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Framework towards more Sustainable Chemical Synthesis Design – A Case Study of Organophosphates

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Abstract

In recent years, the advancement of sustainable chemistry concepts and approaches along with their demonstrated application has become a central part of the design, synthesis, and manufacture of a chemical. Sustainable chemistry not only utilizes the principles of green chemistry, but also expands to incorporate economic, societal, and environmental aspects. This is further elucidated by the incorporation of life cycle assessment/thinking to include the raw material production, manufacture, processing, and use and disposal stages, allowing for a comprehensive evaluation of the environmental and human health impacts attributed to a chemical. This contribution outlines an approach for the development of a preliminary framework for the sustainable synthesis of a chemical that is identified as an alternative for an existing chemical of concern. The framework is introduced concurrently with a case study for organophosphates that are selected as potential replacements for brominated flame retardants (BFRs). This framework is designed to apply existing knowledge of green chemistry to the synthesis of alternatives, along with its integration into Life Cycle Assessment culminating in the development of a more overall sustainable chemical entity when compared to its predecessor.

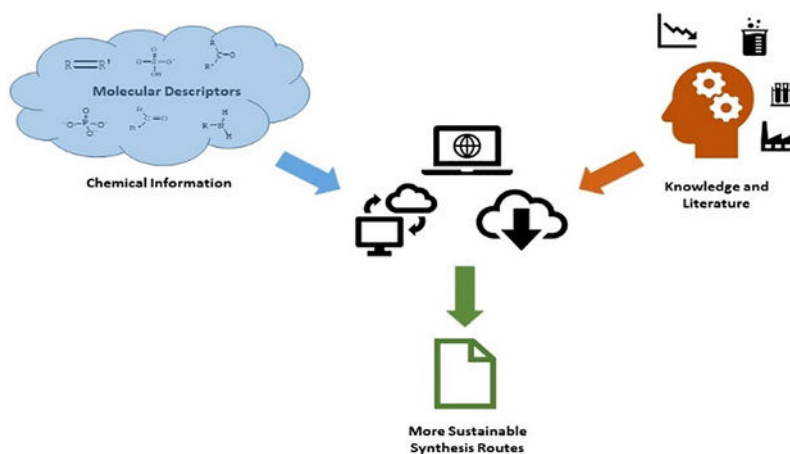
Graphical Abstract

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A framework for using a chemical's molecular descriptor information to link with existing literature and knowledge to arrive at a more sustainable synthesis route for that chemical.

Keywords

Alternative Assessment; Sustainable Synthesis; Design; Green Chemistry; Life Cycle

INTRODUCTION

From the early days of environmental philosophy as introduced by Rachel Carson's *Silent Spring* in 1962,¹ to the publication titled 'Our Common Future' by the Brundtland commission in 1987,² sustainable development has been an ongoing process wherein the events and definitions are in a constant state of progression. The evolutionary course encompasses noble consideration as to how we can guarantee that our offspring have a proper future and shouldering the responsibility for our deeds, but the approach is riddled with varied pathways culminating in rather complex scenarios. This explains why there are numerous and an often-misused interpretation of what constitutes sustainability and sustainable development.

Green Chemistry and its 12 Principles,³ developed in the 1990's, have provided chemists with a design philosophy, which ensures that human health and environmental objectives can be attained. A common working definition of green chemistry is "preventing pollution and impact on the molecular level".⁴ Building on this, and the ensuing, 12 green engineering principles⁵ and armed with the knowledge that sustainability transcends traditional disciplinary boundaries, there is a greater need to extend past solely the environmental considerations, but also include those of economics, and societal. Cumulatively this is an essential outline and definition for sustainable chemistry,⁶ and together with these Principles can provide an outcome that can result in momentous improvement on the raw material usage and energy consumption that eventually defines economic success. However, an integrated approach that incorporates these principles in a cohesive manner throughout the life cycle of a process or product is the key.⁷

As new chemicals are introduced, and existing chemicals continue to be sold on the commercial market, new and faster approaches are needed to evaluate their inherent chemical and physical properties, exposure and toxicity potentials, as well as their impact on the environment and human health either through direct measurement or via the development of correlation models. In addition to the evaluation of these chemicals as final products, there must also be an understanding of all the materials, energy, water, and released emissions associated with their manufacture. Only by comprehending and having this advanced data and knowledge of the chemical and the entirety of the life cycle, can one make a fully informed decision while evaluating the chemical of concern and any potential available alternatives.

Sustainable design is the intent to totally eliminate or minimize the adverse environmental and human health impacts through thoughtful designs; these concepts can be broadly applied across all fields of design including chemical products. The sustainable chemistry framework, when appropriately applied, can address the crucial sustainability challenges that civilization faces today. This entails the advancement of strategies and a set of considerations that ascertain design criteria concerning the properties of the ensuing chemical(s), thus culminating in the development of inherently less harmful substances when compared to those currently deployed.

To capture the 25 years of advancement in the areas of green chemistry, green engineering, and sustainability in chemistry, this contribution outlines an approach for the development of a preliminary framework for the sustainable synthesis of a chemical. This tactic can be used for a direct comparison of an alternative as a replacement for an existing chemical of concern (CoC). The framework is introduced concurrently with a case study for organophosphates that are selected as potential replacements for brominated flame retardants (BFRs). The framework is designed to incorporate existing knowledge of green chemistry and engineering to the synthesis of alternatives with its integration and concomitant application into Life Cycle Assessment, thus leading to the development of a more inclusive sustainable chemical when compared to its predecessor.

METHODOLOGY

In the past decade, there is an ever-increasing demand by the public and stake holders to design new chemicals/products that possess minimal toxicity, and preferably be derived from renewable and sustainable sources. Meeting this mandate requires a novel scientific and systematic approach that distances from the traditional chemistry platform. This is not a trivial change as the use, efficacy, and potency must be maximized to meet consumer requirements, meanwhile human health and environmental toxicity is concurrently minimized. But, this is a change that is currently occurring. In changing our mindset on how chemicals are designed, produced, and used, an eventual proactive cultural change will ensue, resulting in prevention of many potential environmental challenges, as opposed to the often-reactionary practice that arises as a result of man-made chemicals (e.g. the addition of lead to gasoline and the use of chlorofluorocarbons in refrigerants).

