Substantia
An International Journal of the History of Chemistry

Firenze University Press
www.fupress.com/substantia

OPEN ACCESS

Citation: Murphy M. A. (2023) Professors Trost and Sheldon's Promotion of Catalytic Technologies, Atom Economy, and the E-Factor Metrics in Synthetic Organic Chemistry and the Fine Chemical and Pharmaceutical Industries, to Speed the Early Evolution of "Green Chemistry". *Substantia* 7(2): 41-55. doi: 10.36253/Substantia-2140

Received: May 09, 2023

Revised: Jul 10, 2023

Just Accepted Online: Jul 11, 2023

Published: September 21, 2023

Copyright: © 2023 Murphy M. A. This is an open access, peer-reviewed article published by Firenze University Press (http://www.fupress.com/substantia) and distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Competing Interests: The Author(s) declare(s) no conflict of interest.

Feature Article

Professors Trost and Sheldon's Promotion of Catalytic Technologies, Atom Economy, and the E-Factor Metrics in Synthetic Organic Chemistry and the Fine Chemical and Pharmaceutical Industries, to Speed the Early Evolution of "Green Chemistry"

Mark A. Murphy, Ph.D., J.D.

UVLAW Patents LLC, 171 China Creek Rd., Blowing Rock North Carolina 28605
E-mail: uvlawpatents@gmail.com

Abstract. The Academic chemical literature (and much current teaching to University Students) still often describes "Green Chemistry," as having originated in the late 1990s from the United States EPA, the "12 Principles of Green Chemistry", and/or Academia. But all of the "12 Principles" had already been in "un-enunciated" Industrial practice and had produced many commercialized examples of environmentally favorable chemical products and processes in major segments of Industry, long before the 1990s. This article briefly reviews the early 1990s publications of Professor Barry Trost and Roger Sheldon that spread awareness of the importance of catalysis to the evolving "Green Chemical" concepts of "Atom Economy", the "E-Factor" metrics, and into Academic "Green Chemistry" research. Trost and Sheldon's publications admitted that catalysis and "Atom Economy" had been in practice in the commodity chemicals industry for decades, but encouraged more use of those techniques and concepts in the Fine Chemical and Pharmaceutical industry segments, and into Academic research and teaching of organic chemistry, years before the words "Green Chemistry" or the "12 Principles" came into literature use.

Keywords: Green Chemistry, green engineering, history, atom economy, E-Factor, environmental quotient, catalysis, interdisciplinary research, evolution, industry.

1. INTRODUCTION

For the past 25 years, two questionable "narratives" about the origins of "Green Chemistry" have widely propagated in the Academic and Governmental literature, and in the trade and popular press, to the effect that 1) "Green Chemistry originated in the 1990s from the efforts of the US Government, US EPA and/or Academia," and 2) "Green Chemistry" should be "guided" by the '12 Principles' published by Anastas and Warner in 1998."[1,2,3] Over the last several years, this author (who conceived the BHC Ibuprofen Process that won one the earliest Presidential Green Chemistry Awards) has argued to the contrary, and previously documented that "Green Chemistry" was in fact a narrow subset of, and evolved from and renamed, the much earlier and much broader interdisciplinary "Pollution Prevention" efforts, mostly from Industry, during the 1970s and 1980s.[4,5,6]

Separately, the Academic literature has long attributed the "Green Chemistry Principle" of "Atom Economy"[7] to Professor Barry Trost of Stanford University. The Academic literature has also often attributed the "Environmental Factor" (typically called the "E-Factor") and/or "Environmental Quotient" metrics of Green Chemistry to a series of 1990s publications authored by Professor Roger Sheldon. Both men emphasized the importance of the use of catalysis as a technical tool to achieve improved environmental performance in the chemical industries.

Both Trost and Sheldon certainly inspired many subsequent applications of catalysis, to achieve many new examples of good Atom Economy and E-Factors in the fine chemical and pharmaceutical industry segments. But in little noticed early statements, both Trost and Sheldon admitted that use of catalysis, which had been in widespread use in the commodity chemicals industry for many prior decades, had produced many examples of already commercialized commodity chemical processes that were already in fact "Atom Economical," and had excellent E-Factors, decades earlier than the 1990s.

This article will focus on and briefly review early 1990s publications by Professors Trost and Sheldon that described the use of catalysis as a tool, to promote the introduction of the "Atom Economy", "E-Factor", and "Environmental Quotient" concepts into the Academic literature, research, and teaching. Trost's and Sheldon's articles also suggested and/or promoted new applications of catalysis to improve environmental performance in the Fine Chemical and Pharmaceutical industry segments, where the environmental performance had historically been much worse than in the commodity chemical industry.

