediates (derived from renewable feed stocks), in the absence of solvents or in solvents that are 100% recoverable, with no adverse safety

issues, and proceeds quickly in quantitative yield under ambient conditions of temperature and pressure.⁶⁻⁸

The origin of green chemistry can be traced back to the Solvay process which, by 1873, had displaced the older LeBlanc process.^{9,10} Both produced soda ash but the main by-product of the Solvay process is relatively benign CaCl_2 whereas the main by-product of the LeBlanc process is HCl gas. While this is the first practiced example of green chemistry, it was not until 1998 that the first textbook on this subject was published by Anastas and Warner, and 1999 that the first journal, entitled *Green Chemistry*, was published by The Royal Society of Chemistry.⁵

The number of scientific publications explicitly invoking the term green chemistry have grown exponentially to a few thousand and is increasing at a rate of several hundred per year.¹¹ Standard topics include catalysis (homogeneous, heterogeneous, and bio-based), bio-based synthesis and processing, alternative synthesis pathways, green solvents and reaction conditions, and, more generally, safer chemicals and materials.⁵ Advances address both obvious hazards and those associated with much wider global issues such as climate change, energy production, availability of a safe and adequate water supply, food production, and the presences of toxic substances in the environment.³ There are, however, challenges to applying green chemistry such as a lack of awareness and training.⁶ In bypassing challenges, green chemistry can ultimately be used as a means to reach the goal of sustainability.

1.1 Principles

In their pioneering text, Anastas and Warner formulated the well-known and widely reproduced *Twelve Principles of Green Chemistry* which are shown in Figure 1.

These principles allow for a rapid assessment of the “greenness” of a given chemical route or for comparing the environmental acceptability of two rival processes. A simple mnemonic for these twelve principles have been proposed,¹² and an additional twelve principles have been put forward.¹³ There is also a similar set of principles for process engineering,¹⁴ and a corresponding mnemonic.¹⁵ These green engineering principles are useful on a larger scale and will not be considered further here.

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. 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. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Figure 1. The 12 principles of green chemistry.¹⁶

1.2 Metrics

The principles of green chemistry allow chemical professionals to design safer chemicals and qualitatively assess how green a process is. For a quantitative assessment several green chemistry metrics have been developed.^{2,7,8,17-24} A summary of the equations are presented in Figure 2. The derivation and relationship between some of these metrics have been given elsewhere.¹⁷ Some commonly used metrics will be discussed here starting with the traditionally used percent yield.

$\% \varepsilon = \left(\frac{\text{actual yield}}{\text{theoretical yield}} \right) \times 100\%$	$AE = \left(\frac{MW \text{ product}}{\sum MW \text{ reactants}} \right) \times 100\%$
$CE = \left(\frac{\text{mass of carbon in product}}{\text{total mass of carbon in reactants}} \right) \times 100\%$	$E = \left(\frac{\text{Waste (Kg)}}{\text{Product (Kg)}} \right)$
$E_{\text{theoretical}} = \frac{1-AE}{AE}$	$RME = \frac{\text{mass of product}}{\sum \text{masses of reactants}} = (\varepsilon)(AE)$
$(P)MI = \frac{\text{total mass used in process}}{\text{mass of product}} = E + 1$	$\text{Water Intensity} = \frac{\text{mass of all water used}}{\text{mass of product}}$
$EMY = \left(\frac{\text{mass of product}}{\text{mass of non-benign starting materials}} \right) \times 100\% \cong \left(\frac{1}{E} \right) \times 100\%$	
$\text{Solvent Intensity} = \frac{\text{mass of all solvent used excluding water}}{\text{mass of product}}$	

Figure 2. A summary of metrics used to assess how green a process is. Symbols are defined in the text below.

Reaction yield, ε , is not the best metric for assessing how green a process is because it does not take into account stoichiometric excesses and wasted resources.²⁰ Wasted resource may be expensive from both a direct materials cost and a more comprehensive life cycle costing perspective. Also, by purely focusing on improving yield, chemists are often at risk of missing other opportunities to reduce the overall environmental burden associated with a process. Reducing this overall environmental burden has the additional benefit of reducing development costs (example: costs of waste treatment, costs of handling toxic/unsafe reagents, solvent cost)²¹ and such considerations require alternate metrics.

The simplest metric is atom economy (AE) which is the ratio of molecular weight (MW) of the product to the sum of MWs of reactants.^{18-20,22} The ideal reaction would incorporate all of the atoms of the reactants into the product with no by-product formation. Examples of reactions that proceed with high AE include additions and rearrangement.^{18,19} Even if no part of a reactant is present in the final product itself (ex: in the case of addition and removal of a protecting group) it was part of an intermediate and is therefore included in the calculation.²⁰ Thus, high atom economies can serve as a

quantitative measure of green chemistry by emphasizing the minimization of unnecessary derivatization. However, the AE metric has also been criticized for being over-simplified because it does not account for stoichiometric excesses, yield, catalyst losses, solvent usage, or workup materials.^{7,20-22}

Another commonly used metric is the E (environmental) factor.^{2,17,20-22} It can be considered as the amount of waste (excluding water) required to produce 1 kg of product. The E-factor takes the chemical yield into account and includes reagents, solvent losses, all process aids and, in principle, even fuel (although this is often difficult to quantify). The ideal value is zero which denotes a zero waste process. An example that Roger Sheldon uses to highlight the importance of E-factors is a phloroglucinol plant at Océ Andeno (an industrial company) that was forced to shut down because the cost of disposing of the waste was rapidly approaching the selling price of the product.² Thus, a low E-factor is vital for any process to remain economically viable. An interesting limitation on this metric is the atom economy itself which can be used to calculate a theoretical E-factor.^{2,17} Thus a value of zero is only possible for processes with an AE=100%. In using E-factors, consistency is needed in defining what constitutes waste so that a set of processes can be compared. Also, the obtained values give no definite indication of whether the reaction will be equally wasteful at larger reaction scales.

A fourth metric is reaction mass efficiency (RME) which is the ratio of the mass of product isolated to the sum of masses of reactants.^{7,17,21,22} RME takes into account both AE and yield as shown by the equation $RME = (\epsilon)(AE)$, where ϵ is the yield.¹⁷ If one or more reactants are in excess then a stoichiometric factor can be included in the equation and could consequently reduce the RME value even though reaction yields

and/or atom economies may be high. Another consideration is if the solvent acts as a reactant then the mass of the part that reacts needs to be estimated separately or else the resultant RME will be artificially low.²¹ While this metric is more useful than AE, because it takes into account yield and stoichiometric excesses, it is still limited in that it does not take into account the use of catalyst, solvent, or work-up materials. A metric that takes these chemicals into consideration is mass intensity (MI).

MI, also referred to as mass index S^{-1} and process mass intensity (PMI),^{22,24} is the ratio of total mass used in process to the mass of final product.^{2,7,20,21} It is closely related to the E-factor as shown by the equation $MI = E + 1$.²⁰ It can be seen from this equation that the ideal MI is 1. The numerator of MI includes reactants, solvents, reagents, catalysts, acids, bases, salts, and workup chemicals.^{20,22,24} Water is usually excluded from the calculation with the exception of water used in the pharmaceutical industry because it uses highly purified water and there are life cycle impacts related to the chemicals and equipment used to purify the water.²¹ One limitation on the MI metric is that to compare values for a set of processes, consistency is needed in terms of what makes up the total mass used in the process.^{20,22}

There are also other metrics that are less commonly used; these will be presented briefly. Carbon efficiency (CE) takes into account the yield and the amount of carbon in the reactants that is incorporated into the final product.^{7,20} CE is related to AE and offers no additional insights on how one might improve chemistry or process conditions. Mass productivity is a variation on MI since it is equal to $1/MI$ and thus gives no additional information but only a different way of presenting data.²⁰ Effective mass yield (EMY) is the percentage of the mass of desired product relative to the mass of all non-benign

materials used in its synthesis.⁸ It can be approximated as E^{-1} with the additional consideration that benign materials are excluded. However, assessing whether a chemical is benign or non-benign is difficult in practice when working with complex reagents and reactants that have limited environmental or occupational toxicity information.²⁰ Another complication is the fact that toxicity depends on the dose and so, depending on the reaction scale, a chemical may either be benign or non-benign. Solvent intensity is the ratio of mass of all solvent (excluding water) to mass of product.²¹ It is similar to MI except that it isolates the solvent component of total mass used in a process. A related, although less useful metric, is the water intensity which is calculated as the ratio of mass of all water used to mass of product.²¹

None of the above metrics take into account the toxic or hazardous nature of chemicals involved. Attempts have been made to account for these factors.^{2,17,21,24,25} Sheldon introduced an environmental quotient, EQ, obtained by multiplying the E-factor with an arbitrarily assigned unfriendliness quotient, Q.^{2,23} However, the value of Q is debatable and can only be used to give a semi-quantitative assessment of the environmental impact of a chemical process. Eissen and Metzger have developed potential environmental impact values of each compound of the feed and of each compound of the waste, respectively, using EATOS (environmental assessment tool for organic syntheses).²⁴ There also exists safety indices that take into account the hazardous nature of processes.²⁵ Finally, a complete analysis of environmental impact can be given by a life-cycle assessment (LCA) which tracks the resource consumption, pollutants emitted, and their environmental impacts at each step, including extraction of raw

materials, production, transportation, sales, distribution, use, and final fate.²¹ These metrics are outside the scope of this research and will not be considered further.

1.3 Applications of the Principles of Green Chemistry

1.3.1 Microwave-assisted Organic Reactions (MAOS)

In many instances, microwave heating has been shown to dramatically reduce processing times, increase product yields and to enhance product purities compared to conventionally heated experiments.²⁶ Green chemistry principles 5 (use fewer auxiliary substances), 6 (minimize energy requirements), and 9 (use catalytic rather than stoichiometric reagents) usually apply to microwave chemistry.²⁷ Principle 5 applies because microwave heating enables the use of environmentally benign solvents or of solvent-free conditions and so the greenness of this method is largely a consequence of the reaction media. Principle 1 may also apply where microwave-assisted transformations lead to altered product distributions and eliminate wall effects, both of which would reduce waste.²⁷

There is an underlying assumption in the scientific community that microwave heating is more energy efficient (principle 6) than classical heating methods. This has been attributed to the fact that microwaves heat chemicals directly rather than by conduction through reaction vessels, which presumably uses more energy.²⁸ However, the energy efficiency of microwave heating has been questioned.^{27,29} It has been found that, in the case of open-vessel reflux processing, microwave heating requires significantly more energy than conventional techniques using oil baths or heating mantles because of the low energy efficiency (50-65%) of the magnetron in converting electrical to microwave energy.²⁹ Thus, there will be a guaranteed loss of energy before a

microwave reaction is even started. However, significant energy savings can be achieved with sealed-vessel microwave processing at high temperatures; although, this is largely due to reduced reaction times and is not an inherent feature of microwave heating.^{27,29} Another finding is that mono-mode systems are more energy efficient than multi-mode systems on a small scale whereas multi-mode systems become more efficient at larger scales.^{27,29} Further issues with scalability have been discussed elsewhere,²⁷ and it should be noted that most of the reactions published to date were performed on the small (<1 g) scale, which reflects the current limitation of this technology when it comes to processing larger volumes.²⁹ Microwave chemistry will be discussed in more detail in Section 2.

1.3.2 Solvent Choice

Solvents play a large role in many chemical processes. Their uses include: reaction media, reactant, heat transfer, isolation, and purification.^{22,30-33} Furthermore, they can: influence solubility, influence reaction rate, and stabilize ground states or transition states.³⁰ Along with their many benefits there are also several problems with their use, including: environmental hazards (ex: eco-toxicity, biomagnification, ozone depletion, smog-producing volatile organic compounds (VOCs), or water contamination), health hazards (ex: carcinogenicity, sensitization, or reproductive toxicity), and safety concerns (ex: volatility, flammability, or corrosiveness).^{11,22,31,34,35} These problems are related to the disposal of waste solvent which typically comprises between 80-90% of the total waste.^{2,21,22} Furthermore, solvent use consumes about 60% of the overall energy used to produce an active pharmaceutical ingredient (API) and accounts for 50% of the total post-treatment greenhouse gas emissions.³⁶ These percentages are large, especially considering that about 3.8 million tons of solvent are

used in the U.S. each year.¹¹ There is also concern for the large amounts of solvent used in reactor cleaning. For example, in pilot plant operation, the volume of solvent used for cleaning is generally 2–3 times greater than the amount of solvent used in the reaction itself.³⁷ Another consideration is that the cost of solvent usage is three-fold: the cost of the solvent itself, the cost required for safe handling, and the cost for safe disposal.³⁸ Thus, by applying the principles of green chemistry, minimizing the amount of solvent used will provide many advantages.

1.3.2.1 Solvent-free Reactions

In accordance with the principles of green chemistry, the best solvent is no solvent. Such solvent-free reactions have the advantages of: simplifying syntheses and separation procedures, preventing waste, low costs, avoiding hazards and toxicity associated with the use of solvents, increasing energy efficiency, and numerous other advantages.^{32,39-41} Generally these reactions can be classified into three types: reactions between neat reagents, reactions between reactants supported on solid mineral supports, and reactions carried out under phase transfer catalysis (PTC) conditions free of solvent.³² Before going into further detail, it is useful to distinguish between ‘solvent-free’ and other related terms used in the literature, namely solid-phase and solid-state.

Solvent-free synthesis involves any system in which neat reagents react together in the absence of a solvent, solid-phase synthesis involves the reaction of molecules from a fluid phase with a solid reactant, and solid-state synthesis or solid-solid reactions involve two macroscopic solids directly interacting to form a third, solid product.^{39,42} Thus, solid-state reactions are solvent-free and solid-phase reactions are not necessarily solvent-free. Lastly, it should also be considered that solvent-free usually refers to the

reaction stage; solvent will likely be needed at some point for product work-up, purification, and/or analysis.

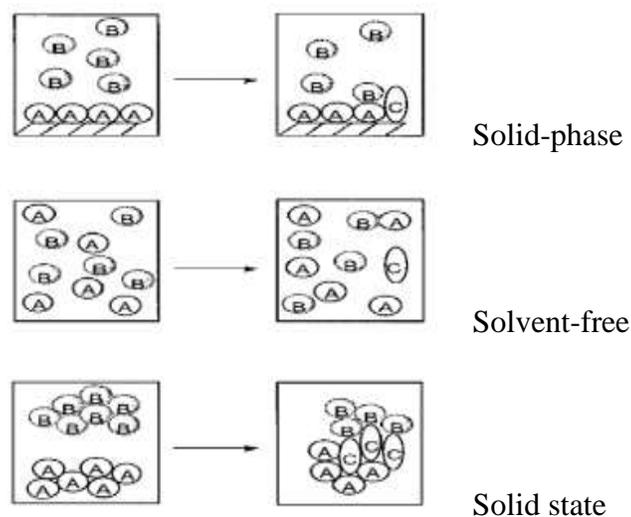


Figure 3. Cartoon of different reaction types.⁴²

In solid-state reactions, rate enhancements may be observed.⁴⁰ This has been attributed to increased concentrations, although this is not necessarily true. Although reactant concentration may be high, the actual number of active reactant molecules would be low because only those molecules at the surface would be able to react. Furthermore, the fixed orientation of the molecules in the solid makes for a lower cross-section, and the energy required to disrupt the crystal lattice to enable the individual molecules to react is often considerable.⁴² Thus, solid-solid reactions would be expected to exhibit diffusion-controlled kinetics which contradicts the rate enhancements observed. Another consideration is that reaction between two solids would form a solid product that may coat the surfaces of the reactants and effectively prevent full conversion. The rate-enhancements observed in solid-state reactions can be explained by either inclusion complexation or the formation of a melt phase.^{41,42} The former does not involve interaction between two discrete solids but rather a reaction between two

components of a single crystalline phase. The latter involves the formation of a liquid phase which enables reactant mobility. Melting may be due to grinding of the mixture and/or the formation of a eutectic mixture with T_{fusion} below ambient temperature.³⁹ Either way, solid-state reactions have not gone without objections. There is the possibility of hot spot formation, runaway reactions, organic reactions proceeding explosively, and difficulties in handling solid or highly viscous material.^{39,41}

1.3.2.2 Green Solvent Alternatives

The choice of solventless or non-organic solvent reaction medium depends on several issues, including: selectivity, stereochemistry, yield, waste, viscosity, ease of recycling, energy usage, ease of isolation of product(s), competing reactions, and heat of reaction.³⁹ Where reactions require solvent, water is the best choice because it is non-toxic, non-inflammable, abundantly available, and inexpensive. If water cannot be used then there are guides and methods that can be used to select alternate, more 'green' solvents.^{31,34-36,43,44} One such guide for the replacement of undesirable solvents is presented in Table 1. Some solvents will be briefly described here in terms of why they are undesirable.