On June 22, 2016, President Obama signed and enacted into law The Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA) which amended the Toxic Substances Control Act (TSCA) of 1976 to meet the needs of the 21st Century.⁸ With more than 96% of all manufactured goods being directly impacted by chemistry, this new bill is aimed to improve public health protection and increase the public's confidence in chemicals that are in the everyday consumer domain. This modernization is also deliberate to encourage increased innovation in chemical design and manufacturing, opportunities for favorable marketing (e.g. product ingredients that are more sustainable and less environmentally consequential) and the prospect of new products with improved sustainability profiles. This, in turn, will increase the need for data availability that comprise the chemical's inherent physical, chemical, exposure, and toxicity properties. Additionally, it should encourage the best (i.e. greener or more sustainable) synthesis routes and manufacturing process information.

As this demand for safer and less toxic chemicals continues to rise, dictated largely by the public and chemical manufacturers, the need for well-thought-out, comprehensive, informed decision criteria, and frameworks has led to the science of Alternative Assessment (AA). This is a process, framework or guidance that aids in identifying and comparing alternative chemicals that are safer, or less toxic or more sustainable when compared to the CoC under evaluation. The practice of AA is to provide informed substitution when suggesting an alternative, in addition to understanding the potential consequences (i.e. tradeoffs) associated when selecting an alternative. This assessment technique differs from safety, risk, or sustainability assessments. But, is a technique based on life-cycle thinking and accordingly does include concepts found in the previously identified and related assessment techniques.

A number of organizations have engendered their own assessment frameworks or guidance: Toxics Use Reduction Institute's (TURI) "*Five Chemicals Study: Alternatives Assessment Process Guidance*",⁹ University of California, Los Angeles (UCLA) Sustainability Technology & Policy Program's "*Multi-criteria Decision Analysis Tool*",¹⁰ European Chemicals Agency's (ECHA) "*Guidance on the Preparation of an Application for Authorization*",¹¹ German Federal Environmental Agency's "*Guide on Sustainable Chemicals: A Decision Tool for Substance Manufacturers, Formulators and End Users of Chemicals*",¹² United Nations Environment Programme's (UNEP) "*General Guidance on Considerations Related to Alternatives and Substitutes for Listed Persistent Organic Pollutants and Candidate Chemicals*",¹³ Lowell Center for Sustainable Production's "*Alternatives Assessment Framework of the Lowell Center for Sustainable Production*",¹⁴ Interstate Chemicals Clearinghouse's (IC2) "*Interstate Chemicals Clearinghouse Alternatives Assessment Guide*",¹⁵ California's Department of Toxic Substance Control "*Safer Consumer Products Regulation*",¹⁶ Business-NGO Working Group's (BizNGO) "*Chemical Alternatives Assessment Protocol: How to Select Safer Alternatives to Chemicals of Concern to Human Health or to the Environment*"¹⁷ and the US Environmental Protection Agency (EPA) Design for the Environment's (DfE) "*Alternatives Assessment Criteria for Hazard Evaluation*",¹⁸ in response to the regulation of chemical substances and stakeholder's interests in having consistent approaches to evaluate alternatives. As expected, each of these frameworks or guidance documents differs in terms of the attributes addressed and the methodologies applied. Additionally, there are a multitude of approaches for using

alternative assessment frameworks described in the literature.^{19–23} While, most of these frameworks considered elements such as assessing human health, ecological hazards, physicochemical properties, life cycle assessment, chemical/product performance, and social considerations, their application and scope for many of these examples diverged.

In 2015, the National Academy of Sciences (NAS) identified several elements, such as importance of accounting for the entire life cycle of a chemical and its alternatives, exposure to a chemical (source and quantity), social impact, the use of novel toxicological data streams, and applicability of *in silico* computational models and methods to estimate physicochemical information that are often missing from a number of existing frameworks. Consequently, the NAS produced the “*Framework to Guide Assessment of Chemical Alternatives*”²⁴, a 13-step alternative assessment framework, which aids in a decision-making process when assessing alternatives to a chemical of concern.

This decision framework contextualizes the aspects for arriving at potentially safer substitute chemicals with respect to human health and ecological risks. By incorporating aspects from previous guidance, needs^{25,26} and aforementioned framework efforts, this framework seeks to provide a greater level of standardization with the goal of providing a more harmonized approach to alternative assessment. As mentioned previously, there is a great need to include life-cycle thinking, which addresses the potential human health and environmental impacts of a chemical at each of its life cycle stages (resource acquisition, production, use, disposal and/or recycle). Also, included are the steps for quantifying product for performance and economic evaluations.

Table 1 identifies the individual stages (mandatory or optional) within the NAS framework, defines the general information needed or generated at each stage with the predecessor framework/guidance applicability to that stage and the type of hierarchical data needed to conduct each stage’s evaluation. The stages which are identified as optional activities are indicated with an asterisk. It is interesting to note that Stage 8, life cycle thinking, was not formally addressed in any of the previously produced guidance or framework documents surveyed for this contribution; but is a new aspect to the NAS framework document and a main driver for this research contribution.

The NAS’s alternative assessment framework offers the needed stepwise progression through the thought- and decision-making processes while considering and ultimately selecting a potential chemical alternative. Within each individual stage, there is a significant amount and variety of quantitative and qualitative data required. Furthermore, with progression from beginning to end, the essential data proceeds from being of high availability and high certainty to data that is not readily available and with greater levels of uncertainty. In order to have full utility of this decision support process and tool, data sources and quality must be properly identified and consistently deployed.

In general, a multitude of both qualitative and quantitative data sources that begin to meet the demands of the NAS framework exist. However, with the wide range of data type and breadth of chemicals there is still a need for further data. The expert synthesis methodology and framework being introduced in this contribution, is not only designed to provide data on

the synthesis data requirements, but also to integrate existing data which can contribute to meeting the NAS's framework data prerequisites. The authors have identified and selected EPA data as initial sources; followed by incorporating missing data from other Federal Agencies and domestic and international sources. As the framework develops additional sources will be integrated. Since this methodology and framework is in the developmental phase, this technique is preferred because of the ease of methodology/database/tool integration and establishment of a cohesive approach to generate data needed for evaluating potential chemical alternatives.

In terms of information needs in Table 1, it is apparent that hierarchical sources of data can be obtained about chemico- and physico- properties and toxicity from prediction software such as EPA's Toxicity Estimation Software Tool (TEST),^{27,28} or from their chemical databases such as EPA's Chemical Safety and Sustainability iCSS Dashboard.²⁹ This interactive webtool is designed for visualization and is a source of chemical screening data EPA's Toxicity Forecaster (ToxCast)³⁰ project and the Toxicity Testing in the 21st century (Tox21) collaboration. The iCSS ToxCast Dashboard integrates data from various sources including: ToxCast and Tox21 - High-throughput chemical screening data, ExpoCast - Chemical exposure data and prediction models, DSSTox - High quality chemical structures and annotations, PhysChemDB - Physical Chemical Properties Database, and CPCat - Chemicals listed by associated categories of chemical and product use. Exposure data and methods can be applied in a Life Cycle and Human Exposure Model (LC-HEM)^{31,32} to identify sources and quantities of exposure across the entire life cycle of the identified chemical alternative, as well as the precursor chemicals that go into creating the desired chemical. Fate and transport data can be sourced from the EPA's Chemical Transformation Simulator (CTS),^{33,34} a web-based screening tool for predicting transformation pathways and physicochemical properties of organic chemicals, allowing for identification and quantification of the species resulting from degradation in a particular environment. Ecotoxicity data can be attained from the ECOTOXicology knowledgebase³⁵ (ECOTOX) which is a comprehensive, publicly available information source that provides single chemical environmental toxicity data on aquatic life, terrestrial plants and wildlife.

