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Simplified Application of Material Efficiency Green Metrics to Synthesis Plans: Pedagogical Case Studies Selected from *Organic Syntheses*

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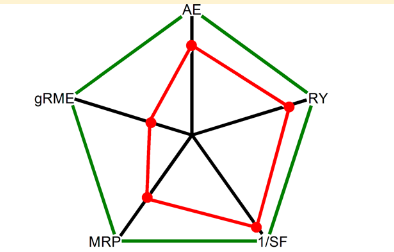
Ⓢ *Supporting Information*

ABSTRACT: This paper presents a simplified approach for the application of material efficiency metrics to linear and convergent synthesis plans encountered in organic synthesis courses. Computations are facilitated and automated using intuitively designed Microsoft Excel spreadsheets without invoking abstract mathematical formulas. The merits of this approach include (a) direct application of green chemistry principles to synthesis planning; (b) strongly linking green metrics calculations and synthesis strategy; (c) pinpoint identification of strengths and weaknesses of any synthesis plan's material efficiency performance using effective visual aids; (d) in-depth quantitative and qualitative critiquing of synthesis plan performance and strategy; and (e) giving opportunities to students to offer insightful suggestions to improve or "green up" published procedures based on their growing personal database of chemical reactions as they continue their education in chemistry. An extensive database of over 600 examples taken from *Organic Syntheses* was created as a repository of reliable examples that instructors can draw upon to create meaningful classroom pedagogical exercises and homework problem sets that couple material efficiency green metrics analyses and traditional learning of organic chemistry.



$$\frac{1}{\text{gRME}} = \text{PMI} = \text{E} + 1$$

KEYWORDS: *Upper-Division Undergraduate, Organic Chemistry, Problem Solving/Decision Making, Green Chemistry, Synthesis*

■ INTRODUCTION

The study of green metrics has now matured over the last two decades as a central pillar of the newly emerging discipline of green chemistry.[1−4] Of the several types of metrics proposed in the literature, they may be classified into four main groups: material efficiency, energy efficiency, environmental impact, and safety-hazard impact metrics. These areas form a hierarchy of complexity from the easily accessible concepts of material efficiency to the most complex involving multivariable life cycle assessment. When students first encounter metrics in the context of their introduction to green chemistry, the key area most focused on is material efficiency since this comparative assessment can be directly applied to experimental procedures that students are already familiar with from traditional lecture and laboratory courses in the chemistry curriculum.

Within this area, the most frequently encountered metrics that students use to evaluate reaction performance are reaction yield (RY), atom economy (AE),[5] E-factor,[6] global or general reaction mass efficiency (gRME),[7−10] and process mass intensity (PMI).[11,12] This choice of material efficiency metrics mirrors what the research literature by academic and industrial groups has also gravitated to and now has been widely accepted.[13−38] Editors of leading journals such as *Organic Process Research & Development* have initiated recent changes to submission guidelines for articles so that they include this suite of metrics to substantiate claims of greenness for chemical reactions or processes.[39,40]

However, in the pedagogical literature most of the laboratory and classroom activities surrounding material efficiency metrics evaluation have focused on the "green" performances of individual chemical reactions,[41−44] while neglecting similar evaluations of synthesis plans. There is a perception that analysis of linked reactions in a synthesis plan, whether linear or convergent, is characterized by complicated and tedious calculations that are beyond the scope of an introductory course in green chemistry, which typically is set up as a general survey course of modern green technologies juxtaposed against traditional technologies that have had a long and lasting negative environmental impact legacy. Indeed, this sentiment is borne out by the few reports[23,45,46] in the literature on this subject, which are unfortunately characterized by complex mathematical symbolism and are thus intractable to most readers of this *Journal*. In this paper we wish to address this issue and convince both instructors and students that material

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efficiency analysis of synthesis plans is indeed not only accessible within the scope and expertise of undergraduate students who are versed in the use of spreadsheet programs such as Microsoft Excel, but also important for their complete education in implementing green chemistry principles to any kind of synthesis plan they may encounter beyond examination of stand alone reactions. We believe these objectives can be achieved using concrete worked examples without compromising on time devoted to teaching basic metrics in a one semester green chemistry course. We present such computations in an accessible manner building on prior work on radial polygon representations of the green performances of individual reactions. This new approach has been modified to accommodate the concept of linking individual reactions to a common target product following a given number of reaction steps using appropriate scaling factors. This easy to understand and intuitive spreadsheet method avoids writing out complex abstract mathematical formulas and at the same time illustrates the results of metrics evaluations using effective visual aids that capture essential attributes for rapid identification and understanding of the strengths and weaknesses of synthesis performances. Exercises that incorporate such analyses offer rich discussions about synthesis strategy in the context of green chemistry principles. We also advance the idea of using actual experimental write-ups taken directly from *Organic Syntheses* as a rich resource of pedagogical examples to illustrate the implementation of basic material efficiency metrics calculations. The main reason for doing so is that experimental procedures written in this publication have amounts of nearly all input materials disclosed. This characteristic circumvents the use of assumptions when encountering missing data, as is often the case in published experimental sections of journal articles, such as those suggested by the EATOS (Environmental Assessment Tool for Organic Syntheses) program,[47,48] which can severely compromise metrics evaluations and subsequent performance rankings of individual reactions or entire synthesis plans. Such assumptions are also open to criticism since they are arguably based on arbitrary cutoffs, though they have been carefully selected. From a pedagogical point of view, it is highly desirable to introduce metrics calculations to students with the least number of assumptions so that they can appreciate their full value in real experimental situations. Furthermore, *Organic Syntheses* is well-known to all practicing chemists since 1921 as a venerable resource of reliable procedures to make chemicals that have been checked independently for both veracity and robustness. This long historical track record covering 91 volumes to date makes this publication ideal for showcasing to students procedures that actually do work for experimenters with a skill level that is commensurate with their own.