Sheldon often praised one of the earliest examples of use of the Atom Efficiency and E-Factor concepts in the Fine Chemical / Pharmaceuticals industries, the BHC Ibuprofen process, that was conceived and developed in the mid-1980s and commercialized in 1992. This author, who conceived the BHC Ibuprofen Process in 1984, will add historical perspective and commentary, to further demonstrate that the origins of "Green Chemistry" were actually a result of long-term, very broad and complex interdisciplinary and evolutionary processes that had their beginnings in Industrial practice decades earlier than the 1990s.

Academic "Green Chemistry" recently appears to be evolving back toward a much broader interdisciplinary approach, a "paradigm change" this author supports.

2. PROFESSOR BARRY TROST'S "ATOM ECONOMY" – "A SEARCH FOR SYNTHETIC EFFICIENCY"

Professor Barry Trost, currently an Emeritus Professor of Chemistry at Stanford University[8], has been very frequently cited in the Academic literature as originating and/or promoting the concept of "Atom Economy", which is now considered the second of the "12 Principles of Green Chemistry" (after "Pollution Prevention"). Trost published many papers in the 1970s and 1980s illustrating the uses of transition metal complexes for coupling organic molecules, but the first Trost paper explicitly describing the "Atom Economy" concept was published in *SCIENCE* in 1991[9], and was titled "The Atom Economy – A Search for Synthetic Efficiency." The abstract of Trost's paper read as follows:

> Efficient synthetic methods required to assemble complex molecular arrays include reactions that are both selective (chemo-, regio-, diastereo-, and enantio-) and **economical in atom count (maximum number of atoms of reactants appearing in the products***)*. Methods that involve simply combining two or more building blocks with any other reactant needed only catalytically constitute the highest degree of atom economy. Transition metal-catalyzed

---

[1] See Anastas, PT., and Warner, J. C., (1998)

[2] See Cann, M.C. and Connelly, M.E. (2000)

[3] See Anastas, P.T. and Beach, E.S., (2009)

[4] Murphy, M.A., (2020a)

[5] Murphy, M.A., (2021)

[6] Murphy, M.A.,(2018)

[7] The graphical abstract for this article, graphically illustrating "Atom Economy", was copied in June 2023 from a Wikipedia article on "Atom Economy available at https://en.wikipedia.org/wiki/Atom_economy , attributed there to a Wikipedia author Astrid 91, and used herein under a Creative Commons CC0 License.

[8] Professor Trost obtained a PhD in Chemistry at MIT in 1965 and moved directly to the University of Wisconsin-Madison, where he became a Villas Professor of Chemistry and remained until his move in 1987 to become a Tamaki Professor of Chemistry at Stanford University. This author (as a graduate student) took a single semester's course in synthetic organic chemistry from Professor Trost at Madison in 1978, and attended many Organic Chemistry seminars where Professor Trost spoke or was present, an experience he will always remember and value.

[9] See Trost, B.M., (1991)

> methods that are both selective and economical for formation of cyclic structures, of great interest for biological purposes, represent an important starting point for this long-term goal. **The limited availability of raw materials, combined with environmental concerns, require the highlighting of these goals**. (Bolding added)

In his second paragraph, Trost stated that:

> In the quest for selectivity, a second feature of efficiency is frequently overlooked – how much of the reactants end up in the product, a feature we might refer to as atom economy … An alternative process that is both selective and atom economical remains a challenge. The ideal reaction would incorporate all of the atoms of the reactants. Major benefits that derive from such processes include more effective use of limited raw materials and decreased emissions and waste disposal… The ability of transition metal complexes to activate organic molecules makes them attractive prospects for developing catalytic processes with high atom economy. **This concept is already embodied in important industrial processes such as Ziegler-Natta polymerization (5) and hydroformylation (6).** However, little or no attention has been focused on developing such methods for the synthesis of complex molecular architecture or for intramolecular processes. (Bolding added).

Then, with little additional commentary on the "theory" of Atom Economy, Trost's 1991 paper described many examples wherein "All of the reactions involve simple summation of the reacting partners to form products, and any additional reagents are used only in catalytic quantities to serve as true catalysts."

In a 1995 follow-up paper in *Angewante Chemie*[10] (entitled "Atom Economy – A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way"), Trost stated in his Graphical Abstract that "If all atoms of the starting materials are found in the product and only catalytic amounts of other reagents are needed, a reaction may be defined as ideal. A promising route to this ideal state is approached by the use of transition metal complexes as catalysts for addition and isomerization reactions."