For the requirement of data to manufacture a potential alternative, information pertaining to their synthesis can be obtained from the Sustainable Chemistry Synthesis and Expert Framework that is being introduced in this contribution. Thereby providing information delineating the synthesis of the identified chemical alternatives and facilitating their generation in a more sustainable manner. This synthesis information can then be fed into EPA's Rapid Life Cycle Inventory methodology,³⁶ which generates high-level inventory information for the immediate production of the identified alternative chemical. The generated inventory will afford process inputs and outputs and utility essential to produce a functional unit of the identified alternative. The integration of these inventories into EPA's Life Cycle Assessment software, based on GreenDelta's openLCA open-source foundation,³⁷ will provide an opportunity to tie the inventory of reactant streams all the way back to environmental flows and inventories, and to the product streams through the use and recycle/reuse/disposal phase. The cumulative inventories can then be evaluated using EPA's Tool for Reduction and Assessment of Chemicals and Other Environmental Impacts (TRACI),^{38,39} an environmental impact assessment tool that provides characterization factors for Life

Cycle Impact Assessment (LCIA), industrial ecology, and sustainability metrics. These characterization factors quantify the potential impacts that inputs and releases have on specific impact categories in common equivalence units. Chemical process and manufacturing specific economic information can be gained from EPA's Gauging Reaction Effectiveness for the ENvironmental Sustainability of Chemistries with a Multi-Objective Process Evaluator (GREENSCOPE) tool^{6,40-45} with additional sustainability evaluation in the areas of energy, environment and efficiency.

It should be pointed out that data required for stages 1, 2, 3, 9-2, 11, 12 and 13 (Table 1) are outside the scope of this methodology; these stages are directed by decisions made by the stakeholder groups performing the assessment. In contrast, the present methodology and eventual tool is geared towards facilitating the availability, incorporation and use of data, thus allowing the assessment to be completed more expeditiously and with a greater level of consistency.

FRAMEWORK

To achieve augmented sustainability with respect to the life cycle of a chemical and/or a process, researchers must minimize or potentially eliminate environmental hazards across its life cycle; also, risk must be assessed and quantified to ensure the activities taken are more sustainable. By mapping out a chemical's life cycle many areas of opportunity for improvement to the current state are identified, as well as segmented avenues for new research. These efforts can validate that enhancement at the synthesis stage can have direct and indirect benefits and consequences. Therefore, reducing the risk associated with the manufacture, processing and use of a chemical, as described above, can bring about greener and more sustainable chemicals and advance the science about making chemicals greener as evidenced by the past 25 years of green chemistry research.⁴⁵⁻⁵⁰

Many eco-friendly outcomes are envisioned by incorporating biomimicry pathways that minimize impact on climate change via diminution of greenhouse gases, curtailing adverse effects on the local eco-system and by limiting resource consumption, while giving predilection to non-toxic, renewable materials, and with lower water and energy utilization during the course of entire life cycle, from cradle to grave. Maintaining the quality and stability of price infrastructure while stressing the recycling of materials via carbon-neutral activities will encompass essential components of the sustainable design.⁵¹⁻⁵⁵ Even with these goals in mind, a researcher must acknowledge the complexity of the system and the fact tradeoffs will exist, and choices will likely be necessary.

The Sustainable Chemistry Synthesis Expert Framework and Database applies a retrosynthetic approach coupled with proven peer-reviewed literature examples of green and sustainable chemistry synthesis materials. The objective of the framework and database is to provide evocative possible sustainable synthetic routes for a chemical by deconstructing the molecule to apply synthetic knowledge. The framework is comprised of three modules that allows for translation of molecular information into literature examples which will facilitate the transfer of scientific knowledge and experience for those new researchers and entities to

green chemistry or surveying for novel methods that improve the eco-friendliness of chemical synthesis. An overview schematic of this framework is provided in Figure 1.

The first module consists of identifying pertinent molecular information present in the potential chemical alternative under evaluation. To execute this, the framework is built on utilizing features in the current version (V4) of the TEST software. This retrosynthetic approach will be accomplished by generating characteristics and molecular descriptors (e.g., using chemotype-based classifiers or molecular fragment counts) generated by TEST.^{27,28}

The TEST software program allows users to rapidly and easily estimate toxicity endpoints using a variety of QSAR methodologies; QSARs are mathematical models used to predict measures of toxicity based on physical characteristics of the structure of chemicals (known as molecular descriptors). Acute toxicities (LD₅₀, the dose needed resulting in half of the population of a species (e.g. Daphnia) to expire) is one example of toxicity measure, which may be predicted from QSARs. Simple QSAR models calculate the toxicity of chemicals using a simple linear function of molecular descriptors. TEST does not require molecular descriptors from external software packages as the required descriptors are calculated within TEST and allows for the toxicity estimation without requiring external programs. To begin an evaluation, users can draw (in an included chem sketch window), enter a structure text file, or import from an included database of structures. Once entered, the chemical's toxicity is estimated.

TEST provides an excellent foundation as it is designed to receive the chemical structure, Chemical Abstract Service (CAS) number or chemical name and able to predict a set of chemical and physical properties, toxicity endpoints and generate molecular descriptors. These molecular descriptors are the features that distinguish chemical reactivity and provide an organic chemist the necessary information on how to develop synthesis strategies for the preparation of that chemical. Table 2 provides an example output of molecular descriptors for a selected set of molecules with unique functional groups. These structural features and descriptors can also be used to cross-reference with other EPA databases (e.g., DSSTox),⁵⁶ ACToR,⁵⁷ iCSSDashboard²⁹. Upon generation of the respective molecular descriptors, this "digitization" of the molecular information is passed along to the Module 2, the translator portion of the framework.