DEFINITIONS OF MATERIALS METRICS USED

We begin with an overview of the material efficiency metrics for an individual chemical reaction. In order to facilitate all computations in this paper we retain all fractional quantities as proper fractions ranging between 0 and 1 rather than expressing them as percentages. The standard interpretation is that a value of 1 corresponds to the ideal green situation for a given parameter and 0 corresponds to a nonideal situation. We note for the analysis discussed in this paper that the metrics do not include secondary processes beyond the primary chemical transformations comprising a synthesis plan, such as waste treatment processes and consumption of other utilities. In principle the same set of metrics may be applied separately to these appropriately mass balanced processes and then summed with the results of the primary reactions. For a given balanced chemical reaction involving reagents A and B and giving a target product P and associated byproduct Q, $\nu_A A + \nu_B B \rightarrow \nu_P P + \nu_Q Q$, with appropriate stoichiometric coefficients ν, we define reaction yield (RY) and atom economy (AE) according to eqs 1 and 2, where we assume that reagent A is the limiting reagent.

$$\mathrm{RY} = \left(\frac{\mathrm{moles}_P}{\mathrm{moles}_A}\right)\left(\frac{\nu_A}{\nu_P}\right) \tag{1}$$

$$\mathrm{AE} = \frac{\nu_P(\mathrm{MW})_P}{\nu_A(\mathrm{MW})_A + \nu_B(\mathrm{MW})_B} \tag{2}$$

where MW corresponds to molecular weight. In such a general reaction, we assume that the following auxiliary materials have been used: a reaction solvent (S), a catalyst (C), workup materials (WPM), and purification materials (PM). Hence, the global reaction mass efficiency (gRME), E-factor (*E*), and process mass intensity (PMI) are given by eqs 3, 4, and 5.

$$\mathrm{gRME} = \frac{m_P}{m_{\mathrm{inputs}}} = \frac{m_P}{m_A + m_B + m_S + m_C + m_{\mathrm{WPM}} + m_{\mathrm{PM}}} \tag{3}$$

$$E = \frac{m_{\mathrm{inputs}} - m_P}{m_P} = \frac{m_A + m_B + m_S + m_C + m_{\mathrm{WPM}} + m_{\mathrm{PM}} - m_P}{m_P} \tag{4}$$

$$\mathrm{PMI} = \frac{m_{\mathrm{inputs}}}{m_P} = \frac{m_A + m_B + m_S + m_C + m_{\mathrm{WPM}} + m_{\mathrm{PM}}}{m_P} \tag{5}$$

where the variables labeled as *m* refer to mass. From eqs 3, 4, and 5 we have the following simple connecting relationships given by eq 6.

$$\mathrm{PMI} = \frac{1}{\mathrm{gRME}} = E + 1 \tag{6}$$

In our formulation of the identities of materials in a stoichiometrically balanced chemical equation, we denote the word “byproducts” to mean those materials formed as a mechanistic consequence of producing the designated product. The EATOS software uses the phrase “coupled products” to describe the same thing since the formation of the target product and associated byproducts is mechanistically linked. We therefore make a distinction between the terms “byproducts” and “side products” which are often used interchangeably. Side products are materials formed by a different reaction (running in parallel to the designated balanced chemical equation) arising from a different reaction mechanism than the reaction leading to the desired product. The side reaction begins with the same set of starting materials, not necessarily with the same stoichiometry, but results in a different set of products which are all called side products. These important distinctions are necessary in determining the balanced chemical equations on which metrics calculations are performed. Fuller discussions with illustrative examples showing the distinction between these terms have been previously given elsewhere.[1,3,10]

SPREADSHEETS

Individual Chemical Reactions

The first task is to determine a fully balanced chemical equation for the reaction. This is a critically important exercise that is intimately linked to the understanding of a reaction mechanism for a given reaction. The reader should be reminded that a reaction mechanism is composed of a series of elementary steps involving formation and decomposition of transient intermediates whose sum is the net overall stoichiometrically balanced chemical equation for a given transformation. Specifically, it reinforces and proves the statement that the overall balanced chemical equation of any reaction is the sum of all balanced elementary steps involved in its associated reaction mechanism. After a balanced chemical equation has been established, material efficiency metrics for any given chemical reaction are evaluated using the REACTION spreadsheet to determine the parameters given by eqs 1 to 5 according to the masses of all input materials used and mass of product collected as prescribed by the experimental procedure. Once a procedure is acquired, this task is self-explanatory since it involves simply inputting the appropriate masses, volumes, and densities in the proper locations in the spreadsheet. It should be noted that the spreadsheet presented in this work has a significant number of upgrades to the one published previously.[41] First, it has a built in check calculation to ensure that a correctly balanced chemical equation is used, otherwise an error message appears which cautions the user to not proceed further until this query is rectified. The limiting reagent is always entered in the first line of the reagents block. The spreadsheet will also determine for each reagent appearing in the balanced chemical equation the ratio of actual moles (mass) used to stoichiometric moles (mass), the mass of excess reagent, and the mass of unreacted reagent. The actual to stoichiometric mole and mass ratios will figure prominently in the SYNTHESIS spreadsheet as we will see shortly. For the limiting reagent this ratio has a value of 1 and all other reagents that are used in excess will have ratio numbers exceeding 1. The REACTION spreadsheet outputs include a new complete breakdown of the E-factor profile according to the following contributions: byproducts, excess reagent consumption, catalyst consumption, workup materials, and purification materials. These results are presented in tabular format as well as a graphical pie chart showing their percent contributions. Finally, a radial polygon is given showing an overall color-coded visual representation of the green performance of a given reaction according to RY, AE, excess reagent consumption, auxiliary material consumption, and gRME as described previously.[41] The green limit is defined by the boundary of the radial polygon where all values are equal to 1 by definition. The prior definitions of stoichiometric factor (SF) and materials recovery parameter (MRP) have also been retained.[41]