In the body of his full 1995 paper, Trost first re-iterated some of the concepts from the 1991 paper, but also stated that:

> …The ideal chemical reaction is also just a simple addition (either inter-or intramolecular) in which any other reactant is required only in catalytic amounts.
> **The producers of commodity chemicals have recognized the importance of these issues**…. 'Newer' processes represented by hydroformylation,[2] Ziegler-Natta Polymerization,[3] and hydrocyanation[4] are spectacular illustrations of how practical and important processes that possess these characteristics are**. On the other hand, such issues have not been emphasized for production of smaller volume chemicals**. Clearly, a high priority goal of any chemical production is an environmentally benign design.
> **With the increasing sophistication of the types of substances that we must produce to meet society's needs, this task in quite daunting**. (Bolding added)

In the rest of the 1995 paper, Trost went on to describe many examples from his laboratories of the use of transition metal catalyzed cross-coupling reactions in the synthesis of complex organic molecules.

In 1998, Professor Trost was awarded one of the EPA / ACS's earliest "Presidential Green Chemistry Challenge" awards[11], for "The Development of the Concept of Atom Economy". The first paragraph of the Award description states:

> Professor Trost developed the concept of atom economy: chemical reactions that do not waste atoms. Professor Trost's concept of atom economy includes reducing the use of nonrenewable resources, minimizing the amount of waste, and reducing the number of steps used to synthesize chemicals. **Atom economy is one of the fundamental cornerstones of green chemistry. This concept is widely used by those who are working to improve the efficiency of chemical reactions**. (Bolding added)

In the second paragraph, the 1997 Presidential Green Chemistry Award document stated:

> **Economics generally dictates the feasibility of processes that are "practical". A criterion that traditionally has not been explicitly recognized relates to the total quantity of raw materials required for the process compared to the quantity of product produced or, simply put, "how much of what you put into your pot ends up in your product."** In considering the question of what constitutes synthetic efficiency, Professor Barry M. Trost has explicitly enunciated a new set of criteria by which chemical processes should be evaluated. (Bolding added).

In the 4th paragraph, in discussing the general acceptance of the need for selectivity in chemical processes, the Green Chemistry Award commented:

> How much of the reactants end up in the product (i.e., atom economy) traditionally has been ignored. When Professor Trost's first paper on atom economy appeared in

---

[10] See Trost, B.M., (1995)

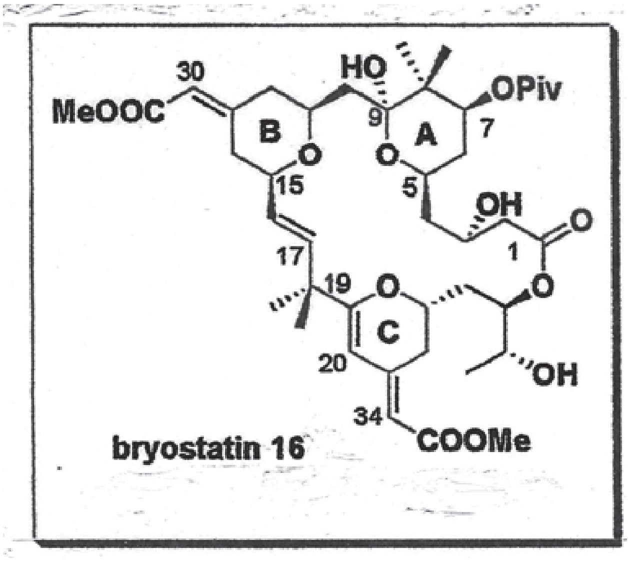
[11] See https://www.epa.gov/sites/default/files/2016-10/documents/award_recipients_1996_2016.pdf , page 96.

> the literature, the idea generally was not adopted by either academia or industry. **Many in industry, however, were practicing this concept without explicitly enunciating it. Others in industry did not consider the concept because it did not appear to have any economic consequence. Today, all of the chemical industry explicitly acknowledges the importance of atom economy.** (Bolding added)

It is important to recognize that prior to the 1990s, while many chemists (especially in Academia) were unaware of or uninterested in the “Atom Economy” and “waste minimization” concepts, both Professor Trost and the 1998 Presidential Green Chemistry Award acknowledged that the concepts of Atom Economy and waste minimization had been previously practiced in the commodity chemical Industry. A much fuller history of the early Industrial evolution of the use of catalysis to produce good Atom Economy and waste minimization will be the focus of another paper in preparation.