Module 2, the translator module, is designed to receive information from both, the TEST side (Module 1), as well as from Module 3, the green chemistry and reference knowledge database. In the translator module, the molecular descriptor information provides identification of the functional groups residing on the molecule of interest and when coupled with nomenclature strategies allows for indexing of the chemical structure with the respective reference database(s) existing on the library side (Module 3) of the framework.

Functional groups are specific groups of atoms or bonds, within a molecule, that are responsible for the characteristics of a chemical. A chemical compound's functional group or groups can produce information such as the reactivity, solubility, stability and possible interaction with other functional groups. However, the fact that some chemicals can have two or more different type of functional groups renders these compounds more complex. By

breaking down a molecule into its component functional groups, not only is functionality identified and the respective organic chemical class(es) identified, but also the potential to produce plausible green and more sustainable synthesis routes. This can be achieved by focusing on the most appropriate reaction strategy, resulting in the framework needing a functional group hierarchy system.

Appropriating from the established rules of general organic chemistry, a systematic hierarchy of functional groups can be developed. At the highest level, chemical compounds are identified as organic or inorganic compounds. Since this framework is designed only for organic chemicals, the next level is according to which atoms (carbon, nitrogen, oxygen, sulfur, and phosphorus) are present in the molecule. For example, if a molecule is an alkane, the atom of highest atomic number is carbon and the hierarchy defines this chemical in the carbon class (See Figure 2). If the molecule is an alcohol, the oxygen atom now dictates the functional group class and the molecule resides in the oxygen class. Figure 3 provides a listing of the proposed hierarchy using a phosphorus containing molecule as an example.

This framework is designed to impart knowledge and experience from the green organic chemistry domain and it is well understood that organic compounds can be quite complex with many exceptions to the rule when performing organic synthesis. Additionally, while this hierarchy is general in its current form and only designed for simple molecules, it is a beginning point and will become more detailed and complex through further development. For a complete listing of functional groups (Table S1), their corresponding molecular descriptors (Tables S2–S9) and their position in the hierarchy to be included in this framework, readers are directed to the Supporting Information section.

The literature references for a particular class of organic chemical and its respective green chemistry expert information is housed in Module 3. Module 2 categorizes the chemical of interest into its relevant organic class by name (i.e. keywords), via functional group, while the reference and expert database houses (Module 3) bins organic class by name with the corresponding synthesis and associated green attributes. By placing each Module in terms of organic class by name, the translator allows the match to occur, thus providing the vital synthesis information with the molecule to be synthesized.

These keywords, structural features and molecular descriptors can also be used to conduct internet searches using publicly available web-based search engines, such as Google Scholar and Web of Science or via subscription services like the American Chemical Society's Sci-Finder for building the synthetic information reference database. Additional information such as green and sustainability evaluation (e.g. atom economy scores, quantification of waste generated or savings, metrics, etc)^{58–61} can be gained as journal articles begin/continue to make this information highly preferred or even mandatory for their submissions. The *ACS Journal of Sustainable Chemistry and Engineering* is one of the first to request their submissions to include such information.⁶²

CASE STUDY

By way of introducing this detailed methodology and framework, we strive to apply it to a case study that demonstrates its applicability and prospects for areas of growth and further integration. For this case study, organophosphates, which have been touted as potential replacements for brominated flame retardants (BFRs),^{63,64} were chosen as a test example to evaluate potentially greener/more sustainable strategies for their synthesis.

Flame retardants are a class of chemical compounds that reduce the flammability of combustible materials or delay their combustion. There are several types of flame retardants that are in use and these compounds typically possess bromine, chlorine, phosphorus, nitrogen, antimony, and metal salts.⁶⁵ Currently, brominated flame retardants (BFRs) are very widely used in the manufacture of textiles, electrical, electronic equipment, and building construction materials; they are the most abundantly used flame retardants comprising approximately 75 different commercial varieties.⁶⁶ Among them, polybrominated diphenyl ethers and biphenyls, hexabromocyclododecanes, and tetrabromobisphenol-A are widely used. Some BFRs and polychlorinated biphenyls have proven to be persistent, bio-accumulative, and toxic to the environment and humans. Consequently, pentabromo- and octabromodiphenyl ethers are banned by the European Union⁶⁷ and the use of decabromodiphenyl ether has been banned in electronic and electrical applications within the EU since July 2008. UNEP has added penta- and octabromodiphenyl ethers to the list of persistent organic pollutants monitored through the Stockholm convention.

In view of the fact that widely used brominated flame retardants have been or are being slowly phased out, phosphorus-based flame retardants (PFRs), which are already in use for several years, are considered as possible alternatives to BFRs. A number of PFRs such as tributyl phosphate, triphenyl phosphate, and triphenyl phosphine oxide, which act in the vapor phase, have been identified as potential substitutes for BFRs used in textile applications.⁶⁸ If these PFRs are possible substitutes for BFRs, it is imperative to ensure these substitutes are not more persistent, bioaccumulative, or toxic to the environment and human health when compared to their predecessor.

To capture on the previous studies^{63, 64} which identified PFRs as potential alternatives to BFRs, this framework evaluates the synthesis routes for each respective chemical recognized. Upon identification of those routes that can offer increased sustainability with respect to the existing chemical, this information can be used to further evaluate the chemical and chemicals involved in its synthesis beyond the synthesis stage. Adding a systems approach (i.e. LCA) allows for the entire impact of the alternative to be quantified and offers a holistic view. For example, while it is recognized triphenyl phosphate exhibits toxicity to aquatic organisms and is possibly carcinogenic, BFRs have been demonstrated to release toxic byproducts during a fire. The release of toxic gases from PFRs is reduced when compared to BFRs with no additional halogenated gases, such as HCl and HBr, produced during their combustion.⁶⁹

There are three different groups of PFRs.⁶⁹ The first group is made up of inorganic phosphates (PO_4^{-3}), which includes frequently used red phosphorus (P_4) and ammonium polyphosphate ($(\text{NH}_4)_3\text{PO}_4$). The second group involve phosphorous-based organic flame retardants for which there are three different classes: organo phosphate esters ($\text{OP}(\text{OR})(\text{OR}')(\text{OR}'')$), phosphonates ($\text{C}-\text{PO}(\text{OH})_2$ or $\text{C}-\text{PO}(\text{OR})_2$) and phosphinates ($\text{OP}(\text{OR})\text{R}_2$). The third group is comprised of halogenated PFRs. Since these PFRs contain both the halogen and phosphorous atoms, they combine the properties of both functional groups. The three different groups of PFRs have been deployed by essentially two pathways: either the flame retardant (i.e. PFR) is reacted with the polymer or alternatively the PFR is an additive. In the first instance, the reactive flame retardant is covalently bound to the polymer, and the loss of fire retardant is limited during the lifetime of the product. The concentration of additive flame retardant during its life time, may decrease, thus diminishing the fire protection it affords relative to an increasing life-time and an increase in probability of exposure to the user or surrounding environment. Additive PFRs include phosphonium derivatives, phosphonates, and phosphate esters compounds.