Synthesis Plans

When dealing with a synthesis plan, we first need to write out the full set of balanced chemical equations for all chemical reactions in the plan. Next we choose a basis scale for the final target product, which for our purposes is consistently set to 1 kg. In order to link all of the reactions appearing in a synthesis plan together to match the final basis scale of the final target product, we need to assign corresponding scaling factors to each reaction so that the masses of all input materials in each reaction are appropriately adjusted. This task needs to be done because the experimental procedures for each reaction in a plan are normally carried out using different mole scales and are disjointed from one another. Hence, all of the masses of intermediate products, their associated originating reagents, and auxiliary materials appearing in the REACTION spreadsheets need this modification. An implicit assumption in our present analysis is that the magnitude of the reaction yield for any reaction is scale invariant. Without this assumption the entire calculation cannot proceed. The last section of the REACTION spreadsheet, labeled as “use for synthesis plans only”, deals with the determination of these scaling factors and the adjusted mass scale of the limiting reagent. Effectively we are working backward from the mass scale of the final target product to work out corresponding mass scales of all input reagents and all other materials (solvents, catalysts, workup materials, and purification materials) used in each reaction. When viewed from the forward sense, the metrics tell us the complete mass throughput of all materials used from start to finish until the final target product is reached according to the specified pathway of the synthesis plan. This means that the entire mass of intermediate product collected in step j is committed as a reactant in step $j + 1$. If we wish to make 1 kg of the final target product and the experimental yield of this material is X g according to the procedure for the last step in a plan, then the scaling factor for the last step is given by eq 7,

$$\text{factor} = \frac{1000}{X} \tag{7}$$

and the mass of limiting reagent leading to this product is given by eq 8.

$$\begin{aligned}&\text{scaled mass of limiting reagent}\\&\quad = \text{experimental mass of limiting reagent} \times (\text{factor})\end{aligned} \tag{8}$$

The scaled mass of limiting reagent calculated in eq 8 is now inserted as the mass of target product used in the preceding step. Equations 7 and 8 are again used to determine the corresponding parameters for the penultimate step. For a linear plan involving only one branch this process is continued all the way back to the first step in the plan in a continuous sequential fashion. A linear plan of N steps will have N scaling factors. For a convergent plan the same process is followed from the final target product in a linear backward fashion until the first convergent step is encountered. In that step there will be two adjusted masses to determine, one for each of the two input reagents involved in the convergent reaction. One adjusted mass will carry over for the rest of the main branch, that is, the branch with the longer number of steps, and the other will carry over to the rest of the shorter branch corresponding to the convergent branch. If there are more convergent steps encountered along the way, then each of these will need to be split into two paths with associated pairs of adjusted masses that are carried over following the appropriate origin of each branch. The total number of scaling factors needed in a convergent plan is equal to the sum of all reactions from all branches. The idea of working backward is highly convenient and advantageous from a computational point of view when dealing with convergent synthesis plans. If we were to work in the forward sense in a multiconvergent plan with M branches and at most $M - 1$ points of convergence, we would need to readjust the mass scaling of each input reagent and auxiliary material appearing in each convergent branch at most $M - 1$ times. This is obviously a tedious and cumbersome task if we have many branches and many contributing input materials in

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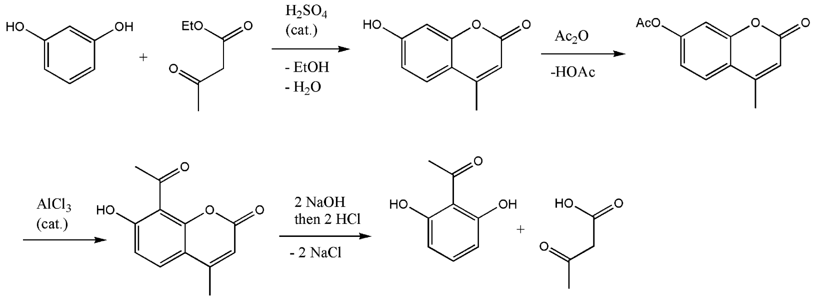
Scheme 1. Four-Step Linear Plan To Synthesize 2,6-Dihydroxyacetophenone from Resorcinol[a]



[a]The reaction yields for steps 1 to 4 are 82, 90, 73, and 73%, respectively.

each branch, and therefore this approach does not lend itself to simple algorithmic programming. Hence, the value of the backward approach to solving the problem is appreciated because the mass scales for all reagents are determined only once. In either case, whether dealing with linear or convergent plans, once the full set of scaling factors from eq 7 is determined, these are then immediately inserted in the SYNTHESIS spreadsheet. Other inputs include the mass of target product (1 kg) and actual masses of all input materials used from each experimental procedure corresponding to each reaction step. Additionally, each input reagent appearing in all balanced chemical equations for the plan requires us to input its own molecular weight, stoichiometric coefficient, and the mass or mole ratio described in the previous section. The spreadsheet will automatically calculate the adjusted masses of all materials used in the plan, the overall PMI, overall E-factor, and overall mass of waste. Furthermore, it will give a breakdown of PMI and *E* according to their contributions from byproducts, excess reagents, unreacted intermediates, and auxiliary materials. The graphical outputs include an overall radial polygon showing the global performances of the same five metrics as for individual reactions, a pie chart showing the percent E-factor breakdown, histograms showing the reagent and auxiliary material consumption, and histograms for the individual reaction performances according to reaction yield, AE, and PMI. Currently, the template spreadsheet given in the Supporting Information is defaulted to a three-step plan, but this can be adjusted easily to accommodate longer plans by adding extra lines and copying and pasting appropriate blocks as needed. When copying lines with embedded formulas in Excel, care must be exercised to ensure that the copied formulas correspond to the correct line numbers and that the boxes designated with sum formulas are also checked to ensure that they cover the correct lines. Wherever possible, locked variables were used in cell formula entries to reduce the number of such adjustments. Modern versions of this spreadsheet program have color coded formula entries to facilitate this task. Instructors may need to take time out to ensure students are fully fluent in the syntax use of this spreadsheet program to ensure correct implementation of the SYNTHESIS spreadsheet. In our experience we have found that aversions to metrics computations of synthesis plans are a direct result of competency issues with the use of the spreadsheet program rather than being overwhelmed by the complexity of the analysis.