Many chlorinated solvents, such as dichloromethane, chloroform, and carbon tetrachloride, are carcinogenic hazardous air pollutants (HAPs) that contribute to ozone depletion.^{34,43} A green solvent selection guide has been developed for the replacement of dichloromethane in chromatography.⁴³ For use as a solvent, dichloromethane and chloroform have been compared with other solvents as shown in Table 2. One replacement for dichloromethane is 2-methylTHF which is increasingly being used in route development at GlaxoSmithKline (GSK). For example, it was used on average in

16% of all pilot plant campaigns in 2007-2009 compared with an average of 3.5% of all pilot plant campaigns in 2005-6.³⁵ However, if a chlorinated solvent needs to be used then dichloromethane is the best choice.³⁴

Table 1. Solvent replacement table.³⁴

Undesirable solvents	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or diethyl ether	2-MeTHF or <i>tert</i> -butyl methyl ether
Dioxane or dimethoxyethane	2-MeTHF or <i>tert</i> -butyl methyl ether
Chloroform, dichloroethane or carbon tetrachloride	Dichloromethane
Dimethyl formamide, dimethyl acetamide or <i>N</i> -methylpyrrolidinone	Acetonitrile
Pyridine	Et ₃ N (if pyridine used as base)
Dichloromethane (extractions)	EtOAc, MTBE, toluene, 2-MeTHF
Dichloromethane (chromatography)	EtOAc/heptane
Benzene	Toluene

Table 2. A comparison of substitute solvents for dichloromethane and chloroform.³⁵

Solvent	Cas number	Melting point °C	Boiling Point °C	Waste	Environmental Impact	Health	Flammability & Explosion	Reactivity/Stability	Life Cycle Score	Legislation Flag
Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7	
Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8	
Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6	
<i>t</i> -Butylmethyl ether	1634-04-4	-109	55	4	5	5	3	9	8	
2-Methyltetrahydrofuran	96-47-9	-137	78	4	5	4	3	6	4	
Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7	
Chloroform	67-66-3	-64	61	3	6	3	6	9	6	

For hydrocarbon solvents, hexane is a HAP and pentane is flammable.^{30,34} Heptane is recommended as a replacement for these solvents.³⁴ Replacements for polar aprotic solvents have been identified as a key green chemistry research area.³⁷ Solvents such as *N*-methylpyrrolidin-2-one (NMP), *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMAc) have been found to have human reproductive risks and are therefore becoming targets of increasing regulatory constraint. They are also problematic because work-up usually involves large quantities of water and the preferred disposal method for mixed aqueous/organic wastes has generally been incineration.³⁷ When

choosing alternate solvents, life-cycle assessments (LCAs) should be considered as they will give an indication of the solvent's 'greenness' over the course of its production and disposal/recycling.³⁶ For example, on the basis of LCAs, tetrahydrofuran, butyl acetate, cyclohexanone, and 1-propanol are not recommended.⁴⁴ Another consideration to take into account is that overall average scores for solvents can be misleading because they can mask a serious issue for a particular solvent which may have a high average score but a low score in either of environmental impacts, health, or safety (referred to as EHS concerns). There are likely to be trade-offs in solvent choice and these should be individually considered for suitability in a selected process.

1.3.3 Catalysts

1.3.3.1 Phase Transfer Catalysis (PTC)

There is a variety of phase transfer catalyzed systems which can be used to minimize waste.⁹ Some benefits of using these systems are: milder/safer reaction conditions, increased rates of very slow reactions, high selectivity, reduction/elimination of solvent, and simplified separation of products. In phase transfer catalysis (PTC), reaction is brought about by the use of small quantities of an agent which transfers one reactant across an interface into the other phase so that reaction can proceed.⁴⁵ Since the phase transfer agent acts catalytically, it performs the transport function repeatedly. It has been demonstrated that a liquid organic phase is necessary to induce the ion-pair exchange.⁴⁶ Furthermore, the catalyst should not bind too tightly to a chemical species or else a reaction will not occur. PTC can be effectively combined with microwave irradiation because the catalysts involved are highly polar species (ex: quaternary

ammonium and phosphonium salts, aka ‘quats’) and so they are prone to microwave activation.⁴⁷

1.3.3.2 Clays

Clays are crystalline materials of very fine particle size ranging from 150 to less than 1 micron and are made up of layered silicates.^{48,49} Minerals that are composed of two tetrahedral layers and one octahedral layer are referring to as a (2:1)-clay mineral or TOT mineral.^{48,50} An example is montmorillonite clays which have the general formula $(Mx^+)^{ex}[(Si_8)^{tet}(M(III)_{4-x}M(II)_x)^{oct}O_{20}(OH)_4]^{x-}$ where M^+ is an exchangeable cation present in the interlayer, M(III) and M(II) are non-exchangeable octahedrally coordinated trivalent and divalent cations respectively, and the layer charge is $0.5 < x < 1.2$.⁴⁹ The generic structure of a montmorillonite clay is shown in Figure 4.

Due to their Bronsted and Lewis acidities, clays function as efficient catalysts for a variety of organic transformations.⁴⁸⁻⁵¹ Their properties can be easily modified,^{48,49,52} and their advantages have been discussed elsewhere.^{48-50,52,53} In the context of green chemistry, clay catalysis applies green chemistry principles 7 (using renewable feedstocks), 9 (catalytic instead of stoichiometric reagents) and 12 (minimizing the potential for accidents).

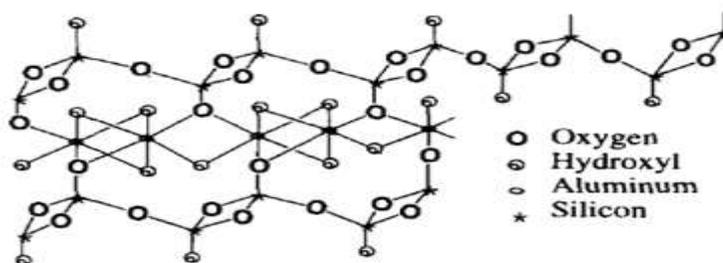


Figure 4. The generic structure of montmorillonite.⁴⁸ Notice the octahedral aluminate layer sandwiched between two tetrahedral silicate layers.

1.3.3.3 Biocatalysis

The use of enzymes in reactions offers many advantages, including: an environmentally benign catalyst (principles 7 and 9), mild reaction conditions (principles 3 and 12), selectivity at different levels (chemo-, regio- and stereo-) and concurrent reduction in waste (principle 1), and avoidance of protection/deprotection sequences (principle 8).⁵⁴ Despite the usual limitation of the need for an aqueous environment for enzyme-catalyzed reactions, biocatalysis is a versatile method and can be combined with the use of ionic liquids,^{55,56} supercritical carbon dioxide,⁵⁷ and microwave irradiation.⁵⁸ With regards to the latter, hyperthermophilic enzymes can be activated at temperatures far below their optimum, proposedly by microwave-induced conformational flexibility.⁵⁸

2 MICROWAVES IN CHEMISTRY

2.1 Development

Microwaves are electromagnetic irradiation in the frequency range of 0.3 to 300 GHz, corresponding to wavelengths of 1 cm to 1 m.^{59,60} Microwave photon energy at the typically used frequency of 2.45 GHz (corresponding to 10 μeV) is too low to cleave molecular bonds and therefore microwaves cannot induce chemical reactions by direct absorption of electromagnetic energy, as opposed to UV-Vis radiation.⁵⁹ Instead, microwaves are absorbed by rotational modes of certain molecules and converted into heat. This interaction is supposedly more efficient (see Section 1.3.1) than conventional heating mechanisms that rely on conduction and convection for heat transfer.^{59,61}

Applications of microwaves in organic chemistry did not occur until 1986 – more than 30 years since the first domestic microwave oven was introduced. Current interest in

microwave chemistry has increased due a greater availability of commercial microwave equipment, the development of solvent-free techniques, and access to shorter reaction times.⁶² Other uses of microwaves besides synthesis include: the regeneration of chromatographic adsorbent, drying material (i.e. desiccant), or molecular sieves; drying of glassware; and activation of TLC plates.⁶³ Another interesting application of microwaves is its combination with UV-Vis radiation.⁶⁴ In the future, microwave chemistry will likely become more popular for conducting analytical and synthetic reactions in laboratories. As evidenced by Figure 5, the number of publications in the field has increased from about 500 in 1997 to over 2000 up to 2004.

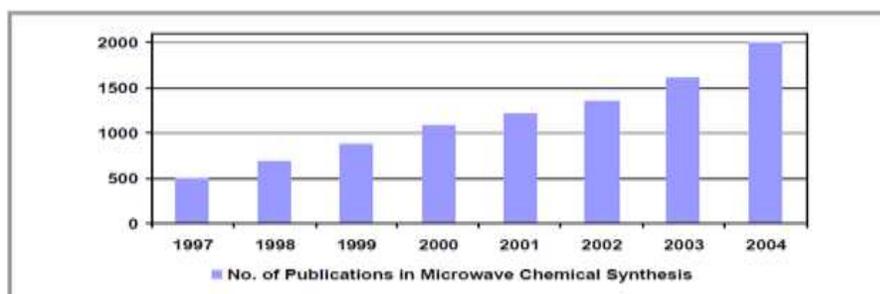


Figure 5. Number of publications in microwave chemistry from 1997-2004.²⁸

2.2 Microwave Systems

Microwave ovens are divided into two categories: multi-mode, which is generally associated with domestic ovens, and mono/single-mode, which is generally associated with commercial ovens. These two categories will be described and contrasted in the following sections.

2.2.1 Multi-mode

Multi-mode units have multiple wavelengths of microwave energy within the cavity of the oven. When microwaves enter a cavity, they are reflected by the walls to create three dimensional stationary wave patterns called modes.^{26,28,65} This results in an

uneven microwave field density with hot spots and cold spots. Consequently, multi-mode ovens are limited in that the heating of samples cannot be controlled efficiently. Another limitation is that, in a domestic microwave oven, the irradiation power is generally controlled by on-off cycles of the magnetron which provide high power for short heating periods.^{28,66} Consequently, it is not possible to reliably monitor the reaction temperature. Domestic microwave ovens have been further critiqued for lack of safety controls, uncontrolled heating and the corresponding risk of explosions, and an inability to stir reactions.^{28,67,68} However, one upside is that, in the much larger multimode instruments, reaction scale-up is possible and a greater number of samples can be accommodated.^{27,29,66}

2.2.2 Mono-mode

Mono-mode units possess a small cavity that holds only one wavelength of microwave energy in which the sample is positioned at the crest.^{26,28,60} This provides a homogeneous, dense field pattern that reduces the occurrence of hot and cold spots. As a result, greater reproducibility can be obtained with mono-mode systems. Another advantage is that the higher microwave power can produce faster reaction rates.^{26,28} With better control of the heating pattern in mono-mode ovens, yields can be optimized as opposed to domestic ovens where such control is not possible.²⁸ Lastly, sufficient microwave energy is available in mono-mode systems for small samples to be used.²⁶ One downside is that while reaction scale-down is possible the converse process of scaling-up is limited to the small cavity size. Typical single-mode instruments available today can process volumes ranging from 0.2 to about 50mL under sealed-vessel conditions and higher volumes (~150mL) under open-vessel reflux conditions.⁶⁶

3 SURVEY OF REACTIONS

The following is a survey of green syntheses which have been considered for this research project. The principles of green chemistry will be applied to reactions selected from the following:

- Amide formation
- Ester formation
- Hydrolysis
- Oxidation/reduction

in order to determine if more effective, environmentally friendly synthesis for these reactions can be acquired. Microwave radiation, solvent-free conditions, catalysis, or some combination of the three will be used in the procedures. Results will be analyzed according to percent yield, reaction time, and appropriate green chemistry metrics. The objectives are as follows:

- Assess the effectiveness (i.e. yield) and greenness for direct amide condensation.
- Compare the effectiveness and greenness of selected catalytic methods of ester formation.
- Assess the effectiveness, selectivity, and greenness of selected oxidation procedures.
- Assess the greenness and selectivity of asymmetric, enzyme catalyzed reductions.

3.1 Amide Formation

Amide formation has been considered a key green chemistry research area.³⁷ This is because many current methods proceed with low atom economy. In general, the

formation of amides involves activation of the carboxyl group by conversion to a more reactive functional group such as an acyl chloride, mixed anhydride, acyl azide or active ester, or via *in situ* activation of carboxyl group by coupling reagents such as DCC.⁶⁹ More atom economical reactions, such as those which involve direct condensation, are needed to reduce wastes produced during these reactions.

3.1.1 Direct Condensation

The simple reaction between an amine and a carboxylic acid has previously been done under microwave conditions.^{69,70} In one experiment by Wang et al., the use of a commercial microwave oven gave amides in high yield.⁷⁰ When aniline was used for the amine, the presence of electron withdrawing groups on the benzene ring resulted in reduced yields whereas the presence of electron donating groups resulted in high yields. The position of substituents also proved to be important as ortho groups resulted in lower yields due to steric hindrance.

In another experiment by Perreux et al., various yields were obtained using a commercial microwave.⁶⁹ In some instances, a 1:1.5 stoichiometric ratio of reactants gave higher yields. They attributed this to electrophilic assistance to nucleophilic attack by the amine as shown in Figure 6. In the case of N-benzyl-2-phenylacetamide, they suggested that π - π interactions contributed to the greater yields observed. Lastly, they proposed that the intermediate formation of an ammonium carboxylate salt should favor the formation of an amide due to an ionic conduction mechanism.

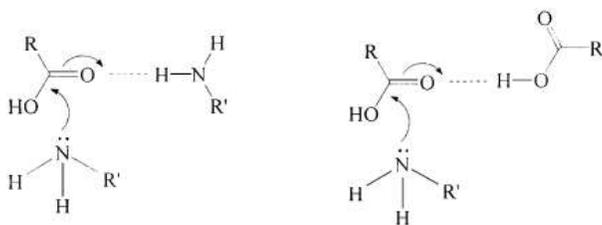


Figure 6. Electrophilic assistance to nucleophilic attack by amine.⁷⁰

3.1.2 Ritter Reaction

The Ritter reaction involves the reaction of an alcohol with a nitrile to form an amide according to Figure 7 below. In this reaction the alcohol forms a carbocation by

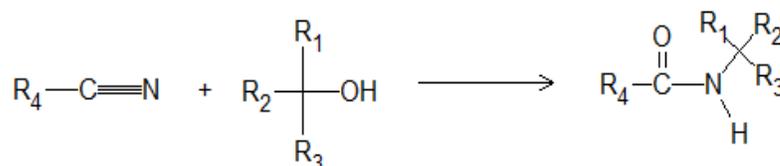


Figure 7. Ritter reaction.

the loss of water and then the nitrile attacks the carbocation to form a nitrilium ion.^{71,72}

The nitrilium ion reacts with water and, upon tautomerization, yields the corresponding amide. According to this mechanism, stabilized carbocations would be more reactive.