Flame retardants can perform either in the gas-phase or in solid phase; halogenated flame retardants act only in the gas phase, whereas non-halogenated flame retardants perform exclusively in the solid phase with few exceptions. When phosphorus containing flame retardants are heated directly in the flame, the compound will decompose and generate polyphosphoric acid. This forms a glassy char layer which inhibits the pyrolysis process (of the substrate), thus inhibiting the formation of flammable gases and resulting in reduced quantities of combustible gas needed to burn the substrate.

When a halogen and phosphorus both are present in the PFR, they act independently and additively of one another, thus acting in the partial gas-phase in flame extinguishing process. Halogen containing PFRs exploit a partial gas-phase radical mechanism which is similar to their traditional brominated flame retardants counterparts.

General Strategies for the Synthesis of Organophosphates

While it is the ultimate intent to have a fully automated web-searchable indexed library available with an ontology⁷⁰ and demonstrating interoperability⁷¹, a methodology needs to be developed first. As organic chemists, we traditionally classify organic chemical reactions by organic functionality (group). As practicing green chemists, we take our organic reaction knowledge and extend it by applying the 12 principles to arrive at improved schemes and reactions that echo the mantra of green chemistry. As sustainability chemists, we take this combined knowledge and incorporate the concept of scale, chemical engineering processing features and demands, economics and the impact of selected choices we make at the molecular level. The focus of this contribution and ensuing framework is to convey this knowledge into an automated format that will advance the state of the art and availability of green and sustainable chemistry in the design, synthesis, and production of alternatives to CoC.

As we automate this framework, the methodology for building a chemical reaction library for a class of organic chemicals is herein exemplified by organophosphates. We collected existing literature relevant to the synthesis of organophosphates using SciFinder, a web-

based database of Chemical Abstracts Service. This was managed by a product structure search in reaction mode to create an initial bibliography. The references were then sorted and refined, using criteria such as product yield, number of steps, and publication year, etc., to create the initial bibliography. The results identified those references that can be utilized or improved for the synthesis of triphenylphosphate as a potential commercial product.^{72–84}

A survey of literature showed that triphenylphosphate has been made via several reaction pathways. Each pathway features a unique chemical inventory including starting materials, intermediates, and waste (i.e., by-products). Although many improvements have been made on the reaction conditions and engineering design, the essential chemicals are the same within a given pathway/mechanism. Therefore, we grouped the reactions by pathway to facilitate the evaluation of green chemistry features. To quantify the green nature and performance of these general reaction schemes, they were characterized by atomic efficiency, yield, and their theoretical yield of by-products, which is essentially the quantity of waste in a reaction.

Figure 4 provides the four general reaction routes (schemes) attained as a result of the literature review. These schemes are displayed with triphenyl phosphate as the ensuing product, as it is the simplest triaryl phosphate, therefore it is a common target in method development for its preparation.

The simplest approach (Scheme A) for the preparation of triphenyl phosphate (**3**) is via a dehydration reaction between phosphoric acid and three equivalents of phenol (Figure 4). In this scheme, high temperature and the presence of a catalyst are required to facilitate the reaction. With water being a by-product, it needs to be removed continuously to shift the equilibrium.

More practically, phosphorus is activated through chlorination, thereby enabling for the nucleophilic substitution by phenol. Two approaches (Scheme B, and C) employ phosphorus trichloride as the starting material. In Scheme B, phosphorus trichloride reacts with phenol to yield triphenyl phosphite (**5**), which is then oxidized to produce the desired product (**3**). Alternatively, phosphorus chloride can be oxidized to generate phosphoryl chloride (**6**), which also arrives at the product (**3**) via an esterification reaction with phenol (Scheme C). Phosphorus pentachloride (**7**) is the most active among the starting materials; it has been used to prepare (**3**) by reacting with phenol, followed by quenching with methanol in one pot reaction (Scheme D).

For Scheme C, an aqueous solution of sodium phenoxide is treated with phosphorus oxychloride to provide triphenyl phosphate (Schotten-Baumann condition). This is a one-pot two-step process and the only by-product formed in this reaction is sodium chloride.

A few selected procedures are described for each scheme presented in Figure 4, along with detailed experimental and a relative greenness/non-greenness description for each is provided in the Supporting Information (Green chemistry evaluation of schemes A-D).

Greenness Evaluation of Available Synthesis Routes

To evaluate the “greenness” of a chemical process and aid in route selection and process development, Li⁸⁵ has proposed a comprehensive mass analysis to inform stakeholders from different disciplines. This is carried out by characterizing the mass intensity for each contributing reactant, and resulting product, by-product or waste component. This analysis is demonstrated for each identified scheme (A-D) along with a respective evaluation. The impacts on inputs and outputs are estimated for synthesis design features such as the choice of starting material, the use of single vs multiple reactions, and effect of materials indirectly used such as solvents and catalysts.

Atom economy has been used to evaluate the theoretical efficiency of a synthetic route, especially those involving multiple steps. The analysis helps synthetic chemists to compare alternative synthetic routes, identify redundant manipulations, and evaluate the feasibility of novel reactions that may improve the synthesis.⁸⁶

In the analysis of synthesis efficiency, the process generates the list of essential chemicals and their stoichiometry relationship. This knowledge also provides the first opportunity to assess the sustainability of a route by enabling evaluation of renewability of feedstock, identification of hazard in synthesis, and projection of the basal waste.

The method identified in Scheme A appears to be a very attractive route. The starting materials, including phosphoric acid and phenol, are stable bulk chemicals. It offers an atom economy as high as 86% (Table 3) and generates three equivalents of water as the sole by-product. However, this approach suffers from poor reactivity and low yield in practice. To prepare triphenyl phosphate, this method requires a catalyst, high temperature (240–255°C), and specialized equipment for water removal and reactant cycling. However, the yield is only 43%, suggesting significant requirement for product isolation and high amount of waste in practice.⁸⁷

Theoretically, methods employing Schemes B and C are very similar. They both have the same atom economy at 74.9%, and 3 equivalents of HCl is the only by-product from the two routes.