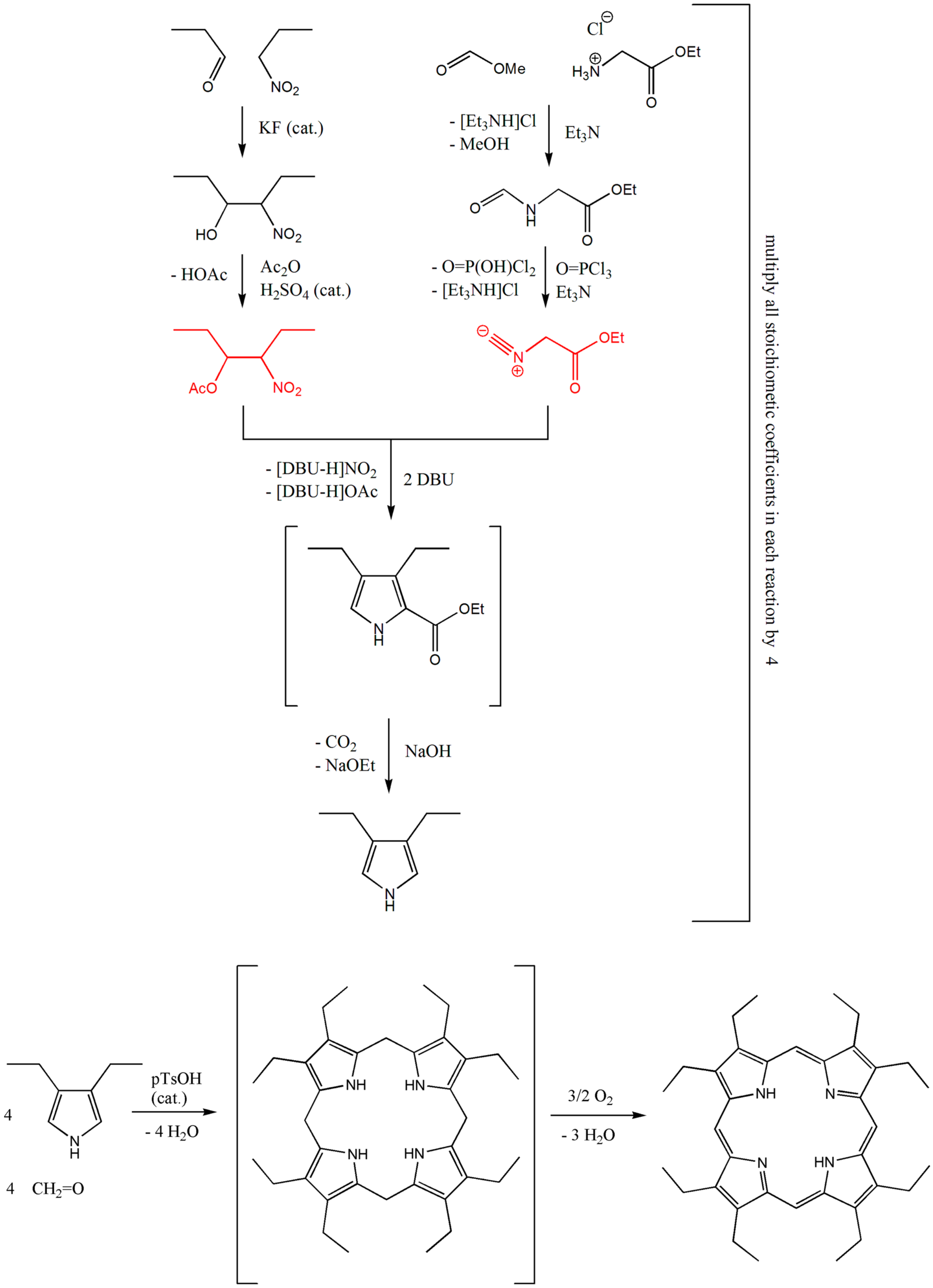
■ ILLUSTRATIVE EXAMPLES

In this section we illustrate implementation of both linear and convergent spreadsheets for representative example linear and convergent plans taken directly from *Organic Syntheses*. Schemes 1 and 2 show reactions involved in both synthesis plans. For each case we note observations about their performances that can springboard classroom discussions about overall reaction and synthesis plan behavior according to various factors. When enough of these exercises are conducted, students can discover generalizations about synthesis planning which are referenced here as appropriate.

■ LINEAR PLAN

Scheme 1 shows a four-step linear plan to synthesize 2,6-dihydroxyacetophenone from resorcinol where all byproducts are identified.[49] The execution of this plan to produce 1 kg of this product in 39% overall yield over 4 steps will result in the production of 390 kg of waste for a PMI of 391 and an overall E-factor of 390. Figure 1 shows the overall radial polygon performance compared to green ideality with respect to material efficiency along with histograms for reaction step performance according to reaction yield, AE, and PMI. Figure 2 shows the overall E-factor profile along with the reagent and auxiliary consumption profiles. We can see that workup solvents accounted for the bulk of the waste produced at 63% while reaction solvents only accounted for 6%. The contribution from excess reagents is small at 2%. For linear plans this contribution originates exclusively from excess reagents, not reaction intermediates, since reaction intermediates along the plan pathway are limiting reagents in each reaction step. The Fries rearrangement in step 3 had the highest atom economy at 100% whereas the fragmentation reaction in step 4 had the lowest atom economy at 41%. These results are perfectly in line with the characteristics of these kinds of reactions. Here instructors have an opportunity to make a strong link between types of reactions encountered in organic chemistry (additions, eliminations, substitutions, condensations, multicomponent, rearrangements, redox reactions) and their typical AE performances. The condensation in step 1 had the highest PMI at 65 and is primarily due to the high workup material consumption though most of it is aqueous in nature. Any poor performance in the first few steps of a synthesis according to yield, atom economy, or PMI will severely impact the performance of the entire synthesis plan because these steps are necessarily conducted at the highest scale in a continuous throughput sense. It is therefore paramount from a materials green metrics perspective to ensure optimized waste reduction for early steps in a plan.

Scheme 2. Six-Step Convergent Plan To Synthesize 2,3,7,8,12,13,17,18-Octaethylporphyrin Involving Two Branches[a]



[a]The reaction yields for steps 1 to 4 along the main branch are 75, 89, 38, and 66%, respectively; whereas those for steps 1* and 2* along the convergent branch are 79 and 76%, respectively.