The Ritter reaction has been done using montmorillonite KSF as an alternative to concentrated H_2SO_4 .⁷³ Microwave and dry media conditions were used to give yields of at least 75% in less than ten minutes.

3.1.3 Schmidt Reaction

A modified procedure for the Schmidt reaction was presented by Eshghi and Hassankhani.⁷⁴ Instead of using hydrazoic acid, they used sodium azide to react with a variety of ketones. Reactions were done under microwave conditions with a P_2O_5/SiO_2 catalyst and without solvent (see Figure 8). Either of the R groups could shift but,

generally, migration of an aryl group predominates over that of an alkyl group. In the other cases, the major product is the one where the more bulky group has migrated.⁷⁴ Yields of at least 70% were obtained in ten minutes or less. This procedure is very green in that it applies the green chemistry principles 1, 5, 6, and 9 (see Section 1.1 Principles). However, it does not apply principle 12 (minimize safety hazards) because sodium azide is unstable and may explode.⁷⁵

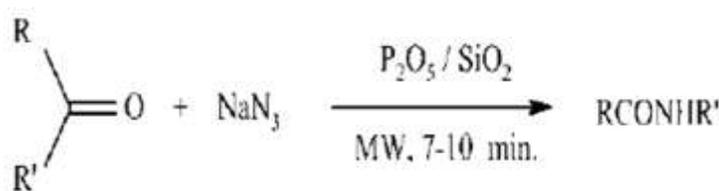


Figure 8. P₂O₅/SiO₂-catalyzed one-pot synthesis of amides from ketones via Schmidt reaction under microwave irradiation in dry media.⁷⁴

3.1.4 Beckmann Rearrangement

The Beckmann Rearrangement occurs when an oxime rearranges to an amide. Oximes can be prepared by reaction of their corresponding ketones with hydroxylamine under dry conditions with^{76,77} or without microwave irradiation.^{76,78} Their rearrangement to amides has been reviewed and a trans-shift is the generally accepted mechanism.⁷⁹ However, two isomeric oximes, cis and trans, can be obtained. Thus, for asymmetric ketones, a mixture of products can be obtained. In one experiment, an AlCl₃-ZnCl₂ mixture on silica gel was used as a catalyst in solvent-free conditions under microwave irradiation.⁸⁰ A conventional microwave oven was used with reaction times ranging from 4.5 to 11.5 min. Yields were good to excellent. It was found that electron-donating groups on an aromatic ring facilitate the reaction to lead to better yields compared to electron-withdrawing groups. Some advantages of this method are: fast reaction times, solvent-free conditions, catalyst reusability, and ease of work-up.

3.1.5 Nitrile Hydrolysis

Primary amides can be formed by partial hydrolysis of nitriles. A green procedure for this reaction involves the use of silica supported MnO_2 reagent under microwave irradiation and dry conditions.⁸¹ It was found that the silica supported MnO_2 could be reused at least three times. Furthermore, silica was shown to be necessary for reuse since MnO_2 by itself failed to show any reusability. It is interesting that this ‘hydrolysis’ reaction is done under dry conditions without water as it seems to be more of an oxidation reaction than a hydrolysis reaction.

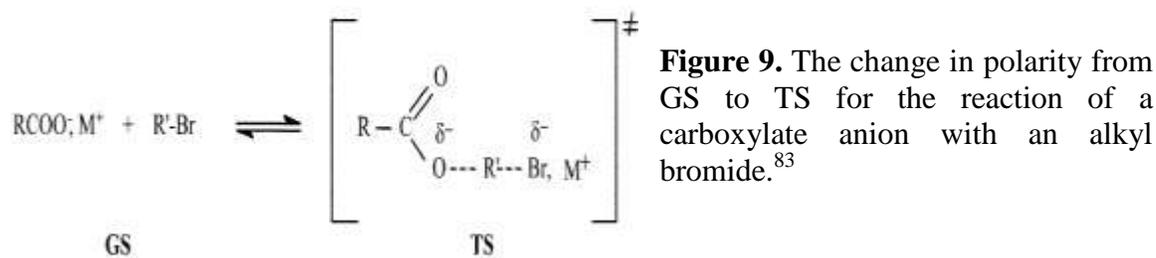
3.2 Ester Formation

Esters are of great importance in organic chemistry since they are intermediates in the synthesis of drugs, plasticizers, perfumes, flavor chemicals, fine chemicals, pharmaceuticals, cosmetics, solvents and chiral auxiliaries.⁸² The common method of preparation involves Brønsted acid catalysts, such as H_2SO_4 or p-toluenesulfonic acid (PTSA), which result in highly acidic wastes. Furthermore, such Brønsted catalysts result in equilibrium conditions that may be difficult to force reactions to go to completion.

3.2.1 Phase Transfer Catalysis (PTC)

Phase transfer catalysis has been used in the formation of esters from carboxylate anions and alkyl bromides under solvent-free conditions and microwave irradiation.^{46,83} Aliquat 336 (methyltri-n-octylammonium chloride) was used as the phase transfer catalyst. Alternately, TBAB could be used. Taking the study by Villa et al. as an example, specific microwave effects were observed for PTC as opposed to acidic catalysis with PTSA.⁸³ The ion pair with M^+ in the transition state (TS) was suggested to be looser than in the ground state (GS) (tighter ion pairs) and consequently more polar as

shown in Figure 9. Therefore, polarity increases from the GS to the TS. The result is an enhancement in electrostatic stabilization with the electric field in TS versus GS. Consequently, the activation energy is decreased and a specific microwave effect is observed. In contrast, Loupy et al. found that the microwave effects were limited to thermal effects.⁴⁶



3.2.2 Clay Catalysis

Various montmorillonite clays have been used in esterification reactions.^{51,52} Hazarika et al. synthesized parabens (p-hydroxy benzoic esters) using montmorillonite K10 clay as catalyst.⁵¹ Parabens find wide applications as preservative agents in food, beverages, drugs and cosmetics due to their anti-microbial activity. In their experiment, high yields (>80%) were obtained and the catalyst was reused two times without appreciable loss of its activity. For comparison, the Fe³⁺-exchanged montmorillonite clay used by Kantam et al. showed consistent activity over six cycles.⁵² In the study by Ramesh et al., they used ion-exchanged montmorillonite catalysts and microwave conditions to effect esterification reaction.⁵³ It was found that: microwave irradiation results in higher yields of ester in shorter reaction period compared to conventional heating, the presence of solvent gives higher yields of ester than in its absence, yield increases with temperature, and yields decrease with an increase in number of carbon atoms in the alkanolic acid.⁵³ This last observation was explained on the basis of the

reaction mechanism as shown in Figure 10. If the alkanolic acid has a longer chain length then there will be a larger positive inductive effect. This effect decreases the electrophilicity of the carbonyl carbon and thus decreases the ease with which protonated species can form.

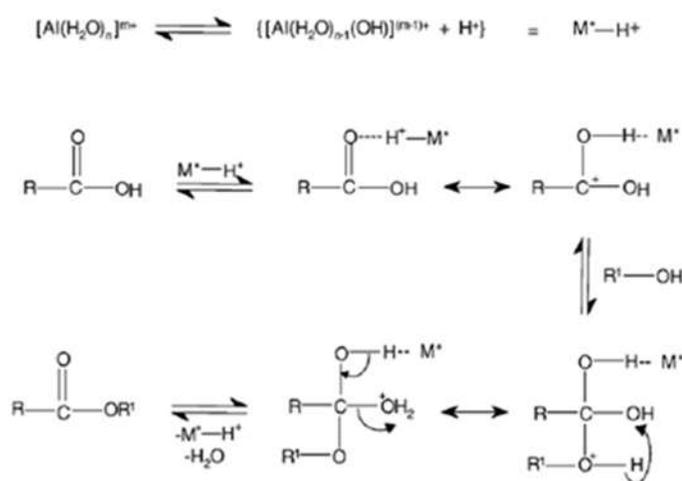


Figure 10. Possible mechanism for esterification with metal ion exchanged montmorillonite catalysts.^{52,53}

3.2.3 Lewis Acid Catalysis

A variety of Lewis acid catalysts can be used to form esters.⁸² The use of Lewis acids as opposed to Bronsted acids is advantageous in that it avoids highly acidic wastes. In the procedure by Barbosa et al., solvent-free conditions were used in conventional and microwave heated systems.⁸² The use of microwave irradiation reduced reaction times and provided higher yields. One limitation of this study is that few reactant combinations were tested (acetic acid with 2-methyl-1-butanol or benzoic acid with ethanol); rather, the focus was on testing different solid-supported Lewis acid catalysts.

3.3 Hydrolysis Reactions

Hydrolysis procedures may involve harsh conditions with large quantities of solvent. If protection/deprotection methods are required then it is important that the intermediates are benign and that the methods require minimum resource inputs and

waste outputs. Furthermore, the methods should be carefully chosen so as to avoid altering acid and base-sensitive functional groups. Due to time constraints, no hydrolysis reactions were done in the lab.

3.3.1 Amides

In one experiment, amides were hydrolyzed using $\text{KF}/\text{Al}_2\text{O}_3$ catalyst under microwave irradiation and solvent-free conditions.⁸⁴ The authors noted that the reaction could be done in the absence of microwaves but the reaction times are relatively long. Using microwave irradiation, high yields ($\geq 90\%$) were obtained in 4 minutes.

3.3.2 Esters

Esters can also be hydrolyzed using $\text{KF}/\text{Al}_2\text{O}_3$ catalyst under microwave irradiation and solvent-free conditions.⁸⁵ High yields ($\geq 90\%$) of the corresponding carboxylic acids were obtained in 2 minutes. Another means of ester hydrolysis involves the use of LiCl and DMF under microwave irradiation.⁸⁶ However, this method is limited to methyl esters; other alkyl substituents are relatively unaffected. Esters may also be simply hydrolyzed by NaOH in aqueous DMF at ambient temperature.⁸⁷

3.4 Oxidation

Oxidation is one of the most widely used reactions in synthetic chemistry because it can introduce an oxygen atom into a compound or transform one functional group into another. Some commonly used stoichiometric oxidizing agents include chromium reagents (ex: Jones reagent, PCC, PDC) and oxo-manganese species (example: permanganate).⁸⁸ However, these metal salts are usually toxic, hazardous, and often cause environmental problems. Consequently, safer and catalytic reagents are preferred.

From the viewpoint of atom efficiency and environmental concerns, the development of methods using molecular oxygen or hydrogen peroxide has attracted much attention.

3.4.1 Use of Clay Supported Reagents

Clays have been used in the oxidation of alcohols.⁸⁹⁻⁹² Some methods use stoichiometric amounts of iron(III) nitrate and result in the evolution of nitrogen oxide gases.^{89,90} In one procedure, oxidation was achieved under microwave irradiation and solvent-free conditions using clayfen (montmorillonite K10 clay-supported iron(III) nitrate).⁸⁹ Alcohols were mixed with clayfen and irradiated for 15-60 seconds to give high yields (>87%) of the oxidized product without over-oxidation to carboxylic acids. One problem with this method is that clayfen loses about 40% of its reactivity upon standing exposed to air for 4 h or under n-pentane for 24 h, and it may thermally decompose.⁹³ The oxidation procedure developed by Eftekhari-Sis et al. seems to be a better means of alcohol oxidation.⁹¹ Their method involved hydrogen peroxide catalyzed by lithium chloride on montmorillonite K10. A proposed mechanism is shown in Figure 11. A non-polar, aprotic solvent gave higher yields than other solvents which were polar and/or protic. High yields (>70%) were obtained for the alcohols tested. A small downside of this method is that more than a stoichiometric amount of H₂O₂ is needed due to its non-selective thermal decomposition to oxygen and water at the reaction temperature.⁹²

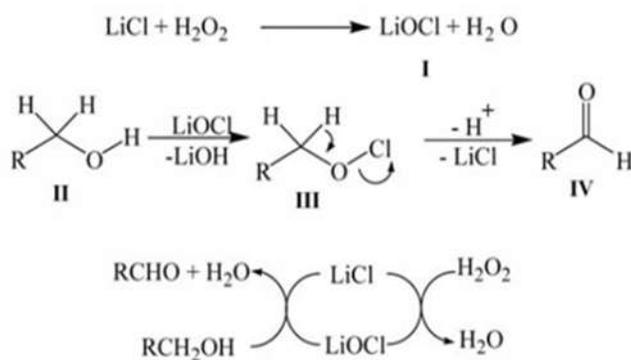


Figure 11. A proposed mechanism for LiCl catalyzed oxidation of alcohols to their corresponding carbonyl compounds.⁹¹

Clays have also been used to oxidize aldehydes to their corresponding alkanolic acids. It was serendipitously found that montmorillonite KSF can be used to air-oxidize aliphatic aldehydes over the course of a week.⁹⁴ However, no reaction was observed for aromatic or α,β -unsaturated systems.

Alkylarenes can also be oxidized using montmorillonite K10 clay-supported oxidizing agents.⁹⁵ Oxidation can be done at room temperature, under ultrasonic irradiation, or under microwave irradiation to give good yields of the carbonyl product. The use of ultrasonic irradiation reduced the time required to obtain good yields and the use of microwave irradiation further reduced the required reaction time. However, in some cases, ultrasonic or microwave irradiation resulted in lower yields. Other means of oxidizing alkylarenes include the use of activated carbon with molecular oxygen⁹⁶ or hydrogen peroxide.⁸⁸

3.4.2 Alcohols to Carbonyl-containing Compounds

There are various ways to oxidize alcohols to their corresponding carbonyl compounds. Aside from the use of clay supported reagents, some other green procedures, under microwave irradiation, include the use of: MagtrieveTM (CrO_2),⁹⁷ silica supported active manganese dioxide,⁹⁸ and cobalt nitrate hexahydrate supported on silica gel.⁹⁹

3.5 Enzyme Catalyzed Reduction

Reduction of prochiral carbonyl compounds could lead to a racemic mixture of alcohols. When only one enantiomer is desired, resolution would lead to waste enantiomer products. Rather than resolve the enantiomers it would be better to selectively produce the desired enantiomer in order to reduce waste. One means of doing so is by using baker's yeast.¹⁰⁰⁻¹⁰² In accordance with the principles of green chemistry,

water is the first solvent of choice for biocatalysis because there are no EHS concerns associated with it. However, the low solubility of many organic molecules in water, the existence of undesired side reactions (ex: hydrolysis), and difficult product separation procedure, limit its applications.¹⁰¹ Alternately, the use of glycerol is advantageous because: it is non-toxic; biodegradable; a recyclable by-product of the transesterification of a triglyceride; has a relatively high polarity that allows the dissolution of glucose, sucrose, and organic compounds that are poorly miscible in water; and it allows easy separation of the product by extraction with glycerol immiscible solvents. In the procedure by Wolf et al. it was found that yields were much lower for ketones than β -keto esters and that enantiomeric excess of the S-product was high regardless of yield.¹⁰²

4 MATERIALS AND METHODS

4.1 Direct Amide Formation

Microwave assisted synthesis of selected amides was attempted using a domestic Sylvania microwave oven (normal maximum output power: 1100 W, operating frequency: 2.45 GHz). Variations on the following procedures were used:

Procedure 1: In a Pyrex flask, 3 mmol of amine and 3 mmol of carboxylic acid were mixed together. The mixture was subjected to microwave irradiation after which the mixture was allowed to cool to room temperature. The mixture was then extracted with 10 mL of dichloromethane. The extract was washed successively with 9 mL of 2 M HCl and 10 mL of 5% NaHCO₃. The organic layer was dried over anhydrous MgSO₄ after which MgSO₄ was filtered off and the solvent was removed under reduced pressure.