Professor Trost then lead the introduction of those concepts into the synthesis of complex organic molecules. For example, in 2002 Professor Trost published a review article in *Accounts of Chemical Research*[12], that described many uses of transition metal complexes (especially Ruthenium complexes) for conducting Atom Economical reactions in the context of the synthesis of complex organic molecules.

One of Trost’s most spectacular subsequent examples was published in 2008 in *NATURE*[13], entitled “Total Synthesis of Bryostatin 16 via Atom Economical and Chemoselective Approaches.” Bryostatins are complex natural products (see the structure drawing below) with potent anti-cancer activity but have extremely limited availability from natural sources. Trost and co-worker’s total synthesis strategy for Bryostatin did employ numerous stoichiometric reagents and reactions traditionally used in synthetic organic chemistry, but also used new key steps employing homogeneous Palladium, Ruthenium, and Gold catalysts, and very substantially minimized the number of steps and stoichiometric reagents used in the prior synthetic schemes for Bryostatins. Trost’s synthetic strategy also provided many opportunities for modifications (for example of the Pivalate derivative is shown in the previous column figure) in order to allow preparation of a much wider variety of Bryostatin derivatives / analogs than had been available previously.



3. PROFESSOR ROGER SHELDON’S “E-FACTOR” AND “ENVIRONMENTAL QUOTIENT” METRICS FOR GREEN CHEMISTRY

Professor Roger A. Sheldon’s contributions to the evolution of “Green Chemistry” were early, many and varied. Sheldon obtained a PhD in chemistry in 1967, worked at Shell Laboratories in Amsterdam for 10 years, then spent 10 years as Vice President for R&D in Fine Chemicals at DSM Andeno. In 1991 he moved to the Delft University of Technology as a Professor of Chemistry, until 2015, when he moved again to the University of Witwatersrand as a Distinguished Professor of Chemistry.

While still working in Industry in the 1980s, Sheldon published several papers on applications of catalytic oxidations in fine chemical manufacture. For example, in 1987[14], Sheldon commented that “There is an increasing trend towards the use of catalytic methods in fine chemicals manufacture. This is largely a result of two effects: the need for cleaner, more efficient technologies due to increasing environmental constraints, and the forward integration of bulk chemical producers who are familiar with catalytic processes.” Sheldon’s comment was entirely consistent with this author’s experiences at Celanese during the 1980s, because during the 1980s Celanese was actively investigating a variety of new technical approaches to fine chemicals and bulk pharmaceuticals involving catalytic methods[6].

Sheldon’s first major literature contribution to “Green Chemistry”[15] occurred very shortly after his

---

[12] See Trost, B.M., (2002)

[13] See Trost, B.M., Dong, G., (2008), “Total Synthesis of Bryostatin 16 Via Atom Economical and Chemoselective Approaches”

[14] Sheldon, R.A., (1987), “Catalytic Oxidation and Fine Chemicals”

[15] The term “Green Chemistry” was coined at the EPA by Paul Anastas in 1991, and first used publicly at an ACS Conference in 1993, then that

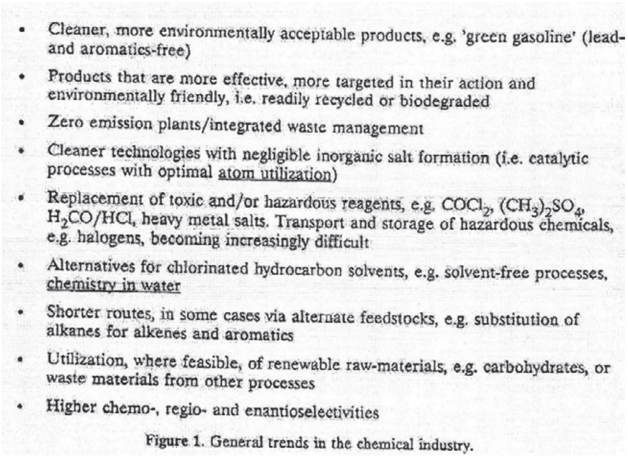
move into Academia, in the published proceedings of an interdisciplinary March 1992 Symposium at Texas A&M, focused on waste minimization in the chemical industry. Sheldon's 1992a paper was entitled "Catalysis, The Atom Utilization Concept, and Waste Minimization."[16] Only one other chemist was a speaker at the conference, most of the speakers were engineers. A monograph of papers from that interdisciplinary conference was published in November 1992, and the introduction to the book stated:

> The subject of this conference reflects the interest that has developed in academic institutions and industry for technological solutions to environmental contamination by industrial wastes. Progress is most likely with strategies that minimize waste production from industrial processes. Clearly the key to the protection and preservation of the environment will be through R&D that optimizes chemical processes to minimize or eliminate waste streams.