Students will be able to make this insight since it correlates well with the results of numerical calculations. With respect to the computation of AE, E-factor, and PMI for individual reactions in comparison to the overall values for these parameters for an entire plan, students quickly discover that individual reaction AE, E-factor, and PMI values are not additive. For example,

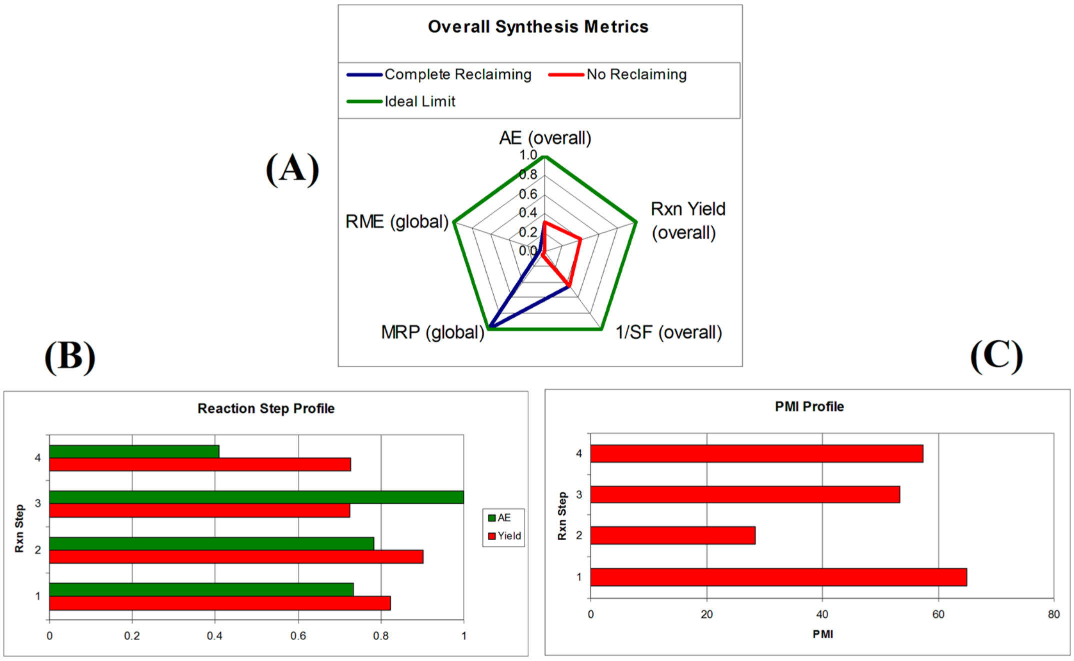


Figure 1. (A) Radial polygon, (B) yield and AE step profile, and (C) PMI step profile for linear plan according to Scheme 1.

overall *E* for a linear plan is not the sum of the E-factors of individual reactions. This, of course, is because of the different mass scales in each reaction as prescribed by the disjointed experimental procedures compared with the calculated mass scales when these reactions are linked together to a common basis scale of target product. We discuss this point and other computational features about synthesis plans more fully with mathematical proofs in the subsequent paper.[50] The Supporting Information contains the REACTION spreadsheets for each step in the plan shown in Scheme 1 as well as the overall SYNTHESIS spreadsheet.

■ CONVERGENT PLAN

Scheme 2 shows a convergent plan containing two branches for the synthesis of 2,3,7,8,12,13,17,18-octaethylporphyrin.[51,52] The main branch leading to this product consists of 4 linear steps while the convergent branch producing ethyl isocyanoacetate consists of 2 steps. Since the structure is a tetramer, all stoichiometric coefficients for all reagents and byproducts appearing in steps preceding the final step must be multiplied by a factor of 4. We chose this plan to illustrate the use of nonunity stoichiometric coefficients so that such variables are visible in the calculations. As before in Scheme 1, all byproducts are identified for each step. Since the final step involves an air oxidation, we assumed a stoichiometric amount of oxygen in our calculations. The execution of this plan to produce 1 kg of porphyrin product results in the production of 1242 kg of waste, for a PMI of 1243 and overall E-factor of 1242. Since this plan by its very nature is convergent, the concept of overall yield where individual reaction yields are multiplied together no longer applies since we have more than one branch, unlike a linear synthesis which has only one branch. This insight can be used to showcase a fundamental difference between linear and convergent plans to the same target product. In the convergent step the scaling factor applied to the masses of 4-acetoxy-3-nitrohexane and ethyl isocyanoacetate input reagents for that step was 65.7. The scaled masses of these two reagents are therefore 6767 and 3331 g, respectively. The 6767 value is carried over to the preceding step in the main branch as a target mass for 4-acetoxy-3-nitrohexane, while the 3331 value is carried over to the preceding step in the convergent branch as a target mass for ethyl isocyanoacetate. Figure 3 shows the overall radial polygon performance compared to green ideality with respect to material efficiency along with histograms for reaction step performance according to reaction yield, AE, and PMI. Figure 4 shows the overall E-factor profile along with the reagent and auxiliary consumption profiles. Workup materials and reaction solvents contribute 42% and 38% of the total E-factor, respectively. Three percent of the total E-factor originates from excess reagents and reaction intermediates. Unlike linear plans, the E-excess contribution for convergent plans accounts for excess reagent consumption from both reagents and reaction intermediates appearing in convergent steps. In such steps, typically one of the two intermediate products arising from the two branches will be the limiting reagent and the other is used in excess. The SYNTHESIS plan spreadsheet automatically determines the overall E-excess contribution as well as the subcontribution from reaction intermediates in convergent steps. In the present plan, E-excess = 31.5 of which a value of 1.2 comes from excess 4-acetoxy-3-nitrohexane used in the convergent step. The convergent reaction step 3 producing 3,4-diethylpyrrole has both the lowest yield at 38% and the lowest AE at 19%. Step 1 involving the addition of propionaldehyde to 1-nitropropane has the highest atom economy at 100%. Step 1* involving condensation of methyl formate with ethyl glycinate hydrochloride had the highest excess reagent contribution because methyl formate had a dual role as a reaction solvent as well as a reagent in this reaction. The last step in the synthesis had the highest PMI at 683 primarily due to the high consumption of benzene as reaction solvent consistent with the high dilution conditions under which this tetramerization reaction was carried out. The Supporting Information contains the REACTION spreadsheets for each step in the plan shown in Scheme 2 as well as the overall SYNTHESIS spreadsheet.