Under Schotten-Baumann favorable conditions, the esterification in Scheme C (Table 4) is efficient under mild conditions; this route is more popular than others.^{72–75, 77, 88–90} However, this route also suffers from incomplete esterification giving mono-, and di- ester impurities, which may be hard to separate from the triester in this route.^{88,90} In light of this concern, Scheme B remains an attractive option (Table 5), so long as the oxidation of triphenylphosphite (**5**) is clean and efficient.^{91–93}

Since phosphorus pentachloride (**7**) is highly reactive (Scheme D), it is therefore expected to react faster and have less issues associated with incomplete substitution,⁹⁴ that provides an advantage for reaction with less reactive phenols.⁹⁵ However, scheme D has the lowest atom economy (Table 6) among all the four cases. Furthermore, the process generates two equivalents of methyl chloride, a hazardous chemical by product, lending to the low green

evaluation. Notably, all activated phosphorus intermediates, including phosphorus chloride, phosphoryl chloride, and phosphorus pentachloride, are highly toxic and water sensitive.

The framework is currently designed to provide a qualitative and initial quantitative evaluation of a proposed alternative synthetic route with the goal of increasing the overall sustainability of the chemical reaction at the synthesis/manufacturing phase. It is also the goal of this information to provide quantitative information that can be used to further demonstrate the effect of these changes and their contribution to offering sustainability improvements to the overall system. With this immediate qualitative and quantitative information, an evaluator can use a tool, for example EATOS⁹⁶, to generate a quick comparison of the greenness of the proposed synthetic strategies. This approach offers the use of additional metrics, mass and environmental sustainability, and can also include auxiliary materials (e.g. solvents and work-up chemicals) involved.

As the tool evolves, the quantitative aspect is to be expanded, beyond solely atom economy, to include additional metrics such as mass intensity, reaction yield, E-factor, effective mass yield and total material consumption to name a few.⁴¹ These metrics also provide information that can be further used to evaluate the human health and environmental impacts of these proposed alternative routes in the life cycle and life cycle impact stages of the overall system evaluation.

CONCLUSION

This Sustainable Chemistry Synthesis and Expert Framework is designed to provide guidance for the synthesis of chemicals, which exemplify green chemistry principles and instances from the literature to contribute to advancing molecular design, aid in the use of decision support methods and tools and contribute to advancing the sustainability of chemicals. While ambitious, the framework has the beginnings to serve as a conduit to merge together the concepts and necessary knowledge, software, databases and tools identified in this contribution.

While a fully automated and searchable library database is desired, the current approach, as demonstrated in this contribution, is for the foundation to be manually created using a collection of journal articles, patents, reports and case studies which exemplify those examples which adhere to the tenants of green chemistry and engineering. This approach can lead to generation of an impressive reference database. However, this method can be time consuming in its creation and implementation. Establishing routes which take advantage of an appropriate infrastructure and searchable features will allow for automated web searching and indexing, which are the necessary and the next steps as this framework matures.

Additionally, structural features (molecular descriptors in particular) can be used to estimate toxicity endpoints such as estrogen receptor binding potential using quantitative structure-activity relationship models.⁹⁷ Thus, providing the user with alerts for potential toxicity and adverse outcomes when coupled with other methodology or software. To further expand this effort, this library database is being designed to provide information for methods being

developed for life cycle inventory generation and life cycle assessment,^{31,35} as described previously in this contribution.

To further advance and integrate these approaches, an alternative assessment-based methodology is concurrently being developed to compare chemical alternatives in terms of hazard profiles. The hazard profile compares alternatives in terms of related human health hazards, ecotoxicity, and physicochemical properties (persistence and bioaccumulation in particular).⁹⁸ The tools developed in these studies can then be exploited to evaluate those chemicals involved in the synthesis of each alternative and thus can be potentially emitted to the environment, leading to further improvement of the synthesis route taken. This approach facilitates the opportunity to evaluate not only the target alternative, but all of the chemicals involved when considering and comparing the hazard profiles of potential alternatives. This can be extended into comparison of alternative in terms of the risk from exposure over the entire life cycle (manufacture, use, and disposal) of all chemicals involved in their creation. An example of this is the use of physicochemical properties are utilized to estimate partitioning within the environment and to estimate exposure from near-field and far-field exposure models.

From the chemical inventory we can identify CoCs and their theoretical amount. The by-products of a pathway are the waste thus providing a direct impact on the environment. The theoretical mass efficiency is evaluated by atom economy leading to reactant efficiency. The type or reactions involved in a pathway also allows to project practical concerns, such as energy consumption, reaction selectivity, occupational hazard, etc. In more complex synthesis, scheme efficiency (synthetic ideality and longest linear sequence) is also extremely important.

However, any limitation would be a lack of existing precedence for a typical molecule in terms of synthetic approaches. As an example, emerging alternative activation methods that exploit the use of mechanochemical, ultrasound, microwave or photochemical strategies,⁹⁹ may not be known in the literature and hence a trained individual can foresee the use of any of these process intensification options depending on the structural features of the target molecule as is the case in organophosphates.

In conclusion, we have outlined an integrated approach for the development of a preliminary framework that caters to the sustainable synthesis of a target chemical identified as a potential alternative for an existing chemical of concern. This Sustainable Chemistry Synthesis and Expert Framework strategy is designed to provide examples of synthesis reactions, which utilize green chemistry and engineering principles. Alternative synthetic opportunities are provided by the identification of functional groups present in the target molecule and the information coupled with the necessary organic chemistry hierarchy allows for the translation of digital molecular information to the corresponding library database. This is further complimented by the advantages of using descriptors where an existing tool like TEST can help assist in the creation of a sustainable chemical design. The framework is introduced concomitantly with a case study of a potential replacement for brominated flame retardants (BFRs), organophosphates. This framework is designed to apply existing knowledge of green chemistry to the synthesis of alternatives, along with its integration into

Life Cycle Assessment culminating in the development of a more overall sustainable chemical entity when compared to its known predecessor.

