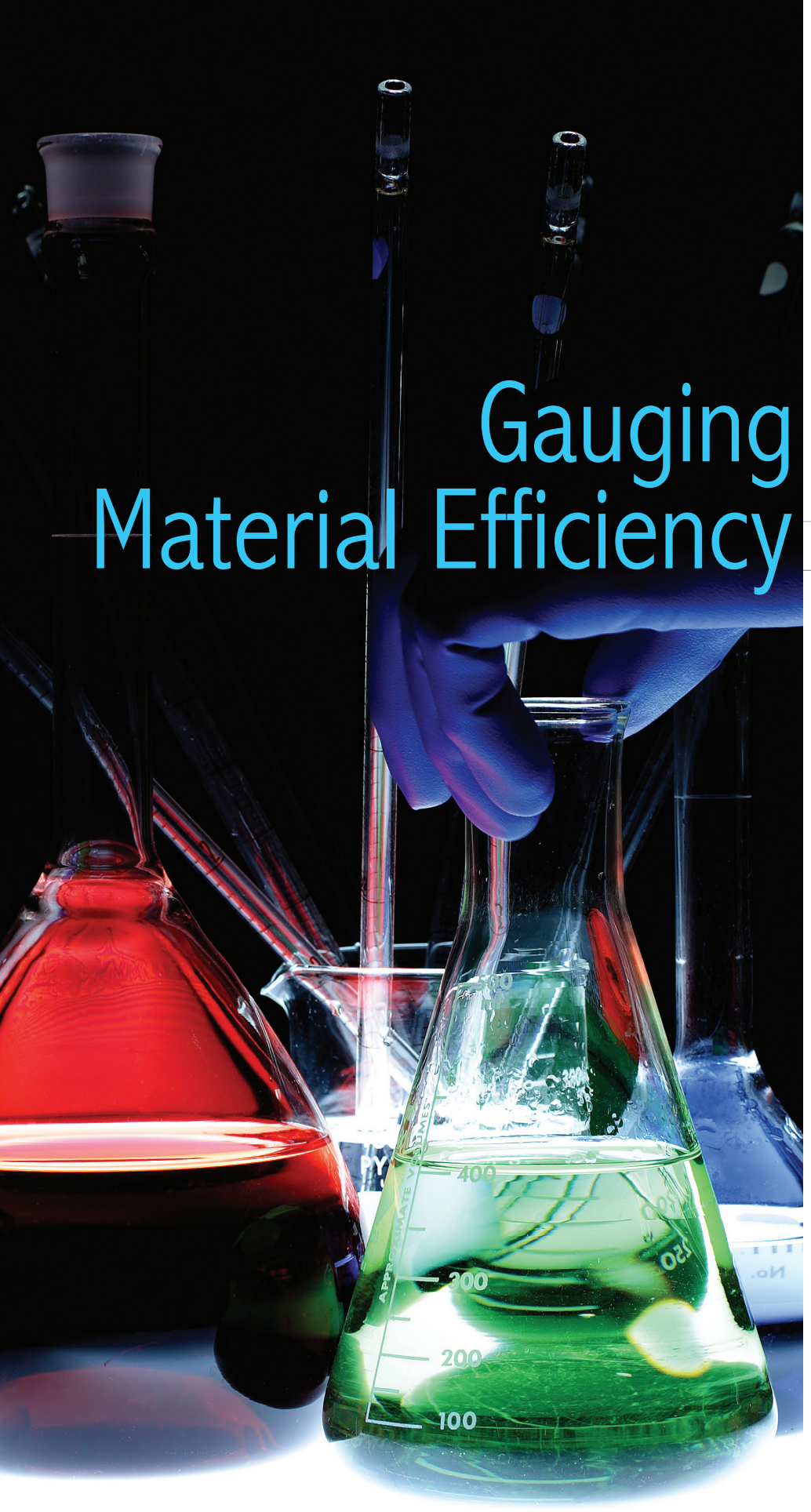


Gauging Material Efficiency

John Andraos, MCIC

How do you determine the material efficiency of a chemical reaction or a synthesis plan?