Procedure 2: A mixture of 3 mmol of amine and 2 mL of carboxylic acid were subjected to microwave irradiation after which the mixture was allowed to cool to room temperature. To the resulting mixture was added 10 mL of 1:50 ethyl acetate: cyclohexane. It was then stored for one day in a refrigerator. After this time the product was filtered off and washed free of acid with water.

The main differences between these two reactions are that the latter uses an excess of carboxylic acid and both use different solvents in the work-up.

4.2 PTC Esterification

Phase transfer catalysis was used for the following combinations:

Carboxylic Acid	Alkyl Halide
Benzoic Acid	Benzyl Bromide
Benzoic Acid	Butyl Bromide
Acetic Acid	Benzyl Bromide
Acetic Acid	Butyl Bromide

The procedure used was based on that used by Loupy et al. and Villa et al.^{46,83} In this order, 10 mmol of carboxylic acid, 10 mmol of anhydrous K_2CO_3 , 1.5 mmol of Aliquat 336, and 10 mmol of alkyl halide were mixed together. The reaction mixture was introduced to an oil bath at 140°C for 15 min. All reactions, except that for benzyl benzoate, were done as a reflux to prevent loss of reactants. After cooling to room temperature, the product was extracted with 50 mL of dichloromethane and was then vacuum filtered through ~2.5 g of florisil. The crude products were analyzed by TLC using 20:80 ethyl acetate: hexane as eluent. Different methods were used to detect the spots, including: UV lamp, bromocresol green stain, and an iodine chamber. Two different methods were attempted to purify the products. Benzyl benzoate and butyl acetate were purified by simple distillation; however, the crude benzyl benzoate

decomposed. Butyl benzoate and benzyl acetate have high boiling points (250°C and 206°C respectively) and so distillation may have resulted in their decomposition as well. Instead, these crude products were vacuum filtered through more florisil for a total of ~15 g of florisil being used (the additional florisil was included in the E-factor). The products were washed out with CH₂Cl₂ (amount not included in the E-factor) and the solvent was removed on a rotavap. These partially purified products and the butyl acetate distillate were analyzed on an IR spectrometer.

4.3 Oxidation Reactions

In a general procedure for the oxidation of alcohols, the matrix was prepared by mixing KMnO₄ and montmorillonite K10 in a mortar in a ratio of 0.95 g:8.05 g. To 9 g of matrix 6 mmol of the alcohol was added and the mixture was stirred for 5 min. Then the mixture was refluxed in 30 mL of CH₂Cl₂ for 1.5 h with stirring. Once cooled, the mixture was suction-filtered through a thin layer of Celite (between 0.5-0.6 g). An additional 30 mL of CH₂Cl₂ was added to the matrix in the round bottom flask. After stirring for 5 min the mixture was filtered. This extraction was repeated a second time (total of 90 mL of dichloromethane). The filtrate was taken in a round bottom flask and the solvent was removed by rotavap. In an alternate procedure, the mixture of matrix and alcohol without any solvent was left for a week in a parafilm beaker. Product was then extracted with CH₂Cl₂ (3x30 mL) and worked-up as before. Analysis involved melting point (if solid), thin layer chromatography (TLC) with 20:80 ethyl acetate: hexane, and infrared (IR) analysis.

A second oxidation procedure involved the use of LiCl as a catalyst with H₂O₂ as reagent. This procedure is based on that developed by Eftekhari-Sis et al.⁹¹ The catalyst

was prepared by dissolving 2 g of LiCl in deionized water. Then 8 g of montmorillonite K10 was added to the solution. The mixture was then refluxed with stirring for 2 h after which the solvent was evaporated off. The removal of solvent was time-consuming and had to be finished a day after it was started. Specifically, the solution was heated for approximately 5.5 h and was then removed from the hot plate until the next day when heating was continued. Once the solvent was removed, the clay-supported LiCl was left in an oven until needed. Reactions involved dissolving 1 mmol of alcohol in 15 mL of toluene. Then 0.25 g of catalyst and 5 mL of 30% hydrogen peroxide were added. The mixture was refluxed with stirring for 1.5 h. After letting the mixture cool, the catalyst was filtered off. Initially, the mixtures were filtered through filter paper but this resulted in clogging and the use of additional filter papers. This was changed to a vacuum filtration procedure. The catalyst was washed with CH_2Cl_2 (2x10 mL) and then anhydrous MgSO_4 was added to the mixture in the filter flask to remove the water used. Weighings were not obtained for the amounts of MgSO_4 used and so it is not included in the E-factor. After letting the mixture set for some time (~10 min) the MgSO_4 was filtered off through filter paper. Then the solvent was rotavaped off.

The procedure for the oxidation of alkylarenes was similar except the ratio of KMnO_4 and montmorillonite K10 was 3.16 g:6 g, 4.5 g of matrix was used, and 2 mmol of alkylarene was used. Reactions for the alkylarenes were also done at 1.5 h and one week. Also, for the alkylarenes, the reactions were repeated at one week with dimethylcarbonate to determine if it is a suitable replacement for dichloromethane in this procedure. As a limited amount of dimethylcarbonate was available for use, the solvent was distilled off rather than rotavaped off in order to collect it for further use. The

collected dimethylcarbonate was distilled a second time in order to purify it. The residue was not distilled to dryness for safety reasons; any remaining dimethylcarbonate was rotavaped off. Reactions were not repeated at 1.5 h with dimethylcarbonate because it is flammable in the presence of oxidizing materials and heat.¹⁰³ Analysis was done as before for the oxidation of alcohols.

4.4 Yeast-catalyzed Reduction

Four β -ketoesters and one β -ketoamide were reduced using a procedure modified from that used by Mori.¹⁰⁰ To an Erlenmeyer flask were added 3.0 g of yeast and then 50 mL of warm (30-35°C) tap water to disperse the yeast. To the dispersion was added 6.0 g of sugar. The flask was swirled for 5-10 min and then 1 mL (corresponding to 7.3 mmol) of ethyl acetoacetate was added. The same molar amounts were used for all other reactants rather than going by volume. The resulting mixture was put in a warm (30-35°C) water bath for 2 h during which it was swirled occasionally. After incubation the flask was taken out of the water bath and put aside uncovered for 2 days.

After 2 days, the yeast was filtered off. This step proved to be a bottleneck in the procedure as the filters tended to clog. Different methods of filtration were attempted and their effectiveness will be discussed in Section 6.5. Because different filtering methods were used, the filtering materials were not included in the E-factors so that a better comparison of this metric could be made between reactions. Thus, the calculated E-factors are slightly lower than they should be. During filtration the yeast would be washed with 20 mL of deionized water and 40 mL of diethyl ether. The filtrate was saturated with NaCl and then the layers were separated. The aqueous layer was returned to the separatory funnel and 40 mL of diethyl ether was added. After separation the

combined organic layers were added back to the sep funnel and 25 mL of brine was added. The layers were again separated. The organic layer was dried over anhydrous MgSO_4 for 10-15 min after which MgSO_4 was filtered off through filter paper. The solution was collected in a round bottom flask and the solvent was removed under reduced pressure on a rotavap. The product was then analyzed by TLC with 20:80 ethyl acetate: hexane as eluent except for acetoacetamide and α -butyrolactone where acetone was used. IR analysis was then done on the crude products as they were or as a solution in CH_2Cl_2 where noted.

5 RESULTS

For all E-factors, the boundary for calculations was set at product isolation. Thus, any waste involved with the analysis of product and cleaning of glassware is not included. Also, any filter papers used were not included, although technically this would also constitute waste. The results of all TLC and IR analyses are in Appendices A and B, respectively.

5.1 Amidification

The following five combinations were attempted:

Carboxylic acid	Amine
Benzoic acid	Aniline
Acetic acid	Aniline
Trichloroacetic acid	Aniline
Acetic acid	Urea
Acetic Acid	4-aminophenol

Reactions with benzoic acid were done using Procedure 1. In one trial, the mixture was heated for 5 min to give a yield of 11%. However, the melting point for this product was

110-114°C, much lower than the literature melting point of N-phenylbenzamide (163°C), but closer the literature melting point of benzoic acid (121-125°C). In a second trial, aniline was distilled before use and the reaction time was extended to 10 min. This gave a yield of 33% but the melting point of the product was 113-118°C. Also, towards the end of the heating period, the neck of the Pyrex flask became charred from the heat.

Using Procedure 1, the combination of trichloroacetic acid and aniline for a 3 min heating period gave no yield. Combining acetic acid and urea also resulted in no yield; most of the urea had decomposed from the heat. Lastly, the combination of acetic acid and 4-aminophenol for 5 min gave a black, tar-like residue.

Multiple attempts were made to form N-phenylacetamide. Following Procedure 2 for a heating period of 10 min gave a yield of 2.3%. This is quite low but the experimental melting point was 109-112°C which was close to the literature melting point of 113-115°C. Also the TLC results using acetone as eluent gave an R_f value of 0.729 which was close to the R_f value of pure acetanilide ($R_f=0.719$). Using equimolar amounts of acetic acid and aniline, as per Procedure 1, for reaction times of 5 min (with product work-up as per procedure 2) and 10 min (with product work-up as per Procedure 1) both gave no yield. In another trial, the amounts of reactants used were scaled up to 8.28 g of acetic acid and 0.81 g of aniline. The reaction time was also increased to 20 min with the reaction being occasionally stopped (about once every 5 min) to prevent overheating and charring of the flask. Keeping the work-up procedure the same as per Procedure 2 gave a yield of 12% with an experimental melting point of 110-112°C. While this is a relatively great improvement from before, by itself this is a very low yield which may partly be due to uneven microwave field density (see Section 2.2).

5.2 PTC Esterification

In all reactions, the crude yields were greater than the theoretical yields. To check for the presence of product, TLC analysis was performed. Unless otherwise indicated, spots were visualized with a UV lamp. The presence of product was confirmed for butyl benzoate and benzyl acetate. Pure benzyl benzoate and butyl acetate were not available for comparison but the R_f values of 0.453 for benzyl benzoate and 0.754 for butyl acetate suggest the presence of product as these values did not match those of either their respective carboxylic acid or alkyl halide. The R_f values of 0.050 and 0.046 for butyl benzoate and butyl acetate, respectively, seem to indicate the presence of butyl bromide although there is some discrepancy with the R_f values obtained for pure butyl bromide. One anomalous finding was the presence of a blue spot at the baseline for each of the products, which appeared after staining the TLC plates with a bromocresol green solution. It was suspected that these spots were due to the presence of Aliquat 336 and so a TLC plate was developed for the catalyst itself. After staining the plate with bromocresol green, a blue spot appeared at the baseline thus confirming the presence of catalyst in each crude product.

The yields of purified products are given in Table 3. Yields were moderate to low. The atom economies were around the 50% mark and decreased with decreasing molecular weight of the product. Correspondingly, the theoretical E-factors increased. It should be noted that during the synthesis of butyl benzoate the temperature of the oil bath had accidentally dropped to $\sim 115^\circ\text{C}$ while the reflux apparatus was being set up and yet this reaction had the highest yield. Also, despite the low yield, AE, and RME for this product, its E-factor was one of the lowest obtained during the course of this project. The

Table 3. Esters via phase transfer catalysis.

Product	% yield	AE (%) (a)	RME	E (theoretical)	E (actual) (b)	Solvent Intensity
Benzyl Benzoate	(c)	49.2	-	1.03	-	-
Butyl Benzoate	54 (d)	44.9	0.24	1.23	88.5	68.3
Benzyl Acetate	38 (d)	40.7	0.15	1.46	149	116
Butyl Acetate	26	34.6	0.090	1.89	242	221

(a) Includes K_2CO_3 .

(b) Includes Aliquat 336.

(c) The crude product decomposed during distillation.

(d) Purified by filtration through florisil.

yield for butyl acetate may be artificially low as some product may have remained in the distillation assembly. Due to the small amount of crude product, the temperature during distillation never exceeded 40°C. One problem with this is that the reactants (acetic acid and butyl bromide) have lower boiling points than the product and if present would also have been collected with butyl acetate. Aliquat 336 has a boiling point of 240°C and so it should not be in the distillate; indeed, some yellow residue remained in the initial round bottom flask which after some time began to decompose.

The partially purified products were analyzed on an infrared spectrometer. The butyl benzoate and benzyl acetate products were compared with the pure esters and the spectra match well as illustrated in Figure 12. This indicates good product purity. Also, none of the product spectra contained an O-H band from the carboxylic acid. These results do not verify that the products are completely pure as there may be some overlap with Aliquat 336 and alkyl bromide if present.

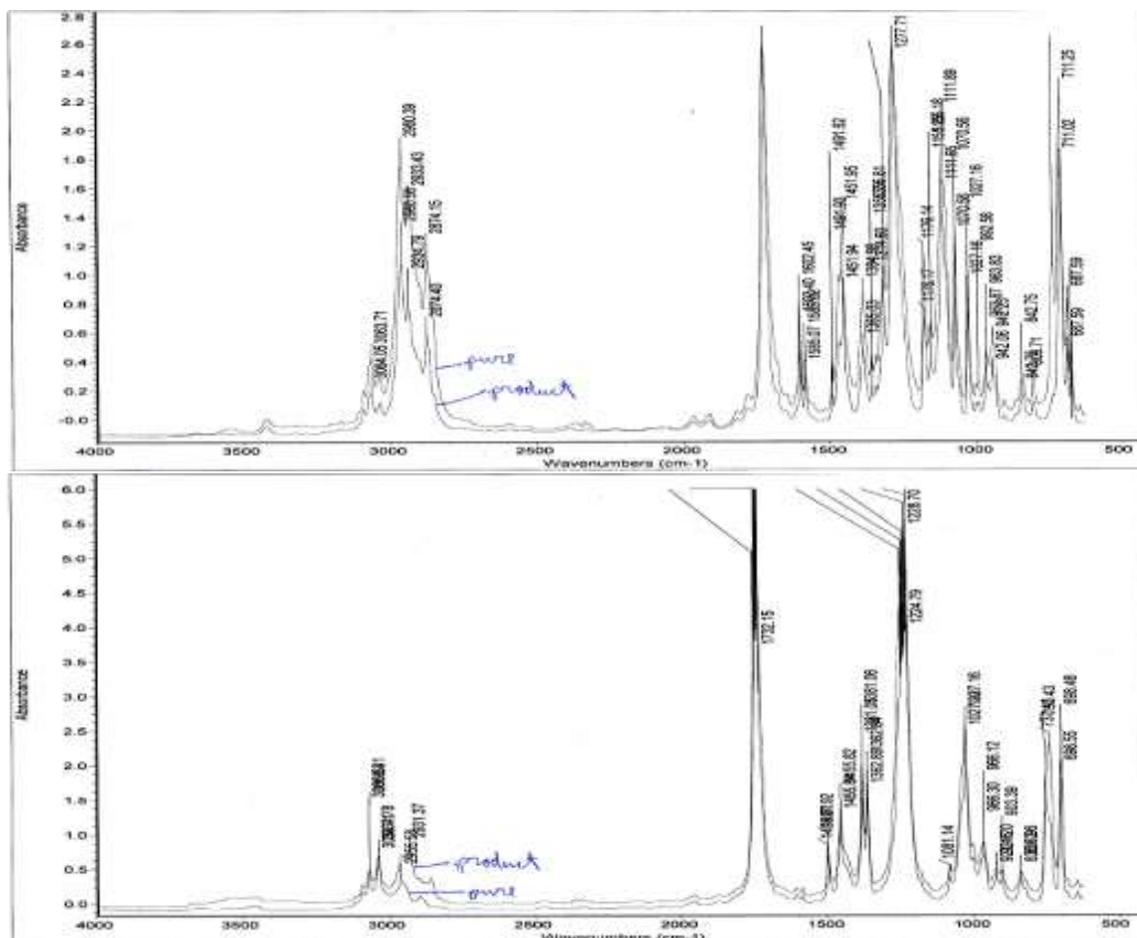


Figure 12. IR analysis of butyl benzoate (top) and benzyl acetate (bottom).