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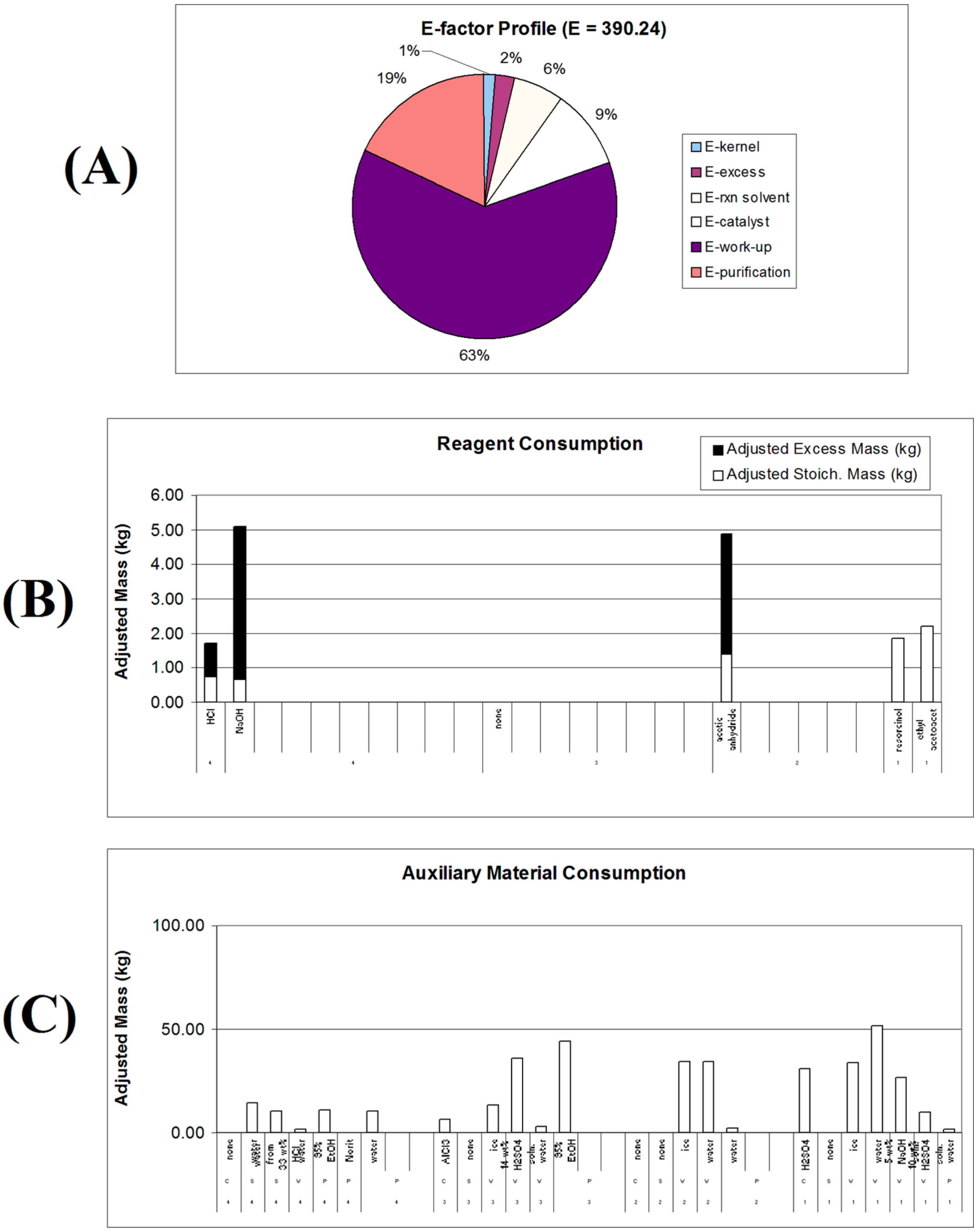


Figure 2. (A) E-factor profile, (B) reagent consumption profile, and (C) auxiliary material profile for linear plan according to Scheme 1.

■ *ORGANIC SYNTHESES* DATABASE

In the final section of this paper we discuss the pedagogical merits of a database (see Supporting Information) of reactions and synthesis plans we created from ten *Collective Volumes* of *Organic Syntheses* and current volumes 80 to 91 that instructors can use to propose pedagogical exercises in green metrics using real and reliable experimental procedures. We have categorized this extensive database of over 600 examples into the following 12 sections that highlight key applications of green metrics to important situations encountered in organic synthesis: (a) asymmetric syntheses; (b) reactions involving catalyst preparation; (c) chemoenzymatic reactions; (d) classical resolutions; (e) convergent synthesis plans; (f) kinetic resolutions; (g) multicomponent reactions; (h) multistep linear plans exceeding 2 steps; (i) natural feedstocks as starting materials; (j) product distributions; (k) sacrificial reagents; and (l) reactions involving nonunity stoichiometric coefficients. For each case we briefly highlight useful pedagogical exercises instructors may consider with students studying green chemistry material efficiency metrics. Asymmetric syntheses present the problem of including the metrics of the synthesis of chiral catalysts and ligands as part of the overall metrics analysis of the final target product. For example, if an asymmetric product A is synthesized in 4 steps and one of these steps (say, step 2) involves a chiral catalyst B, then the materials metrics analysis for the synthesis of product A may be worked out using the REACTION and SYNTHESIS spreadsheets as described in this work. However, this would be incomplete since the synthesis of