This question has preoccupied chemists since Antoine Lavoisier's discovery of the law of conservation of mass for chemical transformations in 1775. In the present context of the new field of green chemistry in which syntheses of chemicals and materials are to be conducted with the least impact on the environment, a quantitative description of material efficiency that can be applied to any synthesis plan in a standard way is important.

Taking a wish list approach, one would like such a method to meet various criteria. For individual reactions it should take into account not only reaction yield to a given target, but also the use of solvents, excess reagents, and other work-up and purification materials. For synthesis plans, it should be robust in its application regardless of their complexity—that is, whether they are linear, convergent, or divergent. It should be possible to rank different plans to a common target according to various parameters in an unbiased way in order to weed out bad performing plans quickly and to understand why good plans are good. When these criteria are met, chemists can better focus their efforts toward synthesis optimization in a reliable way. Above all, we would like the method to be amenable to easy-to-read visual representations so that features of reactions and synthesis plans may be seen quickly by inspection.

This article briefly describes two novel visual diagrams to gauge material efficiency

that the reader can readily apply to their current work in chemistry. The first is a radial pentagon that depicts the global reaction mass efficiency of a chemical reaction and its dependence on reaction yield, atom economy, excess reagents, and all other materials used in the reaction, work-up, and purification phases. The second is a synthesis tree diagram that can be used to determine "green metric" parameters such as overall kernel atom economy and overall kernel reaction mass efficiency by a simple connect-the-dots approach. New parameters such as degree of convergence and degree of asymmetry may be determined from the shapes of such tree diagrams. Each of these parameters will be introduced and defined using illustrative examples. Both methods are rooted in balanced chemical equations as prescribed by Lavoisier's conservation of mass law.

Individual chemical reactions

If for a chemical reaction we designate the mass of target product as our output and the sum of the masses of all reactants as our input, then reaction mass efficiency (RME) is the ratio of output to input and the mass of waste produced and ϖ is the difference between input and output. Reaction mass efficiency may be further decomposed into its four contributing factors each ranging in value between 0 and 1 as shown in Equation (1).[1] For simplicity in calculations, all fractional quantities are written as decimal fractions instead of as percentages

$$RME = (\varepsilon)(AE)\left(\frac{1}{SF}\right)(MRP) \qquad (1)$$

where ε is the reaction yield ($0 < \varepsilon < 1$); AE is atom economy ($0 < AE < 1$); SF is the stoichiometric factor that takes into account the use of excess reagents (SF = 1 for stoichiometric reactions carried out with no excess reagents; SF > 1, otherwise); MRP is the material recovery parameter that takes into account other materials used in the reaction and post-reaction phases (work-up and purification) such as solvents and washings for extractions ($0 < MRP < 1$); c, s, and ε are the masses of reaction catalyst, reaction solvent, and all other post-reaction materials respectively; and m_p is the mass of the collected target product. Atom economy is given by the well known definition:

$$AE = \frac{MW_{product}}{\sum MW_{reagents}} \qquad (2)$$

and the stoichiometric factor, by definition, is given by:

$$SF = 1 + \frac{\sum mass_{excess\ reagents}}{\sum mass_{stoichimoetric\ reagents}} = 1 + \frac{\sum mass_{\ excess\ reagents}}{theoretical\ mass_{product}} \qquad (3)$$