5.3 Oxidation of Alcohols

Six different alcohols were oxidized using two different reaction times each to assess the % yields and ‘greenness’ of the procedure. The results for the oxidation of benzyl alcohol, 4-methoxy benzyl alcohol, 4-nitrobenzyl alcohol, diphenylmethanol, 1-pentanol, and 2-pentanol are shown in Table 4. The procedure involved using 90 mL of CH_2Cl_2 to extract the product. To see if less solvent could be used, two trials of benzyl alcohol oxidation, one with 45mL CH_2Cl_2 and one with 90mL CH_2Cl_2 , were done over one week at room temperature. Using 45 mL resulted in half the yield obtained when 90 mL was used (41% vs. 108%). Similarly, less than half the yield was obtained with the

Table 4. Oxidation of selected alcohols with montmorillonite K10/KMnO₄.

Product	Reaction Time (a)	Crude % yield	AE (%) (b)	RME	E(theoretical)	E(actual) (c)	Solvent Intensity
Benzaldehyde	1 week (d)	41	39.9	0.16	1.51	268	229
	1 week	108	39.9	0.43	1.51	189	175
	1.5 h	83	39.9	0.33	1.51	248	229
4-methoxy benzaldehyde	1 week	88	46.0	0.40	1.17	182	168
	1.5 h	72	46.0	0.33	1.17	208	192
4-nitro benzaldehyde	1 week	43	48.6	0.21	1.06	332	306
	1.5 h	57	48.6	0.28	1.06	253	234
benzophenone	1 week	99	53.2	0.53	0.880	119	110
	1.5 h	87	53.2	0.46	0.880	137	127
pentanal	1 week	70	35.0	0.25	1.86	358	331
	1.5 h	35	35.0	0.12	1.86	718	662
	1.5 h (d)	14	35.0	0.049	1.86	995	852
2-pentanone	1 week	17	35.0	0.060	1.86	1437	1325
	1.5 h	4	35.0	0.014	1.86	6469	5963

Melting points [listed as experimental (literature) in °C]: 4-nitrobenzaldehyde at 1 week: 81-84 (103-106); 4-nitrobenzaldehyde at 1.5 h: 77-84 (103-106)

(a) Reactions at 1 week were at room temperature. Reactions at 1.5 h were at reflux in dichloromethane.

(b) Includes KMnO₄ as it was consumed in the reaction. Mont K10 is not included as it only acted as support.

(c) Includes montmorillonite K10 and celite under the assumption that they are not reclaimed for further use.

(d) 45mL of CH₂Cl₂ was used.

aliphatic alcohol 1-pentanol at 1.5 h reflux (14% vs. 35%). Consequently, the amount of extraction solvent used was kept at 90 mL for all other reactions. Although more solvent is used in this case, the E-factors are lower than if 45 mL are used due to the higher percent yields. The atom economies of the reactions were around the 50% mark or lower due to the use of the stoichiometric reagent KMnO₄. Percent yields were higher for the reactions at one week under room temperature than for the reactions at reflux for 1.5 h, except in the case of 4-nitrobenzyl alcohol. It should be noted that these are crude yields which explains why the yield for benzyl alcohol at one week was 108%. Products were not purified due to the small amounts obtained; the amounts of reactants used were

typically around 1 g. If the reactions can be scaled up then purification would be more feasible/worthwhile. Reaction mass efficiencies (RMEs) were far from the ideal value of 1 with 0.53, in the case of diphenylmethanol at one week, being the closest to this value. The E-factors were found to be much higher for aliphatic alcohols. As evidenced by the solvent intensities a large proportion of the waste was from the use of solvent. Simple calculations will show that the solvent accounted for an average of 91% of the total waste.

Product purity was checked by melting point, TLC, and/or IR analysis. For 4-nitrobenzyl alcohol, the literature mp of the reactant is 92-94°C and that of the product is 103-106°C. The melting points of the crude products obtained were 81-81°C at one week and 77-84°C at 1.5 h reaction times. These melting points are lower than both 4-nitrobenzyl alcohol and 4-nitrobenzaldehyde which seems to indicate that a eutectic mixture of the two was obtained. The TLC results are limited due to the fact that pure 4-methoxybenzaldehyde, 4-nitrobenzaldehyde and pentanal were not available. Also, pure 1-pentanol, 2-pentanol, and 2-pentanone did not show any spots under the UV lamps. Interestingly, spots were visible for the crude pentanal and 2-pentanone products obtained. One possibility that could explain this is the further oxidation of the aldehyde to its trimer.⁹⁴ The TLC results for the crude benzaldehyde and benzophenone products confirmed the presence of product although impurities were also shown to be present. The IR results show that a mixture of reactant and product were obtained for benzaldehyde and 4-nitrobenzaldehyde. The best results were for benzophenone where no hydroxyl bands were observed. The worst results were for the aliphatic alcohols where no carbonyl bands were observed. A carbonyl band was observed for pentanal at

one week but it was small; its intensity was 0.0177 whereas the OH band had an intensity of 0.0578. The 4-methoxybenzaldehyde products were unusual as they were viscous, glue-like yellowish solids whereas pure 4-methoxybenzaldehyde is supposed to be a clear colourless to pale yellow liquid (literature mp: -1°C).

The same reactants were used for oxidation with $\text{LiCl}/\text{H}_2\text{O}_2$. The results are shown in Table 5. Most reactions were done at 1.5 h reflux in toluene. A reaction at one week under room temperature was attempted for benzaldehyde. While the crude yield

Table 5. Oxidation of selected alcohols with $\text{LiCl}/\text{H}_2\text{O}_2$.

Product	crude % yield	AE (%) (a)	RME	E (theoretical)	E (actual) (b)	Solvent Intensity
benzaldehyde (c)	77.5	74.7	0.579	0.339	468	449
benzaldehyde	104.7	74.7	0.782	0.339	354.0	339.5
benzaldehyde (d)	98.35	74.7	0.735	0.339	388.0	370.6
4-methoxy benzaldehyde	51.9	79.1	0.411	0.264	575	551
4-nitro benzaldehyde	45.7	80.7	0.369	0.239	585	561
benzophenone	69.09	83.5	0.577	0.198	306.0	293.4
pentanal (d)	negligible	70.5	-	0.418	-	-
2-pentanone (d)	negligible	70.5	-	0.418	-	-

(a) Excludes LiCl as it acted catalytically.

(b) Excludes LiCl and water.

(c) At room temperature for 1 week.

(d) At reflux for 1.5 h in cyclohexane.

seems decent (77.5%) its IR spectrum indicates that the product mixture consisted mostly of unreacted starting material as the intensity of the OH band was 0.419 whereas the intensity of the carbonyl band was 0.0274. Another reaction was attempted at 1.5 h reflux using cyclohexane as a replacement for toluene. This was done because previous attempts to oxidize 1-pentanol and 2-pentanol proved useless as the boiling point of toluene (111°C) is higher than that of the expected products (103°C for pentanal and 101°C for 2-pentanone).

105°C for 2-pentanone). Initially, benzene was considered but it has health hazards associated with it. From a solvent selection guide³⁵ it was found that cyclohexane had physical properties similar to that of benzene and without the health hazard. Use of cyclohexane gave comparable yields to that of toluene under similar conditions (98.35% vs. 104.7%). Thus it seemed to be a suitable replacement and was used for the reactions with 1-pentanol and 2-pentanol. In all cases, the products obtained were not purified due to the small amounts obtained; the amounts of reactants used were typically around 0.1 g. The solvent intensities show that solvent accounts for an average of 96% of the waste produced in these reactions.

Product purity was checked by TLC and/or IR analysis. Melting points were not available for 4-nitrobenzaldehyde as the crude products were mushy solids that would not compact into capillary tubes. TLC analysis was not done on pentanal and 2-pentanone because there was not enough product available for analysis. The TLC results obtained confirm the presence of both starting material and product except in the case of benzaldehyde (1.5 h, toluene), 4-methoxybenzaldehyde, and 4-nitrobenzaldehyde where the percent discrepancies with their respective starting reactant are greater than 10%. While this does not confirm the presence of alcohol it does at least indicate the presence of impurities. The presence of starting material for benzaldehyde (1.5 h, toluene) and 4-methoxybenzaldehyde was confirmed by the IR results. While no O-H band was observed for the 4-nitrobenzaldehyde product, the C=O band was small. The crude 4-methoxybenzaldehyde product also appeared different from that obtained by oxidation with KMnO_4 as it was a blood-red liquid. The IR spectra for the benzaldehyde products were also interesting. Oxidation in toluene gave a carbonyl band of intensity 0.917 and

oxidation in cyclohexane gave a carbonyl band of intensity 0.854. The O-H bands had intensities of 0.218 for toluene and 0.385 for cyclohexane.

Due to lower yields and higher E-factors the catalytic procedure seems to be worse than the stoichiometric procedure. This will be discussed in more detail in Section 6.3.

5.4 Oxidation of Alkylarenes

Three alkylarenes were oxidized using two different reaction times under method A (using dichloromethane). The same reactants were oxidized using one reaction time under method B (using dimethylcarbonate) for a total of 9 reactions. The results for the oxidation of diphenylmethane, fluorene, and ethylbenzene are shown in Table 6. Using dichloromethane, yields were higher at one week than under reflux for 1.5 h. The atom economies were around the 50% mark due to the use of KMnO_4 - a stoichiometric reagent. Reaction mass efficiencies (RMEs) were far from the ideal value of 1 with 0.50, in the case of benzophenone at one week with dichloromethane, being the closest to this value. The E-factors were inversely proportional to the yields and were far from their theoretical minima. As evidenced by the solvent intensities a large proportion of the waste was from the use of solvent. Simple calculations will show that the solvent accounted for an average of 93% of the total waste. If the solvent can be recovered then the E-factors drop considerably as shown in the last column of Table 6. While yields dropped when dimethylcarbonate (DMC) was used as the extraction solvent, the recovery of solvent brings the E-factors of both methods close together, except in the case of acetophenone where dichloromethane is clearly advantageous over dimethylcarbonate. The assumption is made here that dichloromethane can easily be recovered by distillation

Table 6. Oxidation of selected alkylarenes with montmorillonite K10/KMnO₄.

Method	Product	Reaction Time (a)	Crude % yield	AE (%) (b)	RME	E (theoretical) (b)	E (actual) (c)	Solvent Intensity	E*solv (d)
A: using dichloromethane as extraction solvent	Benzophenone	1 week	90	55.9	0.50	0.789	196	181	15
		1.5h	59	55.9	0.33	0.789	308	284	24
	9-fluorenone	1 week	79	55.6	0.44	0.799	223	205	18
		1.5h	70	55.6	0.39	0.799	259	238.5	20.5
	Acetophenone	1 week	56	45.5	0.25	1.20	462	425.5	36.5
		1.5h	31	45.5	0.14	1.20	811	745	66
B: using dimethylcarbonate as extraction solvent	Benzophenone	1 week	75	55.9	0.42	0.789	338	321	17
	9-fluorenone	1 week	60	55.6	0.33	0.799	423	401	22
	Acetophenone	1 week	4.2	45.5	0.019	1.20	10150	9621	529

Melting points [listed as experimental (literature) in °C]: 9-fluorenone at 1.5h, method A: 105-109 (80-83); 9-fluorenone at one week, method B: 81-94 (80-83).

(a) Reactions at 1 week were at room temperature. Reactions at 1.5 h were at reflux in CH₂Cl₂.

(b) Includes KMnO₄ as it was consumed in the reaction. Mont K10 is not included as it only acted as a support.

(c) Includes montmorillonite K10 and Celite under the assumption that they are not reclaimed for further use.

(d) Solvent-corrected E-factor which assumes that the solvent can be recovered. Calculated as E (actual) minus Solvent Intensity

although this was not done in the lab. Dimethylcarbonate was recovered and its IR spectrum was compared with that of pure dimethylcarbonate as shown in Figure 13. The overlapping spectra indicate that dimethylcarbonate can be recovered with good purity. However, yields at one week reaction time gave lower yields with dimethylcarbonate than dichloromethane.

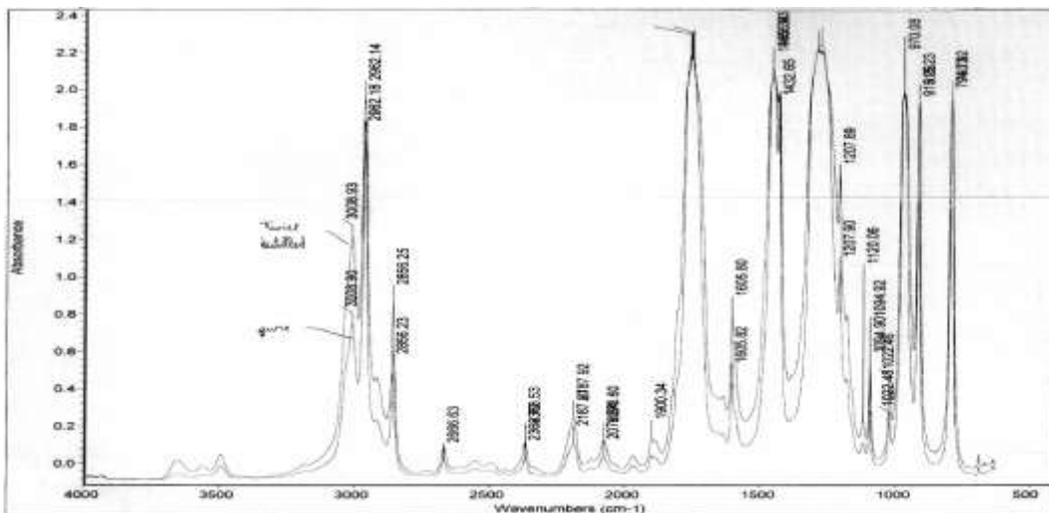


Figure 13. Comparison of IR spectra of twice distilled DMC and pure DMC.

The melting points of 9-fluorenone products were intermediate between the literature melting points for fluorene (111-114°C) and 9-fluorenone (80-83°C). Thus, a mixture of product and unreacted starting material was obtained for the oxidation of fluorene. Similarly, mixtures were also obtained for the oxidation of diphenylmethane and ethylbenzene as evidenced by the TLC and IR results. Spots on TLC plates were observed for both the starting material and the product except in the case of ethylbenzene which had no discernible spot, although it is still suspected to be a mixture. All products showed a distinctive carbonyl band between 1600-1700 cm^{-1} which indicates that there was indeed some oxidized product present. One exception was the case of acetophenone at 1.5 h reflux with CH_2Cl_2 where no carbonyl band was observed. However, a spot was

observed for acetophenone on the product's TLC plate. This likely means that the amount of acetophenone present was small. TLC analysis was also done to compare the products obtained using CH_2Cl_2 . It can be seen that the reaction time did not affect the purity of product as mixtures were obtained in either case.