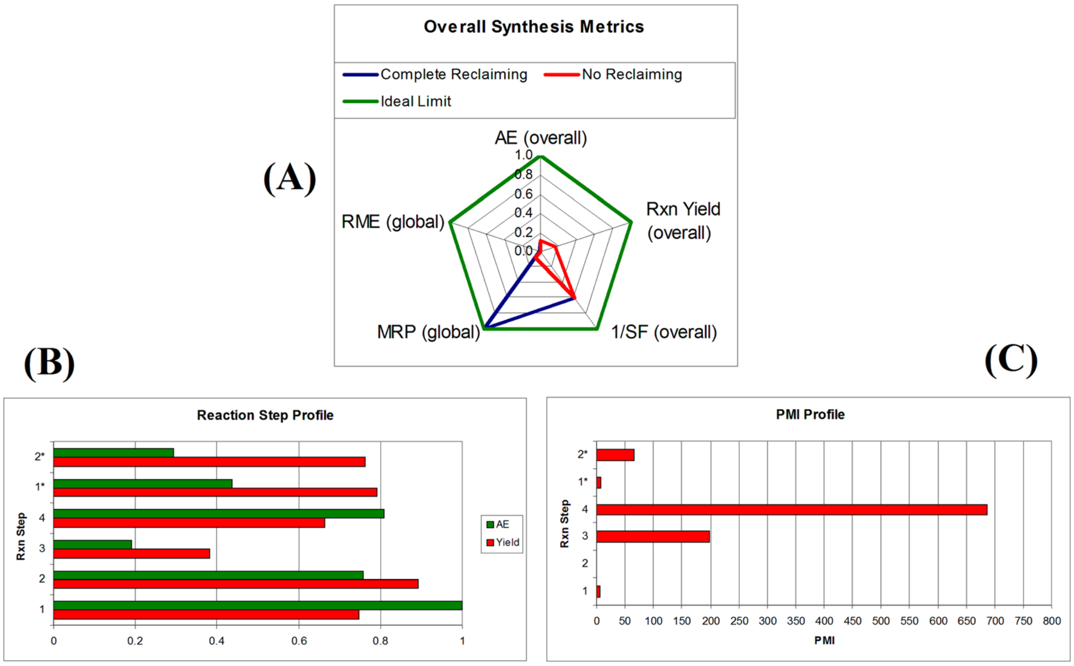


Figure 3. (A) Radial polygon, (B) yield and AE step profile, and (C) PMI step profile for linear plan according to Scheme 2.

chiral catalyst B also involves its own synthetic route which must be taken into account. In order to do so, the scaled mass of catalyst determined from the asymmetric step (step 2) in the main synthesis route to product A is used as the basis target mass of this substance for its own synthesis route which itself may involve several steps. Hence, a parallel analysis of the synthesis of the chiral catalyst using the same spreadsheets is required. The overall PMI to produce asymmetric product A would then be the sum of the PMI values for its synthesis and the synthesis of the chiral catalyst which are both referenced to the mass of product A.

Classical resolutions involve the use of a resolving agent such as L-tartaric acid to produce a diastereomeric salt in a given step which then is treated with acid or base to release the desired enantiomeric product. Metrics analysis of such a synthesis must take into account the consumption of the resolving agent and all of the materials used in the crystallizations involved and, ultimately, account for the fact that the maximum yield for producing the desired enantiomeric product is 50%. Kinetic resolutions using lipase and vinyl acetate, for example, allow the production of two useful products, one enantiomer which is not acetylated and the other which is. Separate metrics analyses may be applied to both desired products. Multicomponent reactions are an excellent kind of reaction to showcase both green chemistry principles and synthetic strategy techniques because they feature the construction of a complex product structure, often involving heterocyclic rings, in one reaction step using at least three separate reagents. Atom economy discussions are highly relevant for this type of reaction. Metrics analyses of such reactions may be juxtaposed against sequential reactions leading to the same complex product, but where intermediate products are isolated. These kinds of examples can drive home the merits of waste reduction. Syntheses of products from known masses of natural feedstocks such as corncobs, human hair, or nutmeg to produce furfural,[53] L-cystine,[54] and trimyristin,[55] respectively, pose a significant challenge to basic materials metrics calculations. For a start, no balanced chemical equation can be written down because none exists. However, PMI and E-factors may still be worked out based only on the masses of input materials used and the mass of target product collected. What is missing is a determination of AE for the reaction. A challenging question for students to consider is how such a scenario alters the traditional definition of reaction yield (see eq 1). Reactions producing multiple products can be used to show how metrics analyses may be applied along with product ratios to compare the efficiencies of production of different desired products. For example, the nitration of substituted aromatics which theoretically can produce ortho-, meta-, and para-substituted products is a good example that students are familiar with from traditional organic chemistry courses. Reactions involving sacrificial reagents such as in the synthesis plan shown in Scheme 3 can be used to highlight atom economy issues as well as elements of synthesis strategy. Essentially students need to ponder the role of using a given sacrificial reagent. Students first have to track atoms from step to step and recognize which parts of reagents end up in the product or not at all. Metrics analysis and these structural arguments strongly complement one another to produce a unifying picture of what is going on in a synthesis plan. It can also offer opportunities to discuss new synthesis routes to avoid such sacrificial reagents and also to discuss if electronic, steric, or chiral constraints associated with various functional groups may preclude their avoidance in the first place. In the case of Scheme 3, the role of the sacrificial reagent alpha-pinene is a chiral directing group.[56] The next consideration in this vein would be exploring opportunities for recycling the sacrificial reagent or its byproducts back to starting materials as suggested by the reaction shown in Scheme 4.[57] If a recycling reaction is possible, then a material efficiency metrics analysis must also be applied to it in the same way that the syntheses of chiral catalysts were handled in asymmetric syntheses. Finally, reactions involving nonunity stoichiometric coefficients are a great way to train students in balancing chemical equations and determining atom economies. Of particular note are the so-called redox class of reactions involving coupled oxidation and reduction reactions which offer