Each of the four factors in master equation (1) acts to attenuate RME with the MRP factor being the strongest attenuator since solvents normally account for the bulk mass of reaction materials used in a chemical reaction. The five parameters RME, AE, ε, 1/SF, and MRP may be displayed graphically in the form of a radial pentagon depicting a "materials usage footprint" so that one can recognize at once which of the four factors on the right hand-side of Equation 1 are contributing to an attenuation of RME. Each axis corresponding to one of the five parameters emanates from the centre and ranges in value between zero and one. The values of these parameters are depicted as dots and these are connected to form a pentagonal figure. The ideal "green" situation is depicted by a regular pentagon of unit radius where each parameter is equal to one. The less "green" a reaction is, the more the resultant pentagon is distorted toward the centre. These diagrams may therefore be used to compare the RME performances of different classes of reactions so that a chemist can ascertain which reaction classes are inherently "green" and which are not by visual inspection. The degree of distortion of the radial pentagon from its regular ideal shape may be directly linked to parameters responsible for that distortion. These diagrams therefore inform chemists as to what to do if they wish to "green up" their experimental procedure, whether it is to reduce reaction solvent usage, cut down on unnecessary washes and extractions, avoid using excess reagents unless there is a chemical reason for doing so as in driving equilibria toward product, select lower mass reagents to effect improved atom economical performance, or optimize reaction yield by tweaking with such parameters as reaction time, reaction temperature, reaction pressure, or the use of catalysts.

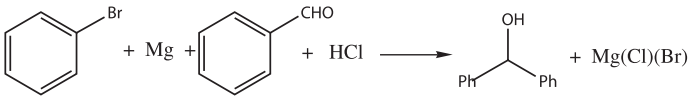
The following undergraduate laboratory procedure for the synthesis of diphenylmethanol using the Grignard methodology according to Scheme 1 is given as an illustrative example where the present analysis is employed.

Figure 1 shows the corresponding resultant radial pentagon. Under conditions of using excess reagents (benzaldehyde is the limiting reagent) and committing all materials other than target product to waste, the overall RME for production of diphenylmethanol is 1.1 percent with a reaction yield of 80 percent and an atom economy of 56.9 percent. From this visual representation it is clear that the low overall RME is due to a modest AE of 60 percent, the use of 61 percent excess reagents (SF = 1.61), and a minimum MRP of about 4 percent. The best RME possible for synthesizing diphenylmethanol by this procedure is 28.2 percent if work-up and purification materials are recovered. When the material efficiencies of organic reactions are analyzed in a similar way according to their classification type, one can explore and discover important general trends that are useful in planning material efficient total syntheses of target molecules.

A Microsoft Excel (Version 5.0 or higher) spreadsheet template form with embedded formulas[2] has been developed that allows easy calculation of reaction mass efficiency and other "green" metrics, including raw material costs (RMC), for any chemical transformation. With this tool, students and seasoned practitioners may employ green metrics to evaluate the "greenness" of their experiment in a rigorous quantitative way and to determine the bottom line cost of carrying it out. It also gives user direction in assessing improvements experiment under various reclaiming and (or) recycling options with respect to materials usage and cost savings.

Synthesis plans

The synthesis tree method[2] is illustrated for the convergent synthesis of the alkaloid papaverine as shown by the traditional representation in Scheme 2. The corresponding synthesis tree diagram is shown in Figure 2. In this new representation input materials, isolated intermediates, and target product are represented as filled, open, and shaded dots respectively. The x-axis represents the number of reaction stages each with its designated reaction yield and the y-axis represents the number of input



Scheme 1. To a 25 mL round-bottomed flask charged with 0.4 g dry magnesium turnings is added dropwise a solution of 1.8 mL bromobenzene in 9 mL dry ether over 20 minutes. The reaction solution is gently refluxed for a further 20 minutes. A second solution of 1.5 mL benzaldehyde in 4 mL dry ether is added dropwise over a period of 20 minutes. After addition is complete the mixture is refluxed for 15 minutes then cooled. The reaction mixture is then poured over 10 g crushed ice followed by addition of 3 mL of 5 percent aqueous HCl solution. The ether layer is separated and washed successively with water (30 mL), saturated sodium bisulphite ($NaHSO_3$) solution (30 mL), and again with water (30 mL). After drying with 5 g $MgSO_4$, filtration, and evaporation of the solvent, the crude product is recrystallized from petroleum ether (100 mL) to afford 2.18 g of pure diphenylmethanol.