5.5 Reduction by Yeast

Results for the reduction of selected compounds are shown in Table 7. Yields varied depending on the substrate used. The best yield of 75% was obtained for ethyl

Table 7. Yeast catalyzed reduction of selected compounds.

Substrate	crude % yield	PMI (a)	Solvent Intensity (a)	1/EMY (b)
ethyl acetoacetate	75	113	79.3	83.7
ethyl acetoacetate (c)	71	125	81.6	84.9
acetoacetamide	15	760	519	544
ethyl 4,4,4,- trifluoroacetoacetate	64	99.5	66.4	76.4
tert-butyl acetoacetate	16	435	301	321
α -acetylbutyrolactone	37	231	159	172

(a) Excludes water and brine.

(b) Excludes water, brine, sucrose, NaCl, and yeast.

(c) After one week.

acetoacetate. The process-mass intensity (PMI) for this reaction was 113 - much lower than the E-factors obtained for the oxidation procedures (reminder: $\text{PMI}=\text{E}+1$). However, other substrates gave lower yields and consequently higher PMIs. Effective mass yields (EMYs) and solvent intensities were also calculated for these reactions. The inverse of EMY was taken so that it could be directly compared with the PMI values. The EMY^{-1} values are slightly higher than the solvent intensities because magnesium sulfate, reactant, and solvent are included whereas the solvent intensity only considers the solvent used. On average, the solvent accounted for 68% of the input and non-benign

material accounted for 73% of the input (calculated as percentages of PMI values). Thus, if the solvent is recovered then the E-factors would approach zero. However, the PMI and EMY values would remain the same because these metrics account for the mass of input with the implicit assumption that everything other than the product is waste. Also, regarding the use of solvent, workers would still be exposed to the same amount with additional exposure from double-handling.

The products were analyzed by TLC and IR to determine if reduced product was obtained. Analysis of enantiomeric excess was not done as a polarimeter was not available. Pure products were not available for comparison. Thus, for the TLC results, different R_f values suggest but do not verify the presence of product. Also, R_f values which are similar (as obtained for ethyl 4,4,4,-trifluoro-3-hydroxybutanoate, tert-butyl 3-hydroxybutanoate, and dihydro-3-(1-hydroxyethyl)-2(3H)-furanone) do not necessarily indicate that no product was obtained; it could just mean that a poor separation was obtained. The IR results verify that product was present for all reactions as shown by an O-H band around 3400 cm^{-1} in all cases. The O-H band was the smallest for t-butyl 3-hydroxybutanoate. Also, for 3-hydroxybutanamide the O-H band overlapped with the N-H bands which caused a split in the O-H band. A second indicator of product was a decrease in the carbonyl band which appeared at a lower wavelength. This was observed for ethyl 3-hydroxybutanoate, 3-hydroxybutanamide, and t-butyl 3-hydroxybutanoate. However, this was not clearly observed from the spectra of the other two products, although there were definite O-H bands.

6 DISCUSSION

6.1 Microwave Condensation of Amides

Using a domestic microwave oven resulted in very poor or no yield for the direct condensation of amides. In contrast, the use of a commercial microwave oven gave good yields. For example,⁷⁰ N-phenylacetamide was obtained in 98% compared with only 2.3% from the results of this project. Scaling up the amounts used by a factor of approximately 3 and extending the reaction time to 20 min gave a yield of 12% which is still much lower than the literature result. This illustrates the vast difference between domestic and commercial ovens at least for the direct condensation of amides. Aside from the ovens used, glassware is another important consideration as the Pyrex flasks used in this experiment tended to char. Thus, glassware specialized for microwave ovens should be used.

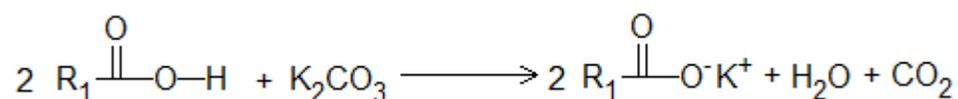
6.2 Esterification Reactions

The phase transfer catalysis method employed was meant to mimic microwave heating. Loupy et al. reported no specific microwave effects for the synthesis of long-chain aromatic esters.⁴⁶ However, in a later publication, Villa et al. reported a specific microwave effect whereby yields at 5 min were higher for microwave heating than conventional heating.⁸³ This effect disappeared by extending the reaction times up to 15 min.

Two advantages of the PTC procedure are that it is solvent-free and previous preparation of the potassium salt is not necessary. Regarding the former, the absence of solvent eliminates the requirement for costly, toxic, and difficult to recover dipolar aprotic solvents like DMF or dimethylsulfoxide (DMSO). Furthermore, the use of a

solid-liquid system rather than a liquid-liquid system lowers the degree of hydration of the ion pair, leading to an increase in its reactivity. Secondly, Loupy et al. have shown that equivalent or better yields can be obtained by generating the salt *in situ*.⁴⁶ Thus, a two-step process is reduced to a one-pot synthesis. One downside of the procedure is that Aliquat 336 has environmental and health hazards associated with it.

Regarding the mechanism for PTC esterification, the first step is the formation of the potassium carboxylate salt as shown in the following equation:



Once the salt is formed, the catalyst facilitates the transport of the anion from one phase into another, immiscible phase wherein the other reagent exists.^{45,104} Thus, reaction is made possible by bringing together reagents which are originally in different phases. Two general mechanisms for solid-liquid phase transfer catalysis (SLPTC) have been proposed: homogeneous and heterogeneous solubilization as shown in Figure 14. In the homogeneous mechanism, the inorganic solid is slightly soluble in the organic phase. After dissolution, ion exchange occurs with the catalyst and then the nucleophile is ferried into the organic bulk. This mechanism is important for asymmetric quats, such as Aliquat 336, which cannot easily approach the solid surface. The heterogeneous mechanism involves reaction of the catalyst with the surface of the solid and subsequent transfer of the nucleophilic anion to the organic phase. Byproduct output of these processes are usually low, since the desired reaction is phase transfer catalyzed and other side reactions, if any, are noncatalyzed.¹⁰⁴ However, the choice of base is important as a

more nucleophilic base such as KOH may cause saponification and a bulky base such as KOtBu may lead to competitive etherification.⁴⁶

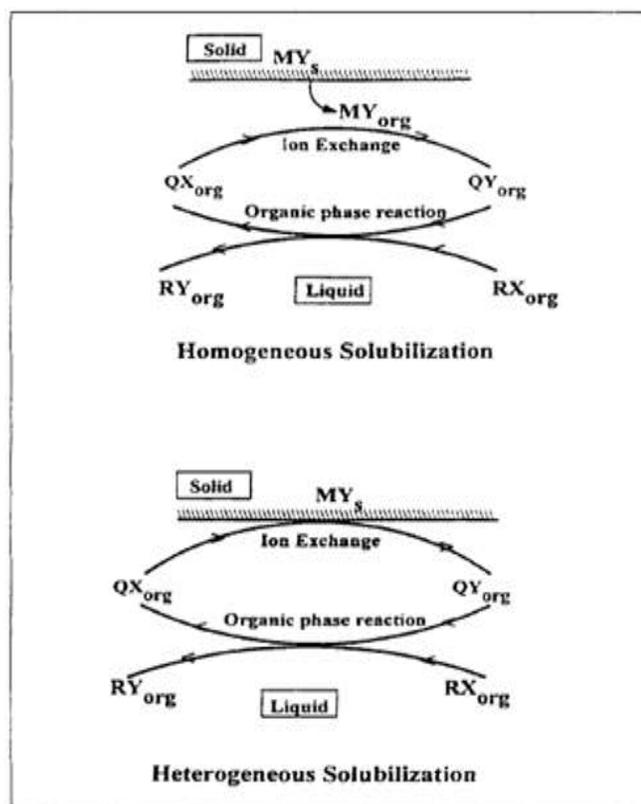


Figure 14. Mechanisms of SLPTC.¹⁰⁴

Previous ester synthesis has concerned octylation of aromatic carboxylic acids⁴⁶ and synthesis of long-chain aliphatic esters.⁸³ This project has briefly looked at different combinations of aromatic and aliphatic compounds. All combinations resulted in product as evidenced by the TLC results. It is difficult to compare the yields of purified products as different purification procedures were used. Column chromatography, a time-consuming procedure, is an alternate method that should be considered for further reactions. For butylation, benzoic acid is a stronger acid than acetic acid and thus its conjugate base is weaker. It should be expected then that the more nucleophilic acetate anion would give a higher yield but instead butyl acetate was obtained in 26% yield and

butyl benzoate in 54% yield. For reactions with acetate, benzyl acetate was obtained in a higher yield (38%) than butyl acetate (26%). It should be considered that butyl bromide is a gas at 140°C and thus the solid-liquid system for the preparation of butyl acetate becomes a triphasic, gas-liquid-solid system. It may be possible that using an airtight, structurally sound reaction vessel would give greater yields than a reflux set-up and this presents an opportunity for further research. Other research areas may include mechanistic studies and consideration of the following: effects of the leaving group, yields with tertiary alkyl halides, and whether or not S_NAr2 type reactions can be done.

Lastly, the atom economies of the phase transfer catalysis reactions were low because potassium carbonate was used to form the carboxylate salt and thus was consumed by the reaction. Despite only modest AEs and yields the E-factors obtained were decent, especially for butyl benzoate. The extraction solvent accounted for an average of 82% of the waste and so, if recovered, the reaction becomes much greener. The preliminary results obtained herein suggest that phase transfer catalyzed esterification has the potential to be a versatile method for the synthesis of a variety of esters.

6.3 Oxidation of Alcohols

Many reagents exist for oxidation but, in the context of green chemistry, not all of these are desirable in terms of environmental, health, and/or safety (EHS) concerns. This paper considers two commonly used reagents: dichromate and permanganate, as well as one catalytic reagent: lithium chloride. A summary of these procedures is given in Figure 15. Firstly, dichromate is the least 'green' of the three because it acts stoichiometrically

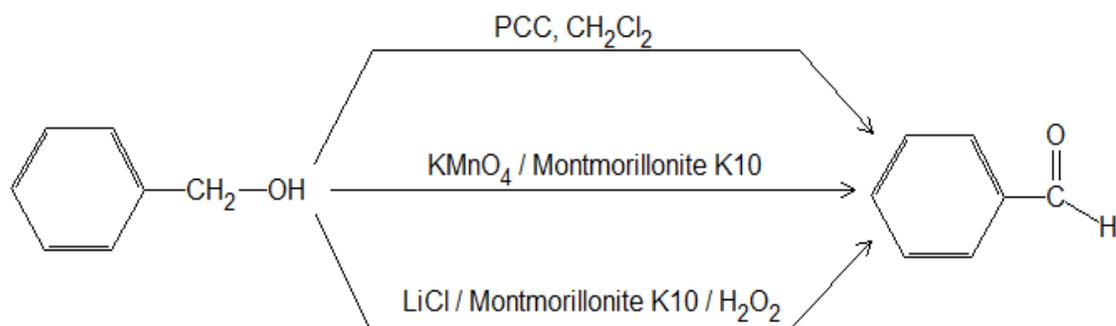


Figure 15. Procedures for the oxidation of alcohols to aldehydes (or ketones).

and various health hazards are associated with its use. These health hazards have been investigated elsewhere.¹⁰⁵ In general, Cr(VI) compounds are carcinogenic, mutagenic and teratogenic towards humans and animals. Once Cr(VI) compounds enter the cells they undergo metabolic reduction to Cr(III), resulting in the formation of reactive oxygen species (ROSs) to produce a state known as oxidative stress. Alternatively, permanganate is less toxic than dichromate and so it is favourable over dichromate. However, it is still a stoichiometric reagent. To take things one step further, catalytic reagents such as lithium chloride can be used. In accordance with the principles of green chemistry, this is much preferable on the basis that it is non-toxic, catalytic, and is expected to reduce waste. The latter condition arises from the higher atom economies; however, it assumes that similar yields can be obtained.

Before comparing the results obtained with KMnO_4 and LiCl there are a couple of points to note from each procedure. One is that the catalytic procedure is limited by the boiling point of the solvent chosen, which in this case was toluene (bp: 111°C). This means that reactants whose expected products have lower boiling points, such as 1-pentanol and 2-pentanol, cannot be used in this procedure. Rather than use toluene, cyclohexane (with a lower boiling point of 81°C) was tested as an alternate solvent. It

was found that cyclohexane can be used to give similar yields as toluene. However, this was only one result for the oxidation of benzyl alcohol. Further reactions will be needed to confirm whether or not cyclohexane can be used as a replacement for toluene in this procedure. If it can be used then, according to a solvent selection guide,³⁵ this would reduce the health hazard as opposed to if toluene or benzene were used, with the main trade-off being an increased risk of flammability and explosion.

Second, using montmorillonite K10/ KMnO_4 it was found that yields were higher at one week under room temperature with no solvent than at 1.5 h reflux in solvent. The former involved a solvent-free system under ambient conditions and the latter was not solvent-free and involved more energy. While the same amount of solvent was used for both reaction times, solvent-free only refers to the reaction itself and not subsequent work-up. If the reactant used was a solid then the system can be further classified as solid-state and if the reactant was a liquid then it can be classified as solid-phase (see Section 1.3.2.1). A possible explanation for the results obtained under these different conditions is that the addition of solvent dilutes the system whereas solvent-free conditions are more concentrated. However, solvent-free systems may exhibit diffusion controlled kinetics and hence require longer reaction times. While longer reaction times may be undesirable this has the benefit of reduced energy requirements.

The crude percent yields, AEs, and E-factors are summarized for both procedures (at 1.5 h reflux) in Table 8. On average, the atom economies for the catalytic method are approximately 34% higher than for the stoichiometric method. Theoretically this would predict lower E-factors for the use of LiCl but this was not the case. This is partly due to

Table 8. Comparison of results for the oxidation of selected alcohols with KMnO_4 and $\text{LiCl}/\text{H}_2\text{O}_2$ at 1.5 h reflux.

Parameter	crude % yield		AE		E	
	KMnO_4	LiCl	KMnO_4	LiCl	KMnO_4	LiCl
Reaction type	KMnO_4	LiCl	KMnO_4	LiCl	KMnO_4	LiCl
benzaldehyde	83	104.7 (a)	39.9	74.7	248	354.0
4-methoxybenzaldehyde	72	51.9	46.0	79.1	208	575
4-nitrobenzaldehyde	57	45.7	48.6	80.7	253	585
benzophenone	87	69.09	53.2	83.5	137	306.0
pentanal	35	-	35.0	70.5	718	-
2-pentanone	4	-	35.0	70.5	6469	-

(a) At reflux for 1.5h in toluene.

the lower yields obtained as the catalytic method gave lower yields for 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, and benzophenone. The resulting E-factors for the catalytic method were roughly twice as large as for the stoichiometric method in either reaction. It is especially telling that even where the yield was higher with benzaldehyde the E-factor was still higher than with KMnO_4 . Another possible explanation for the higher E-factors is the scale of reaction. The stoichiometric method worked on a 1 g scale whereas the catalytic method worked on a 0.1 g scale. Given that the solvent accounted for more than 90% of the total waste on average and ignoring the other waste for a moment, the corresponding solvent to reactant ratios are 119g/g reactant (from 90mL of CH_2Cl_2) and 395g/g reactant (from 15 mL of toluene and 20 mL of CH_2Cl_2) for KMnO_4 and LiCl respectively. Even from these rough calculations it can be seen that, before even the starting a reaction, the catalytic method is expected to produce on average more waste per gram of product than the stoichiometric method. However, if the solvent is recovered then the catalytic method may turn out to be ‘greener’ than the stoichiometric method but then energy usage would also have to be taken into consideration.