SUPPORTING INFORMATION

Matrix of organic functional groups identified and included in this methodology, tables for molecular descriptors representing each functional group, molecular descriptors and fragment counts for: carbon and hydrogen organic functional groups; carbon, nitrogen and hydrogen organic functional groups; carbon, oxygen and hydrogen organic functional groups; carbon, nitrogen, oxygen and hydrogen organic functional groups; carbon, phosphorous and hydrogen organic functional groups; carbon, oxygen, phosphorous and hydrogen organic functional groups; carbon, sulfur and hydrogen organic functional groups; carbon, nitrogen, oxygen, phosphorous, sulfur and hydrogen organic functional groups, description of green chemistry evaluation to arrive at the four general schemes, synthesis of triphenyl phosphates via catalysis, and synthesis of triphenyl phosphate via oxidation of phosphites (Scheme B)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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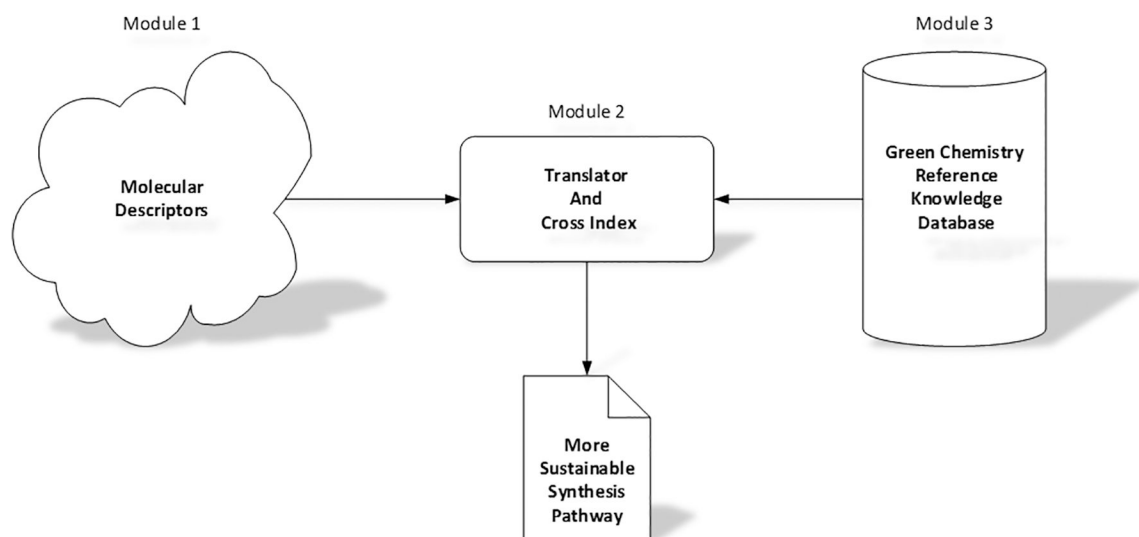


Figure 1.
General scheme for the Sustainable Chemistry Synthesis Expert Framework and Database

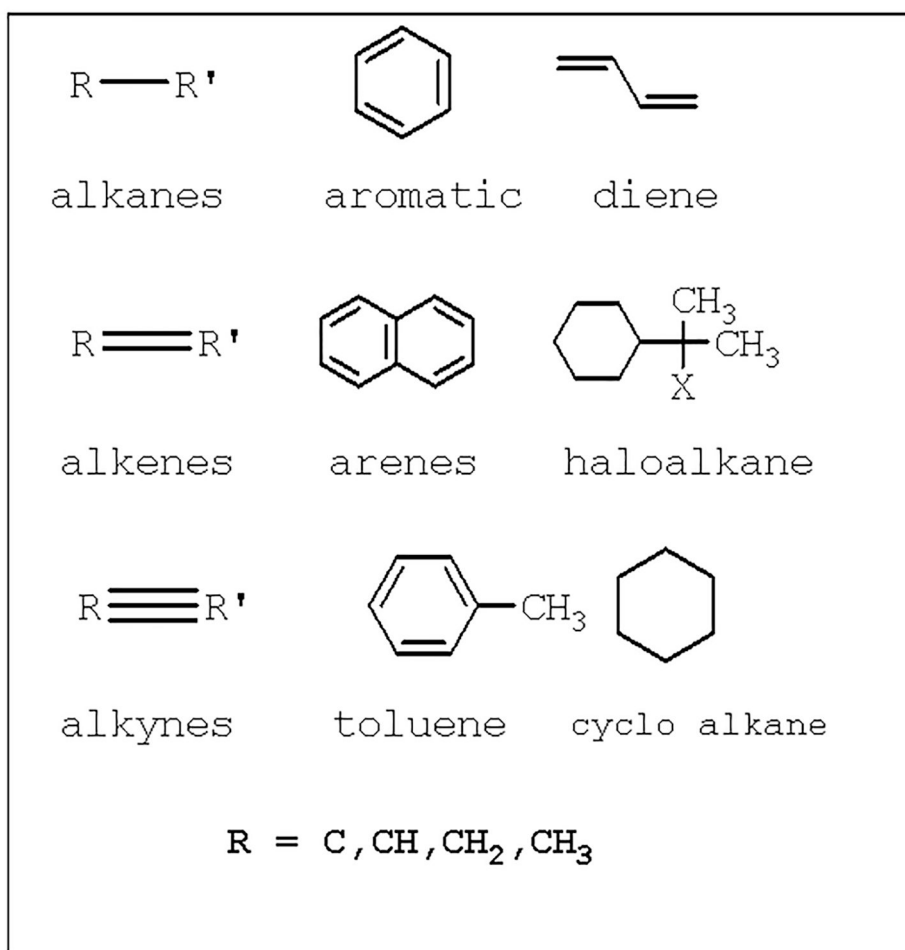


Figure 2:
Carbon-based functional groups

Level 1	Organic	Inorganic
Level 2 (in Organic)	Carbon	
	Nitrogen	
	Phosphorous	
	Sulfur	
	Oxygen	
Level 3 (in Phos)	Phosphates	
	Phosponates	
Level 4 (in P-hates)	Non-Halogenated	Halogenated
Level 5 (in n-halo)	Alkyl	
	Aryl	

Figure 3:
Proposed functional group hierarchy for a phosphorus containing molecule

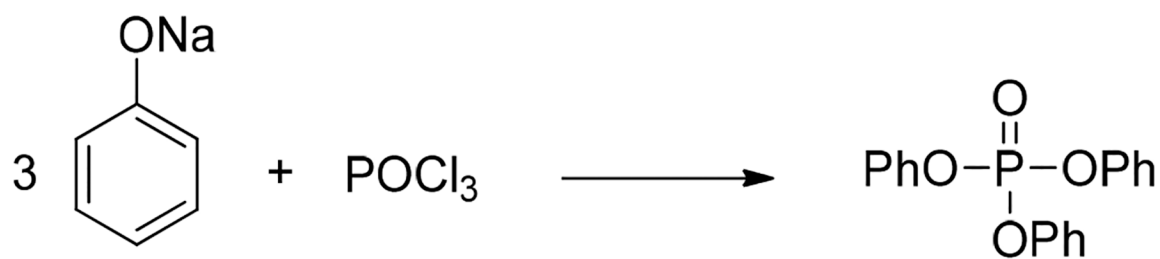


Figure 5.
Esterification of phosphoryl chloride under Schotten-Baumann conditions (Scheme C)

Table 1.