Notes
(i) Densities (g/mL): diethyl ether (0.708), petroleum ether (0.64), bromobenzene (1.495), benzaldehyde (1.046), water (1), 5 percent HCl solution (1.02), saturated $NaHSO_3$ solution (1.345).

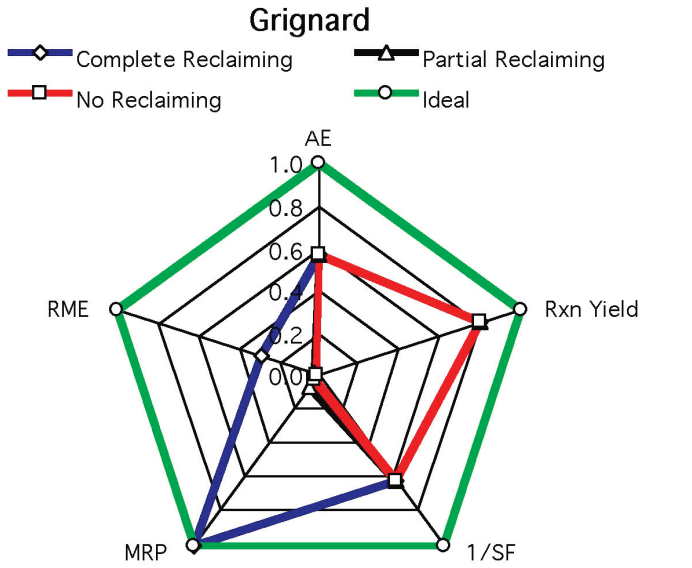
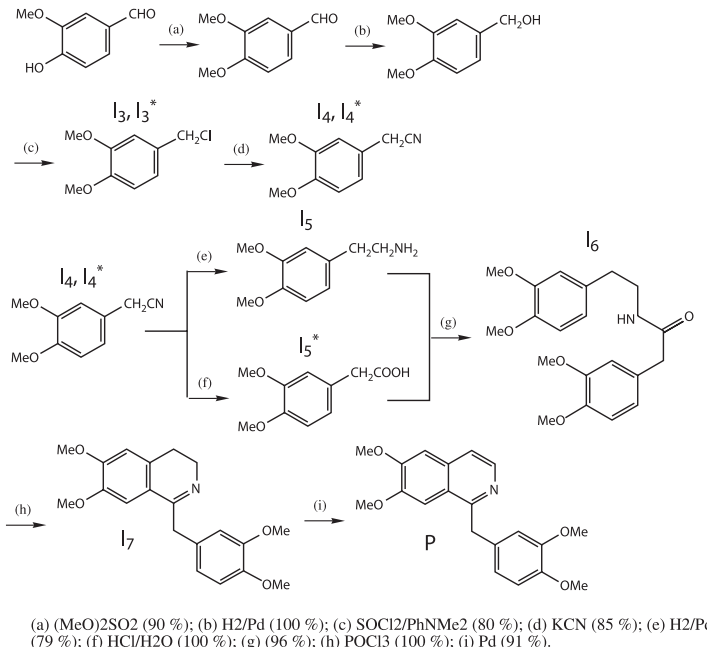


Figure 1. Radial pentagon representing RME values for the synthesis of diphenylmethanol using the Grignard methodology under various scenarios. See Scheme 1 for balanced chemical reaction.



(a) $(MeO)_2SO_2$ (90 %); (b) H2/Pd (100 %); (c) SOCl2/PhNMe2 (80 %); (d) KCN (85 %); (e) H2/Pd (79 %); (f) HCl/H2O (100 %); (g) (96 %); (h) POCl3 (100 %); (i) Pd (91 %).