The experimental results obtained with the oxidation of alcohols by LiCl/H₂O₂ are compared with literature results⁹¹ in Table 9. Except for benzaldehyde, yields were lower and the E-factors were higher in the experimental results. The reaction times may

Table 9. Comparison of experimental and literature results for the oxidation of selected alcohols with LiCl/H₂O₂.

Product	Exptl. Crude % Yield (Reaction Time)	Lit. Pure % Yield (Reaction Time)	Exptl. E-factor	Lit. E-factor (b)
benzaldehyde	104.7 (1.5h) (a)	93 (1.5h)	354.0	417
4-methoxybenzaldehyde	51.9 (1.5h)	95 (1h)	575	318
4-nitrobenzaldehyde	45.7 (1.5h)	76 (2h)	585	358
benzophenone	69.09 (1.5h)	95 (2h)	306.0	238
pentanal	-	N/A	-	N/A
2-pentanone	-	78 (4h)	-	613
hexanal	N/A	80 (4h)	N/A	514

(a) At reflux in toluene.

(b) Assuming exact amounts are used as per the procedure.

play a role in this difference they varied by ± 30 min with respect to the literature reaction times. The reaction time used in this research was kept at 1.5 h so that the results could be compared with each other under similar conditions. With 4-methoxybenzaldehyde lower yields, notably of crude product, were obtained at a higher reaction time than used in the literature.

Another factor that may help to explain the difference in yields is the quality of the catalyst. Additional catalyst was not prepared; rather a batch was made and kept in the oven until needed. The reactions with 4-methoxybenzyl alcohol and 4-nitrobenzyl alcohol were done seven days after preparation of the catalyst whereas reactions with benzyl alcohol and diphenylmethanol were done one day after the catalyst was prepared. The lower yield obtained for benzophenone may be explained by the smaller reaction time. The results for 4-methoxybenzyl alcohol and 4-nitrobenzyl alcohol suggest that the

catalyst may have to be used fresh. Further studies on the catalyst will be needed to prove this. Also, the effect of mesh size on the yields may be worth investigating as the catalyst prepared for this project had a range of sizes from granular to clay size; it was not homogeneous.

Lastly, comparing the E-factors of the literature procedure with the E-factors obtained with oxidation by KMnO_4 (see Table 8 above) reveal that even if high yields can be obtained by the catalytic method the waste produced per gram of product is still higher than for the stoichiometric method. One way to redeem the catalytic procedure would be to scale up the amounts of reactant used without changing the amount of solvent used or to reduce the amounts of solvent used. Further studies would be needed to investigate these possibilities.

Yields for aliphatic alcohols via oxidation by KMnO_4 or $\text{LiCl}/\text{H}_2\text{O}_2$ were negligible or, if present, consisted mostly of unreacted starting material. In the experimental results of Shaabani et al. (see Table 9 above for selected results),⁹⁵ good yields were obtained for aliphatic alcohols but at higher reaction times. Therefore it seems that both the stoichiometric and catalytic methods used favoured oxidation at benzylic carbons. While no mechanistic experiments were done in this project the literature offers a suggestion of why this may be so for oxidation with KMnO_4 .¹⁰⁶ As shown in Figure 16, electron deficient, adsorbed manganese forms a η^6 complex with the benzene ring. That is, electron donation occurs from the aromatic HOMOs to the manganese LUMO. Consequently, the α -hydrogen is positioned close to the manganese oxo and hydride transfer is facilitated. A similar mechanism is expected for other

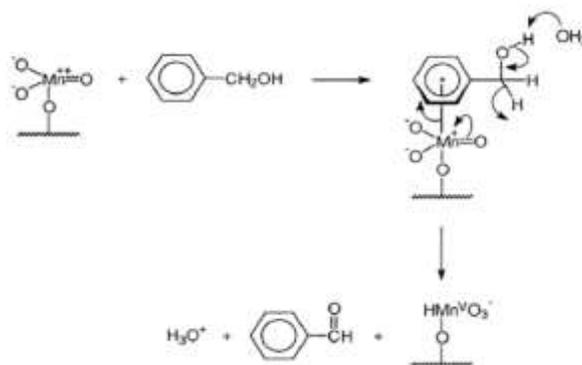


Figure 16. Proposed reaction scheme for the oxidation of benzyl alcohol.¹⁰⁶

aromatic alcohols with a benzylic hydroxyl group. As depicted in the proposed mechanism, water removes a second hydrogen. However, in the procedure for this project water was not used. An alternate proton acceptor may be cation exchange sites on the clay used but this would have to be verified. Aside from aromatic alcohols, the aliphatic compounds do not form such complexes and thus are less likely to be correctly oriented for hydride transfer and consequent oxidation. An exception is that α,β -unsaturated alcohols can form a η^2 complex with manganese. However, if the hydroxyl group is further removed from the double bond then oxidation does not occur.¹⁰⁶ As for the catalytic procedure a different mechanism applies (see Figure 11). It could be that $\text{S}_{\text{N}}1$ is favoured over $\text{S}_{\text{N}}2$ and thus carbocation formation would be favoured by benzylic alcohols. Detailed mechanistic studies would be needed to explain the difference in yield and reaction time between different reactants as per the literature results.⁹¹

One last point to comment on is that the products obtained for 4-methoxybenzaldehyde did not fit the physical description of the pure product being a clear colourless to pale yellow liquid. The products obtained from reaction with KMnO_4 at both one week and 1.5 h were viscous, glue-like yellowish solids and the product

obtained from reaction with LiCl/H₂O₂ was a blood red liquid. Some possible side reactions that could explain these results are: formation of a dimer from the alcohol (etherification), formation of a trimer from the aldehyde,⁹⁴ or polymerization of alcohol with aldehyde.

6.4 Oxidation of Alkylarenes

Potassium permanganate was used to oxidize diphenylmethane, fluorene, and ethylbenzene to their corresponding carbonyl-containing compounds. Using dichloromethane as solvent, yields were higher at one week under solvent-free conditions than at 1.5 h reflux with solvent. As with the oxidation of alcohols with KMnO₄, the former reaction time involved a solvent-free system under ambient conditions and the latter was not solvent-free and involved more energy. Reactions can be further classified as solid-state if the reactant is solid (as for diphenylmethane and fluorene) or solid-phase if the reactant is liquid (as for ethylbenzene). Again, a possible explanation for these results is that the addition of solvent dilutes the system whereas solvent-free conditions are more concentrated (see Section 6.3 for more details). Notably, the reaction times for this procedure do not have to be as long as one week; Shaabani et al. achieved good yields of benzophenone (86%), 9-fluorenone (89%), and acetophenone (64%) within 24 h by reaction at room temperature with continuous stirring.⁹⁵ If time is of concern, ultrasonic or microwave irradiation can be used to reduce reaction times, albeit with the trade-off for more energy input and slightly lower yields.

The yields of diaryl as opposed to aryl compounds were found to be higher and these results are supported by those of Shaabani et al.⁹⁵ The presence of the additional aromatic ring seems to favour formation of the product. Mechanistic studies will be

needed to explain why this is so. A second part of this experiment was testing dimethyl carbonate as a replacement for dichloromethane. Reactions were repeated at one week using dimethylcarbonate as extraction solvent and the yields were found to be lower, especially with acetophenone. Correspondingly, the E-factors were higher. Reactions were not attempted at 1.5 h reflux because dimethylcarbonate is flammable in the presence of oxidizing materials and heat.¹⁰³ Another problem with dimethylcarbonate is that it has a higher boiling point than dichloromethane (90°C vs. 40°C) and therefore would require more energy to evaporate. Consequently, dimethylcarbonate is not a suitable replacement for dichloromethane in this procedure because of lower yields, higher E-factors, safety issues, and larger energy requirements.

6.5 Reduction by Yeast

There are different means by which reduction can be carried out and two such methods are shown in Figure 17. Baker's yeast was used as a biocatalyst to reduce selected β -ketoesters. The use of enzymes for reduction is advantageous over traditionally used reducing agents, such as metal hydrides (ex: NaBH_4 and LiAlH_4), because it is a renewable starting material (principle 7). Other advantages include: being an environmentally benign catalyst, its ability to work under mild reaction conditions, and selectivity at different levels (chemo-, regio- and stereo-). Also, waste biocatalyst decomposes easily in the environment after use.

The enzyme involved in the reduction of β -ketoesters by yeast is called alcohol dehydrogenase.¹⁰⁷ Natural substrates of this enzyme are alcohols such as ethanol, lactate, glycerol and the corresponding carbonyl compounds; however, other ketones can also be reduced enantioselectively. Regardless of the substrate used, the coenzyme

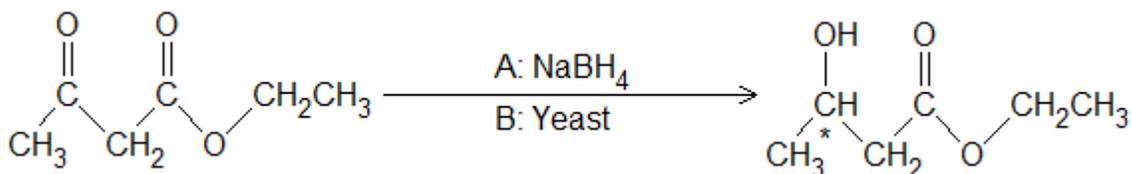


Figure 17. Reduction of a carbonyl group. Method A: traditional reduction with NaBH₄. Method B: biocatalytic reduction with yeast. The asterisk denotes that a chiral center has been formed.

nicotinamide adenine dinucleotide (NADH, reduced form) or NADPH (phosphate form) is needed for the transfer of a hydride to the substrate's carbonyl group. During the course of the reaction, the coenzyme becomes oxidized and must be regenerated. This reverse reaction requires a hydrogen source, such as sugars, to give back the reduced coenzyme for further reaction (see Figure 18). Usually, an excess of the hydrogen source is used to

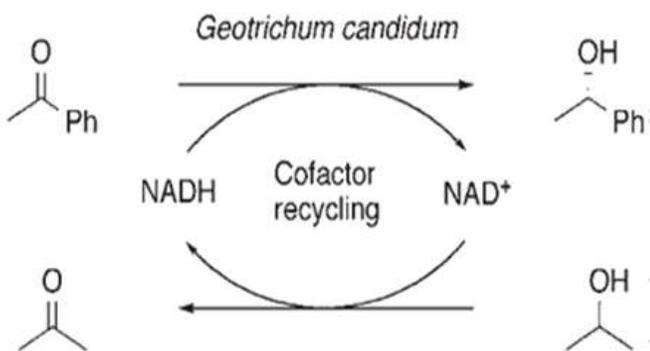


Figure 18. NADH recycling using alcohol as a hydrogen source for reduction.¹⁰⁷

push the equilibrium towards the formation of the desired products. This explains why sucrose was used in the procedure. A second part of the reaction mechanism is the means by which stereo-selectivity is achieved. There are four stereochemical patterns by which a hydride can be transferred from NADPH to the substrate as shown in Figure 19. With E1 and E2 enzymes, the hydride attacks the si - face of the carbonyl group to produce (R)-alcohols whereas with E3 and E4 enzymes the hydride attacks the re - face to produce (S)-alcohols. Yeast alcohol dehydrogenase follows the E3 pathway.

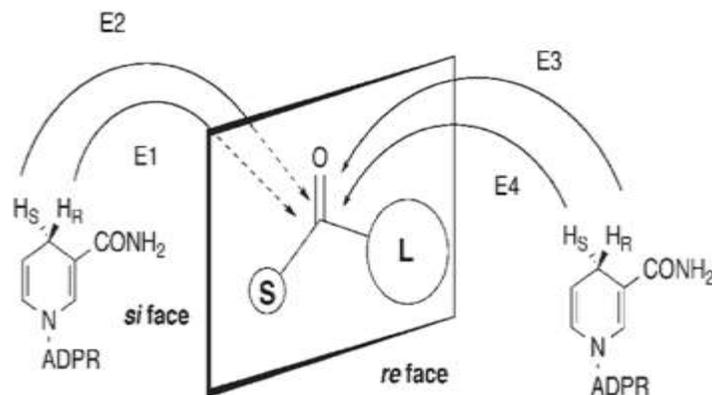


Figure 19. Stereochemistry of the hydride transfer from NAD(P)H to the carbonyl carbon on the substrate, where S is a small group and L is a large group.¹⁰⁷

There are a few parts of the procedure used that deserve special mention. One is that tap water is used to incubate the yeast. This is favourable over the use of deionized or distilled water in that less energy is required to obtain it. At the same time, this can introduce some unwanted variability into the reaction which may influence reproducibility. A second note is that the filtration of the yeast was a bottleneck in the procedure. Different methods were attempted for an easier and quicker filtration:

~Vacuum filtration through celite resulted in clogging. Using anhydrous MgSO_4 as suggested¹⁰⁸ before vacuum filtration to remove the emulsion still resulted in clogging.

~Vacuum filtration through filter paper worked but took a long time.

~Filtration through a cotton plug was ineffective as yeast remained in the filtrate. Even if the cotton plug was covered with a layer of sand yeast was still observed in the filtrate.

~Centrifugation for 5 min did not compact the yeast. However, extending the time to 20 min did compact the yeast and the supernatant could easily be decanted off and vacuum filtered through filter paper.

~Vacuum filtration through a 47 mm glass microfiber filter resulted in clogging. However, scraping the yeast with a glass rod, and being careful so as not to tear the filter, enabled the solvent to pass through. A clear filtrate was obtained by this method.

The last two methods worked the best. It should be noted that for centrifugation the yeast should be washed with portions of diethyl ether so as to maximize recovery of the product.

Regarding crude percent yields, ethyl acetoacetate gave the best result of 75%. Other substrates were tested to determine just how specific the enzyme is. Acetoacetamide was tested to see if a substrate other than a β -ketoester could be used. The yield was much lower for this substrate (15%) which suggests functional group specificity. However, this was the only alternate functional group tested. Further research may involve testing compounds containing other functional groups such as acyl halides and nitriles. Secondly, three other β -ketoesters were used in the procedure. α -Acetylbutyrolactone gave a yield (37%) approximately half that of ethyl acetoacetate. *t*-Butyl acetoacetate gave an even lower yield (16%). However, ethyl 4,4,4-trifluoroacetoacetate, with a structure very similar to ethyl acetoacetate, gave a decent yield of 64%. These results suggest that steric factors play a large role in the reaction with more sterically hindered substrates giving lower yields.

Aside from percent yield, the results were also analyzed by the green metrics PMI, solvent intensity, and EMY. An interesting observation is that the PMI values for acetoacetamide and *tert*-butyl acetoacetate differed by 325 despite the difference in crude percent yield being only 1%. However, for these two results, the absolute amount of waste is approximately the same; the main difference in calculating the PMI values is

that the denominator for acetoacetamide was smaller. Yet the same molar amounts of substrate were used. If the PMI values are re-calculated using molar amounts (excluding yeast) then this brings the difference down to 125. A source of variability is that no set amounts of sodium chloride and magnesium sulfate were used; however much was needed was used. Excluding the amounts of these two chemicals from the calculations brings the difference down to 75. At this point the difference can only be attributed to the slight difference in the amounts of sucrose, reactant, and diethyl ether used. This suggests that green metrics such as PMI, E-factor, and EMY are very sensitive to the mass of starting materials used. Thus, taking an average of values from replicate syntheses may give more accurate values for the metrics used.