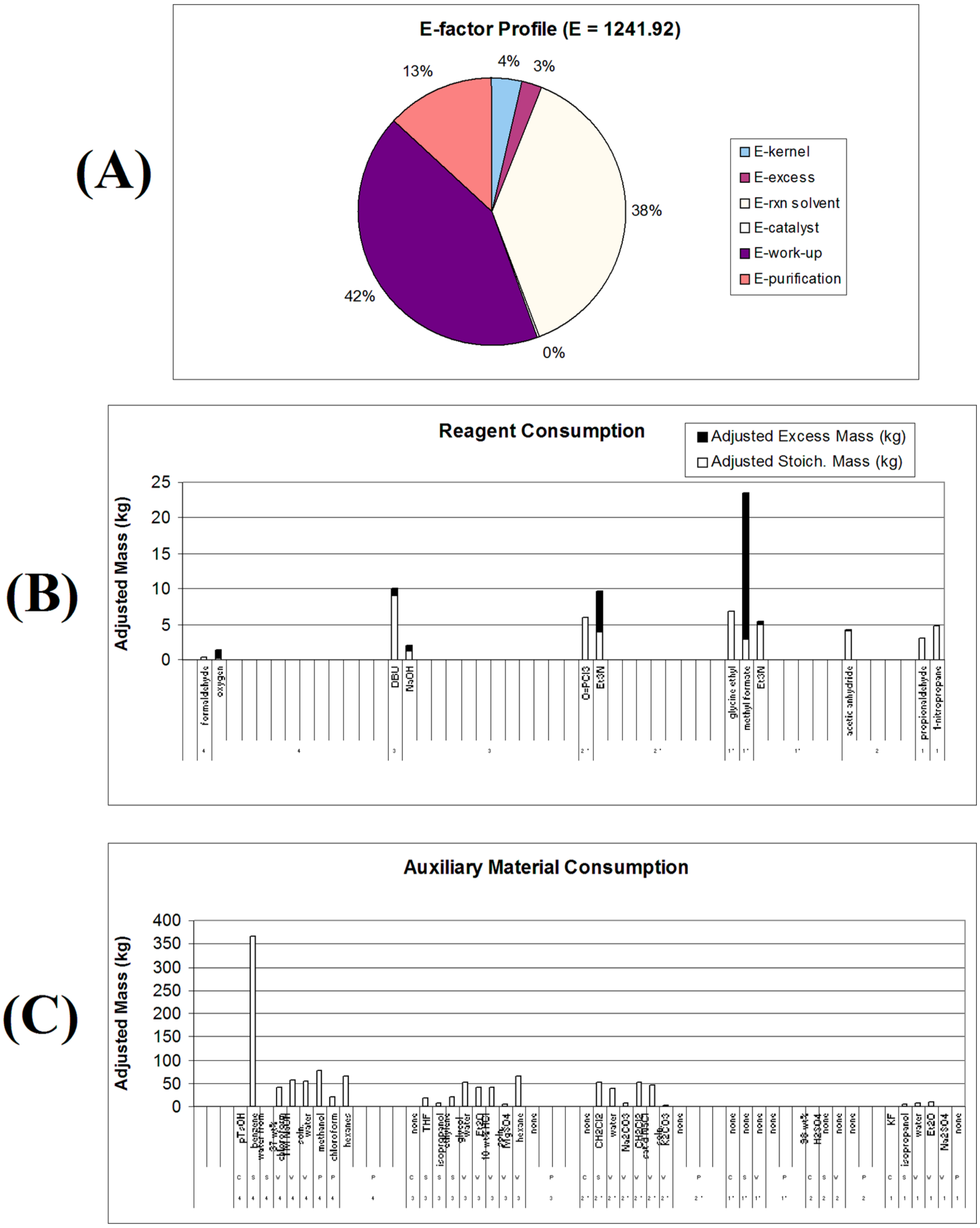
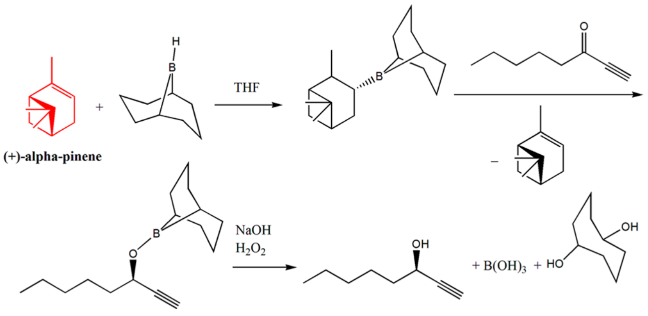
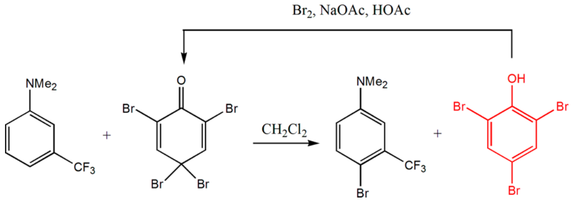


Figure 4. (A) E-factor profile, (B) reagent consumption profile, and (C) auxiliary material profile for linear plan according to Scheme 2.

Scheme 3. Synthesis Plan Involving a Sacrificial Reagent That Acts as a Chiral Directing Group



Scheme 4. Reaction Using a Sacrificial Reagent That Partly Gets Incorporated in the Desired Product, but Produces a Byproduct That Can Be Recycled Back to the Starting Reagent



rich opportunities to link the overall balanced chemical equations with their associated reaction mechanisms. Both students and instructors can spend many enjoyable hours using this database to learn about new and classical chemistry and apply green metrics analysis under various scenarios using the convenient spreadsheets presented in this work.

■ CONCLUDING REMARKS

This paper presents a simplified approach for the application of material efficiency metrics to linear and convergent synthesis plans encountered in organic synthesis courses. Computations are facilitated and automated using intuitively designed Microsoft Excel spreadsheets without invoking abstract mathematical formulas. The merits of this approach include (a) direct application of green chemistry principles to synthesis planning; (b) strongly linking green metrics calculations and synthesis strategy; (c) pinpoint identification of strengths and weaknesses of any synthesis plan's material efficiency performance using effective visual aids; (d) thorough quantitative and qualitative critiquing of synthesis plan performance and strategy; and (e) giving opportunities to students to offer insightful suggestions to improve or "green up" published procedures based on their growing personal database of chemical reactions as they continue their education in chemistry. An extensive database of examples taken from *Organic Syntheses* was created as a repository of reliable examples that instructors can draw upon to create meaningful pedagogical exercises that couple material efficiency green metrics analyses and traditional learning of organic chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00058.

> Template REACTION and SYNTHESIS Excel spreadsheets; Excel spreadsheets corresponding to linear and convergent plans given in Schemes 1 and 2; database of reactions and references from *Organic Syntheses* (ZIP)

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Notes

The authors declare no competing financial interest.

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