Scheme 2. Kindler-Peschke-Pal Synthesis of Papaverine

(a) $(MeO)_2SO_2$ (90 percent); (b) H_2/Pd (100 percent); (c) $SOCl_2$/PhNMe$_2$ (80 percent); (d) KCN (85 percent); (e) H_2/Pd (79 percent); (f) HCl/H_2O (100 percent); (g) (96 percent); (h) $POCl_3$ (100 percent); (i) Pd (91 percent)

materials. Since this is a convergent plan, the first five stages involve parallel reactions, hence the total number of reactions in the plan (13) exceeds the number of stages (8). Linear plans have an equal number of reactions and stages. The input dots are entered one unit apart in the y-direction and the ordinates of the intermediate dots are the centroids of the ordinates of the immediately preceding input dots. For a target scale in moles of the product, it is possible to calculate the mass of any input reactant by following the connections between that input dot and the target dot in the diagram. This is done by working backwards remembering that going from right to left represents amplification in reaction scale. For example, for 1 mole of papaverine the masses of intermediates I5* and I5 required are $MW_{15*}\left(1/\varepsilon_6\varepsilon_7\varepsilon_8\right)$ and $MW_{15}\left(1/\varepsilon_6\varepsilon_7\varepsilon_8\right)$ grams, respectively. The mass of dimethylsulfate (DMS) required is $MW_{DMS}0.5\left[\left(1/\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8\right)+\left(1/\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8\right)\right]$ grams. The total mass of hydrogen required for the entire synthesis is $MW_{H2}\left[\left(1/\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8\right)+\left(1/\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5*\varepsilon_6\varepsilon_7\varepsilon_8\right)+2\left(1/\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8\right)\right]$ grams. The kernel reaction mass efficiency for this plan is obtained from a reduced form of Equation (1) using the masses of input materials determined by the above procedure, where it is assumed that no excess reagents are used and solvents and work-up and purification materials are recovered. In effect the kernel RME for each reaction is the product of AE and the reaction yield. This gives the best possible RME performance corresponding to the chemistry in the plan. Such a parameter is a truer measure of material efficiency than overall yield. Other parameters such as degree of convergence, degree of asymmetry, and molecular weight building-up index may also be easily deduced from the tree diagram (see reference 3 for details). One can see that tree diagrams give a compact visualization of synthesis plans from which important quantitative parameters may be easily calculated. It is also an excellent method of proofreading plans reported in the literature and of bookkeeping the correct balancing of all chemical reactions. Table 1 summarizes the "green metrics" results of this synthesis plan and others for this target molecule from different starting materials (see Scheme 3). Optimization is achieved by an iterative process until "good" attributes for all metrics occur in the same plan. One can see that the Kindler-Peschke-Pal plan is the most satisfactory plan since it has the highest overall kernel RME, the second-highest overall atom economy, the least number of reaction stages, the highest (most negative) building-up parameter,[4] the highest degree of convergence, the least asymmetry, and most importantly, is the least costly in terms of input materials.