7 CONCLUSION

The principles of green chemistry and green metrics have been applied to selected traditional organic chemistry reactions in order to determine if more efficient, environmentally friendly synthesis for these reactions can be accomplished. The types of reactions which have been carried out in this project include: amidification by microwave irradiation, oxidation of alcohols with montmorillonite K10/KMnO₄ and montmorillonite K10/LiCl/H₂O₂, oxidation of alkylarenes with montmorillonite K10/KMnO₄, reduction by yeast, and esterification using phase transfer catalysis.

For amidification it was found that, even though both domestic and commercial ovens use microwave irradiation, drastically different results can be obtained from the system chosen/available for use. The use of a commercial oven consistently produced

better results⁷⁰ whereas the use of a domestic oven resulted in poor yield of the products studied in this project.

The phase transfer catalysis (PTC) esterification results, while only preliminary, show that despite low reaction mass efficiencies (RMEs), atom economies (AEs), and yields, decent E-factors can be obtained. In fact, the lowest E-factor obtained in this research was 88.5 for butyl benzoate. Other benefits of this procedure are that the reaction is solvent-free and the potassium salt does not have to be pre-formed. This procedure has the potential to be a versatile method for the synthesis of a variety of esters. It may be worthwhile to study these reactions further with better product purification, possibly by column chromatography. Other reactant combinations should also be tested.

Theoretically, in terms of waste and environmental, health, and safety (EHS) concerns, catalytic procedures are better than stoichiometric procedures because the catalyst can be reused whereas stoichiometric reagents are consumed by the reaction and cannot be reused. That is, catalytic methods have higher atom economies. In spite of this, the E-factors for the catalytic method which used montmorillonite K10/LiCl/H₂O₂ were higher than for the stoichiometric method which used montmorillonite K10/KMnO₄. While, for the catalytic method, lower yields than those in the literature⁹⁵ were obtained, it was shown that, even if high yields can be obtained, this particular catalytic method is more wasteful than the stoichiometric one.

For oxidation with KMnO₄ it was found that there is a tradeoff between reaction yield and reaction time. Reactions at one week gave higher yields and also had the benefit of less energy usage. For oxidation with LiCl/H₂O₂ it was found that cyclohexane

may be a suitable replacement for toluene in this reaction. However, this solvent was only used for one reaction and products were not purified. Further research would be necessary to explore fully the use of cyclohexane instead of toluene. Lastly, both oxidation methods showed a preference for oxidation at benzylic positions with aliphatic alcohols giving low yields or requiring longer reaction times to achieve high yields.⁹⁵

For the oxidation of alkylarenes, as with the oxidation of alcohols, there appears to be a tradeoff between reaction yield and reaction time. Higher yields were obtained for the longer reaction time of one week under solvent-free and ambient conditions as opposed to reflux for 1.5 h in dichloromethane. However, mixtures of product and reactant were obtained in all cases. Lastly, the use of dimethylcarbonate was explored as an alternative extraction solvent for dichloromethane. While it was recovered with good purity the yields were lower with this solvent. In addition to other concerns (see Section 6.4) it is concluded that dimethylcarbonate is not a suitable replacement for dichloromethane in this procedure.

In the yeast catalyzed reduction, isolation of the product by filtration proved to be a time consuming and difficult step. Centrifugation or vacuum filtration through a glass microfiber assembly is recommended. The results obtained show that yeast reactions have low process mass intensity (PMI) values for products obtained in decent (>50%) yield. Steric factors seem to play a large role in the reaction with more sterically hindered substrates giving lower yields. This merits further investigation as only a few substrates were tested. Lastly, it was shown that green metrics should be calculated as averages. A difference in 1% yield may result in a difference of 325 for the PMI value.

Finally, for all reactions it was found that the solvent accounted for a majority of the waste with average values ranging between 68-96%. This is more than half of the waste and so solvent choice, recycling, and reuse can have a large impact on making chemical synthesis more efficient and greener. This is an example of applying principles 1 (reduce waste), 2 (use benign materials), 5 (reduce the use of auxiliary substances), and/or 12 (reduce EHS concerns). While the *Twelve Principles of Green Chemistry* provide a good guideline for improving synthetic procedures they do not guarantee better synthesis as illustrated by the results of direct amide condensation, oxidation of alcohols, and oxidation of alkylarenes. Any greener approaches to traditional organic synthesis should be fully explored and analyzed with appropriate green chemistry metrics.

Appendix A: Results of TLC analyses

Table 10. TLC analysis of crude ester products.

Product	R _f values	R _f values of carboxylic acid/ alkyl halide	R _f value of pure ester
Benzyl Benzoate	0 (a), 0.453	0.258 (b)/ 0.547	N/A
Butyl Benzoate	0 (a), 0.050 (d), 0.215, 0.529	0.264 (b)/ 0.058 (d)	0.529
Benzyl Acetate	0 (a), 0.430	0.182 (c)/ 0.579	0.430
Butyl Acetate	0 (a), 0.046 (d), 0.754	0.175 (c)/ 0.062 (d)	N/A

(a) A blue spot appeared after dipping the plate in a bromocresol green stain.

(b) The spot turned yellow after dipping the plate in a bromocresol green stain.

(c) A yellow spot appeared after dipping the plate in a bromocresol green stain.

(d) A brown spot appeared after using an iodine stain.

Table 11. TLC analysis of oxidized alcohol products from reaction with LiCl/H₂O₂.

Product	R _f values	Pure Compounds	R _f values
benzaldehyde (a)	0.228, 0.456	benzaldehyde	0.456 (d)
		benzyl alcohol	0.228
benzaldehyde (b)	0.196 (small), 0.431	benzaldehyde	0.431
		benzyl alcohol	0.235
benzaldehyde (c)	0.198, 0.425 (d)	benzaldehyde	0.415 (d)
		benzyl alcohol	0.217
4-methoxy benzaldehyde	0.183, 0.283	4-methoxybenzyl alcohol	0.125
		4-methoxy benzaldehyde	N/A
4-nitrobenzaldehyde	0.083, 0.271	4-nitrobenzyl alcohol	0.073
		4-nitrobenzaldehyde	N/A
benzophenone	0.352, 0.451	benzophenone	0.459
		diphenylmethanol	0.369

(a) At room temperature for 1 week.

(b) At reflux for 1.5 h in toluene.

(c) At reflux for 1.5h in cyclohexane.

(d) Other spot(s) were present.

Table 12. TLC analysis of oxidized alcohol products from reaction with KMnO_4 .

Product	Reaction Time	R _f values	Pure Compounds	R _f values
Benzaldehyde	1 week (a)	0.427 (b)	benzaldehyde	0.427 (b)
	1 week	0.203, 0.438	benzaldehyde	0.461 (b)
			benzyl alcohol	0.234 (b)
1.5 h	0.458 (b)	benzaldehyde	0.458 (b)	
4-methoxy benzaldehyde	1 week	0.286 (c)	4-methoxybenzyl alcohol	0.159
	1.5 h	0.261 (c)	4-methoxybenzyl alcohol	0.118
			4-methoxybenzaldehyde	N/A
4-nitro benzaldehyde	1 week	0.079, 0.254	4-nitrobenzyl alcohol	0.071
	1.5 h	0.049, 0.236	4-nitrobenzyl alcohol	0.065
			4-nitrobenzaldehyde	N/A
Benzophenone	1 week	0.310 (faint), 0.452, 0.532	benzophenone	0.460
	1.5 h	0.469 (b)	benzophenone	0.469
			diphenylmethanol	0.359
Pentanal	1 week	0.576	pentanal	N/A
			1-pentanol	(d)
	1.5 h	N/A	-	N/A
	1.5 h (a)	N/A	-	N/A
2-pentanone	1 week	0.047, 0.719	2-pentanone	(d)
	1.5 h	0.047, 0.461, 0.695	2-pentanone	(d)
			2-pentanol	(d)

(a) 45mL of dichloromethane was used.

(b) Other spot(s) were present.

(c) Trailing of the spot was observed.

(d) No spot was visible under the UV lamp.

Table 13. TLC analysis of oxidized alkylarene products.

Method	Product	Reaction Time	R _f values	Pure Compounds	R _f values
A: using dichloromethane as extraction solvent	Benzophenone	1 week	0.565, 0.509	diphenylmethane	0.565
				benzophenone	0.519
		1.5 h	0.627, 0.429	diphenylmethane	0.635
				benzophenone	0.444
	9-fluorenone	1 week	0.639, 0.459	fluorene	0.656
				9-fluorenone	0.443
		1.5 h	0.568, 0.400	fluorene	0.576
				9-fluorenone	0.392
	Acetophenone	1 week	0.400, (a)	ethylbenzene	(b)
				acetophenone	0.400
		1.5 h	0.408, (a)	ethylbenzene	(b)
				acetophenone	0.408
B: using dimethylcarbonate as extraction solvent	Benzophenone	1 week	0.633, 0.467	diphenylmethane	0.642 (a)
				benzophenone	0.458
	9-fluorenone	1 week	0.607, 0.434	fluorene	0.615
				9-fluorenone	0.434
	Acetophenone	1 week	0.380, (a)	ethylbenzene	(b)
				acetophenone	0.395

(a) Other spot(s) were present.

(b) No spot was clearly discernible.

Table 14. TLC comparison of oxidized alkylarene products obtained using dichloromethane as the extraction solvent.

Product	Reaction Time	R _f values	% difference (a)
Benzophenone	1 week	0.467, 0.667	3.6%, 2.5%
	1.5h	0.450, 0.650	
9-fluorenone	1 week	0.467, 0.667	3.6%, 2.5%
	1.5h	0.450, 0.650	
Acetophenone	1 week	0.394, (b)	2.0%
	1.5h	0.386, (b)	

(a) Listed in order from lowest to highest R_f values. Calculated as $[(x-y)/\max(x,y)] \times 100\%$.

(b) Other spot(s) were present.

Table 15. TLC analysis of reduced ketones.

Product	R _f values	R _f value of pure reactant
ethyl 3-hydroxybutanoate	0.227	0.328
ethyl 3-hydroxybutanoate (a)	0.237	0.290
3-hydroxybutanamide	0.726 (b)	0.516 (b)
ethyl 4,4,4,-trifluoro-3-hydroxybutanoate	0.322	0.314
tert-butyl 3-hydroxybutanoate	0.373	0.390
dihydro-3-(1-hydroxyethyl)-2(3H)-furanone	0.071	0.071
	0.686 (b)	0.678 (b)

(a) After one week.

(b) Using acetone as eluent.

Appendix B: Summary of the results of IR analyses

Table 16. IR analysis of oxidized alcohol products from reaction with KMnO_4 .

Compound	Reaction Time (a)	Diagnostic peaks (cm^{-1})	Means of Sample Preparation
Benzaldehyde	1 week (b)	1700.97, 3331.57 (broad)	one drop
	1 week	1701.68, 3346.63	one drop
	1.5 h	1701.78, 3385.45	one drop
	(a)	1701.14, 1704.81	one drop
Benzyl Alcohol	(a)	3300.65 (broad)	one drop
4-methoxybenzaldehyde	1 week	1610.80	CH_2Cl_2 solution
	1.5 h	1610.20 (small)	CH_2Cl_2 solution
4-methoxybenzyl alcohol	(a)	3347.07	CH_2Cl_2 solution
4-nitrobenzaldehyde	1 week	1709.74 (small), 3520.45	KBr pellet
	1.5 h	1710.00, 3520.37	KBr pellet
4-nitrobenzyl alcohol	(a)	3519.62	KBr pellet
Benzophenone	1 week	1659.25	CH_2Cl_2 solution
	1.5 h	1659.33	CH_2Cl_2 solution
	(a)	1659.17	CH_2Cl_2 solution
Diphenylmethanol	(a)	3592.09	CH_2Cl_2 solution
Pentanal	1 week	1721.57 (small), 3420.01 (broad)	CH_2Cl_2 solution
	1.5 h (b)	3343.05 (broad)	one drop
	1.5 h	3335.03 (broad)	one drop
	(a)	1745.29	library search
1-pentanol	(a)	3331.50 (broad)	one drop
2-pentanone	1 week	not present	CH_2Cl_2 solution
	1.5 h	not present	CH_2Cl_2 solution
	(a)	1716.59	one drop
2-pentanol	(a)	3346.72	one drop

(a) Pure compound.

(b) 45mL of dichloromethane was used.

Table 17. IR analysis of oxidized alcohol products from reaction with LiCl/H₂O₂.

Compound	Diagnostic peaks (cm ⁻¹)	Means of Sample Preparation
Benzaldehyde (a)	1702.80 (small), 3342.37 (broad)	one drop
(b)	1702.82, 3390.84 (broad)	one drop
(c)	1701.88, 3358.12 (broad)	one drop
(d)	1701.14, 1704.81	one drop
Benzyl Alcohol	3300.65 (broad)	one drop
4-methoxybenzaldehyde	1655.94 (messy), 3400.66 (broad)	one drop
4-methoxybenzyl alcohol	3347.07	CH ₂ Cl ₂ solution
4-nitrobenzaldehyde	1709.90 (small)	CH ₂ Cl ₂ solution
4-nitrobenzyl alcohol	3519.62	KBr pellet
Benzophenone	1654.63, 1691.61, 3385.12 (broad)	one drop
(d)	1659.17	CH ₂ Cl ₂ solution
Diphenylmethanol	3592.09	CH ₂ Cl ₂ solution

(a) At room temperature for one week.

(b) At reflux for 1.5h in toluene.

(c) At reflux for 1.5h in cyclohexane.

(d) Pure compound.

Table 18. IR analysis of oxidized alkylarene products.

Method	Compound	Reaction Time	Diagnostic peaks (cm ⁻¹)	Means of Sample Preparation
A: using dichloromethane as extraction solvent	Benzophenone	1 week	1660.20	CH ₂ Cl ₂ solution
		1.5 h	1660.99	CH ₂ Cl ₂ solution
		(a)	1659.22	CH ₂ Cl ₂ solution
	9-fluorenone	1 week	1714.58	KBr pellet
		1.5 h	1714.86	KBr pellet
		(a)	1714.22	KBr pellet
	Acetophenone	1 week	1685.30	CH ₂ Cl ₂ solution
		1.5 h	not present	CH ₂ Cl ₂ solution
		(a)	1685.63	CH ₂ Cl ₂ solution
B: using dimethylcarbonate as extraction solvent	Benzophenone	1 week	1659.99	one drop
	9-fluorenone	1 week	1714.96	KBr pellet
	Acetophenone	1 week	1684.57	CH ₂ Cl ₂ solution

(a) Pure compound.

Table 19. IR analysis of reduced ketones.

Compound	Diagnostic Peaks (cm ⁻¹)
ethyl acetoacetate (a)	1651.08, 1716.72
ethyl 3-hydroxybutanoate (b)	1735.98, 3435.61 (broad)
ethyl 3-hydroxybutanoate	1720.60, 3400.88 (broad)
acetoacetamide (a, d)	1608.61, 1682.29, 1720.05
3-hydroxybutanamide (d)	1716.84, 3377.96 (broad)
ethyl 4,4,4-trifluoroacetoacetate (a)	1670.95 (c), 1748.64, 1778.13
ethyl 4,4,4-trifluoro-3-hydroxybutanoate	1716.95 (c), 3435.44 (broad)
tert-butyl acetoacetate (a)	1648.64, 1716.72
tert-butyl 3-hydroxybutanoate	1648.94, 1716.77 (c), 3439.64 (broad)
α -acetylbutyrolactone (a)	1712.57 (c), 1762.70 (c)
dihydro-3-(1-hydroxyethyl)-2(3H)-furanone	1712.72 (c), 1762.82 (c), 3420.00 (broad)

(a) Pure compound.

(b) After one week.

(c) Other peaks were nearby.

(d) Analyzed as a solution in dichloromethane.

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