Individual stages in NAS Framework with Information Gained and Data Requirements at each Stage

Stage	Title	Information	Frameworks included the activity/Reference Tools	Example Types of Data Needed
1	Identify chemical of concern	Identify the chemical of concern in need of a substitute.	DfE, BizNGO, Lowell, German Federal Environmental	Human Health, Environmental and Legal Concerns
2	Scoping and problem formulation	Identify scope of assessment, goals, principles, and decision rules. Obtain information on chemical of concern and determine assessment methods.	All Frameworks	Function of CoC, System Boundaries and Impact of change
3	Identify potential alternatives	Identify chemical, material, and design alternatives on the basis of the requirements established in Stage 2.	All Frameworks	Role of CoC, Simulations, Molecular Modeling, and Chemical Expertise
4	Initial Screening of Identified alternatives	Results of initial screening of selected alternatives. If alternatives failed to meet the requirements initiate research to develop new alternatives or improve the existing ones.	CA SCP, BizNGO, ECHA, UNEP	Efficacy of Alternative, Upstream and Downstream Implications
5	Assess Physicochemical Properties	Physicochemical properties will help to evaluate hazard and exposure.	All Frameworks	Chemico-, Physico-, Toxicological
6-1	Assess Human Health Hazards	Evaluate human health hazards of a chemical exposure.	All Frameworks	Human Health Fate, Exposure, Toxicity
6-2	Assess Ecotoxicity	Asses the ecological hazards of an alternate chemical.	All Frameworks	Fate and Transport, Environmental Exposure, Food Chain, Aquatic and Terrestrial Toxicity, Air and Land Impacts
6-3	Conduct Comparative Exposure Assessment	Compares the chemical of concern and alternate chemical exposure.	DfE, IC2, BizNGO, CA DTSC	Fate, Transport, Exposure
7	Integration of Information to Identify Safer Alternatives	Identify the safer alternative based on the information obtained in the previous Stages. If no safer alternative is identified, initiate research to develop new alternatives.	Alternatives safer: All Frameworks. Alternatives not safer, initiate research: CA DTSC, BizNGO, ECHA, UNEP	Decision Frameworks
8	Life Cycle Thinking	Determine whether risks to human health, environment, or society exist during its life cycle.		Sustainability Related – LC Inventory, Fate, Transport, Exposure, Toxicity, Impact Category Specific Potency
9-1*	Life Cycle Assessment*	Estimate energy consumed materials emitted and consumed. Assess potential social and socioeconomic impacts.	Energy/resources: IC2, CA DTSC, BizNGO, ECHA, UCLA, German Federal Environmental Social impacts: IC2, Lowell, ECHA, UCLA, UNEP	LC Inventory - Manufacturing, Utilities, Emissions. Fate, Transport, Exposure, Toxicity, Impact Category Specific Potency
9-2*	Performance Assessment	Assess the performance of alternatives against the requirements established in Stage 2.	All Frameworks	Performance Metrics
9-3*	Economic Assessment	Assess economic impacts associated with each alternative.	All Frameworks	Material, Processing, Waste, Regulatory Requirements and Transportation Costs
10	Integrate Data and Identify Acceptable Alternatives	Identify acceptable alternatives on the basis of information compiled in previous steps.	All Frameworks	Decision Frameworks

Stage	Title	Information	Frameworks included the activity/Reference Tools	Example Types of Data Needed
11*	Compare Alternatives	Compare the identified alternatives and select an alternative for implementation.	IC2, CA DTSC, Lowell, and UCLA	Comparative and Sustainability Assessments, Decision Frameworks
12	Implement Alternatives	Transition to the identified alternative for the chemical of concern and implement the process.	CA DTSC, BizNGO, Lowell, ECHA, and UNEP	Manufacturing and Supply Chain Changes
13*	Research and Innovation	Create new designs and processes to identify alternatives for chemicals of concern and to improve the overall safety of chemical products.	CA DTSC, BizNGO, ECHA, and UNEP	Green Chemistry, Green Engineering, Molecular Design

Table 2.

TEST's descriptors fragmentation output for some chosen functional groups.

Functional Group	Structure	Fragments		
Alkenes	$R=C=R'$	2x CH ₂ Aliphatic Attachment		
Amines	$R-NH_2$	R Aliphatic Attachment	NH Aliphatic Attachment	
Ketone	$R-C(=O)-R'$	R Aliphatic Attachment	C=O Ketone Aliphatic Attachment	
Amides	$R-C(=O)-N(R')R''$	C(=O) Nitrogen Aliphatic Attachment	R Aliphatic Attachment	N< Aliphatic Attachment
Sulfate	$O=S(=O)(OH)O^-$	OH Aliphatic Attachment	S(=O)(=O) Aliphatic Attachment	[O-H] [O-R]
Phosphate	$O=P(=O)(O^-)O^-$	[O-]	3x P(=O)	[O-R]

Table 3.

Chemical inventory and atom economy for Scheme A

Reaction	Input	Output	MW (amu)	Equivalent	Input Mass (amu)	Product Mass (amu)
1	H ₃ PO ₄		98	1	98	
	PhOH		94.11	3	282.33	
		Product (3)	326.28	1		326.28
		Water	18.02	3		54.06
Total mass (amu)					380.33	380.34
Atom Economy						85.8%

Table 4:

Chemical inventory and atom economy for Scheme C

Reaction	Input	Output	MW (amu)	Equivalent	Input Mass (amu)	Product Mass (amu)
1	P(O)Cl ₃		153.33	1	153.33	
	PhOH		94.11	3	282.33	
		Product (3)	326.28	1		326.28
		HCl	36.46	3		109.38
Total mass (amu)					435.66	435.66
Atom Economy						74.9%

Table 5.

Chemical inventory and atom economy for Scheme B

Reaction	Input	Output	MW (amu)	Equivalent	Input mass (amu)	Product Mass (amu)
1	PCl ₃		137.33	1	137.33	
	PhOH		94.11	3	282.33	
		P(OPh) ₃	310.28	1		109.38
		HCl	36.46	3		
2	O ₂		32	0.5	16	
		Product 3	326.28	1		326.28
Total mass (amu)					435.66	435.66
Atom Economy						74.9%

Table 6.

Chemical inventory and atom economy for Scheme D

Reaction	Input	Output	MW (amu)	Equivalent	Input Mass (amu)	Product Mass (amu)
1	PCl ₅		208.24	1	208.24	
	PhOH		94.11	3	282.33	
	MeOH		32.04	2	64.08	
		CH ₃ Cl	50.49	2		100.98
		H ₂ O	18.02	1		18.02
		HCl	36.46	3		109.38
		Product (3)	326.28	1		326.28
Total Mass (amu)					554.65	554.66
Atom Economy						58.8%