Acknowledgements

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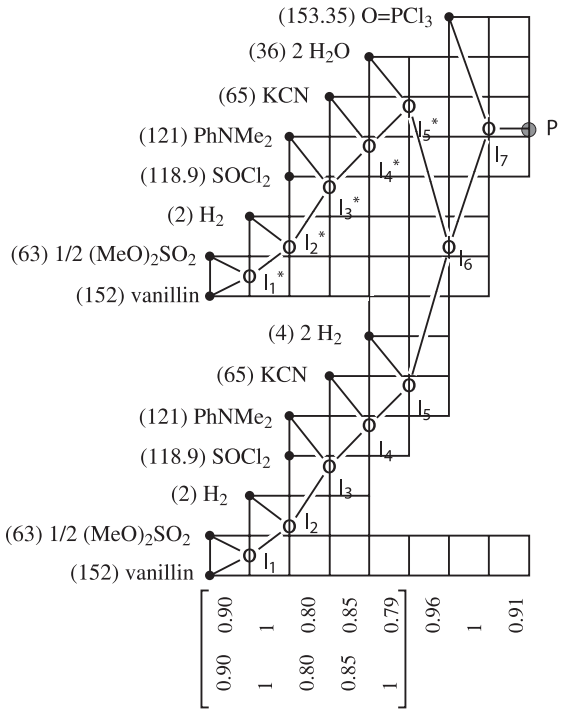
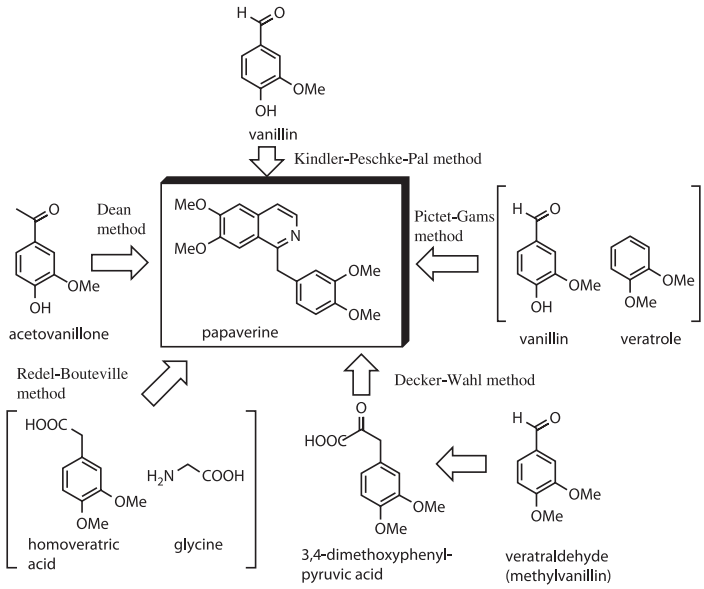


Figure 2. Synthesis tree for Kindler-Peschke-Pal synthesis of papaverine (see Scheme 2)



Scheme 3. Various documented synthesis plans for papaverine from different starting materials

Table 1. Summary of reaction metrics and synthesis tree parameters for papaverine synthesis plans

	Pictet-Gams	Decker-Wahl	Redel-Bouteville	Kindler-Peschke-Pal	Dean
Kernel reaction metrics					
AE	0.136	0.197	**0.317**	0.274	0.199
RME	0.0052	0.0275	0.0404	**0.151**	0.0796
$e_{pseudo\text{-}overall}$	0.038	0.138	0.127	**0.550**	0.400
Number of reaction inputs, *I*	18	20	**11**	15	12
Number of reaction steps, *M*	11	12	**8**	13	10
Number of reaction stages, *N*	8	9	8	8	8
m_1 (g per mole per reaction stage)	-223.18	-83.10	-29.96	**-280.23**	-212.89
RMC[a] ($ CAD per gram)	29.04	4.72	8.17	**0.45**	22.05
Tree parameters					
Degree of convergence, δ	0.443	0.423	0.359	**0.450**	0.392
Asymmetry, β	0.813	0.861	0.746	**0.604**	0.630

References:

1. John Andraos *J. Org. Process Res. Develop*. 2005, *9*, 149.
2. John Andraos, M. Sayed, *J. Chem. Educ.* 84 (2007) in press.
3. John Andraos, *J. Org. Process Res. Develop*. 2006, *10*, 212.
4. Synthesis plans beginning from low molecular weight starting materials that react to produce progressively heavier intermediates along the way until the target product is reached have large negative molecular weight first moments.

John Andraos, MCIC, is a lecturer and course director in the department of chemistry at York University. His research is in the areas of quantitative analysis of synthesis plans, reaction optimization, green chemistry, and kinetic analysis of homogeneous and heterogeneous systems. In 2000, he founded CareerChem, which is an educational and career mentoring Web site for chemists (www.careerchem.com/MainFrame.html). He has also given career workshops at national CIC meetings for those seeking academic positions.