Sheldon's 1992a Texas A&M paper received little attention and few literature citations in the Academic literature, but in view of several important contributions by Sheldon that first appeared in that paper, this paper will reproduce below some important quotes and Figures from Sheldon's 1992a paper. Sheldon's Abstract stated:

> Following the advent of the petrochemicals industry in the 1920s, catalysis was widely applied in the manufacture of bulk chemicals. Traditionally environmentally unacceptable processes have largely been replaced by cleaner catalytic technologies. Fine chemicals, in contrast, have remained largely the domain the synthetic organic chemist who has generally clung to the use of stoichiometric methods.
>
> But times are rapidly changing. Increasingly stringent environmental requirements are making the use of classical stoichiometric methods prohibitive. Consequently, there is a general trend towards substitution of such antiquated technologies by cleaner catalytic methods that do not generate large amounts of inorganic salts.
>
> A useful concept for evaluating the environmental acceptability of various processes for producing a particular substance is atom utilization. The latter is defined as the ratio of the molecular weight of the desired product to the sum of all the materials (excluding solvents) used."

In his Introduction, Sheldon further stated:



- Cleaner, more environmentally acceptable products, e.g. 'green gasoline' (lead- and aromatics-free)
- Products that are more effective, more targeted in their action and environmentally friendly, i.e. readily recycled or biodegraded
- Zero emission plants/integrated waste management
- Cleaner technologies with negligible inorganic salt formation (i.e. catalytic processes with optimal atom utilization)
- Replacement of toxic and/or hazardous reagents, e.g. $COCl_2$, $(CH_3)_2SO_4$, H_2CO/HCl, heavy metal salts. Transport and storage of hazardous chemicals, e.g. halogens, becoming increasingly difficult
- Alternatives for chlorinated hydrocarbon solvents, e.g. solvent-free processes, chemistry in water
- Shorter routes, in some cases via alternate feedstocks, e.g. substitution of alkanes for alkenes and aromatics
- Utilization, where feasible, of renewable raw-materials, e.g. carbohydrates, or waste materials from other processes
- Higher chemo-, regio- and enantioselectivities

Figure 1. General trends in the chemical industry.

Figure 1. From Sheldon 1992a.

> After an induction period of a few decades, we now appear to be in the age of "environmentality". This is reflected both in the general trends in society as a whole, and in the chemical industry in particular. (see Figure 1)…. Indeed, **integrated waste management and zero emission plants are the catch-words in the chemical corridors of power these days**. (Bolding added)

Sheldon's Figure 1 is shown above.

Readers inspecting Sheldon's Figure 1 should recognize that this was analysis and commentary from a highly informed 20-year Industrial veteran, regarding the status and trends in Chemical Industry in the early 1990s. This author, who was a 7-year veteran of the Chemical Industry in 1990, agrees with Sheldon's description of the status of industry at that time, especially in view of the already widespread popularity and prevalence of the "Pollution Prevention" efforts in Chemical Industry during the 1980s.[4,5]

Readers should also notice that there is very considerable overlap between the "General trends in the chemical industry" described by Sheldon's Figure 1 and the "12 Principles of Green Chemistry" that were only published six years later, in 1998.[1] Sheldon's Figure 1 also supports this author's previous documentation that each of the individual "12 Principles of Green Chemistry" were already in commercial practice in Chemical Industry, and also used in combinations, long before 1998.[4]

Later in his Texas A&M paper, Sheldon supported his Figure 1 "trends" by noting that "In the bulk chemical industry classically environmentally unacceptable processes have largely (but not completely) been supplanted with cleaner catalytic alternatives. In particular, catalytic oxidation and carbonylation are widely used for the conversion of petrochemical feedstocks to industrial

---

terminology rose steeply in popularity in the Academic literature (and replaced the prior "Pollution Prevention" terminology) after the beginning of grants for Academic research by the NSF/ACS, and the initiation of the EPA / ACS Presidential Green Chemistry Challenge Awards in 1996.[4,5]

[16] See Sheldon, R.A. (1992a). Sheldon's text, Figures, and Tables from that paper reproduced in this paper are used herein with the permission of the current copyright holder, Springer Nature, see References.

Table 1. From Sheldon 1992a.

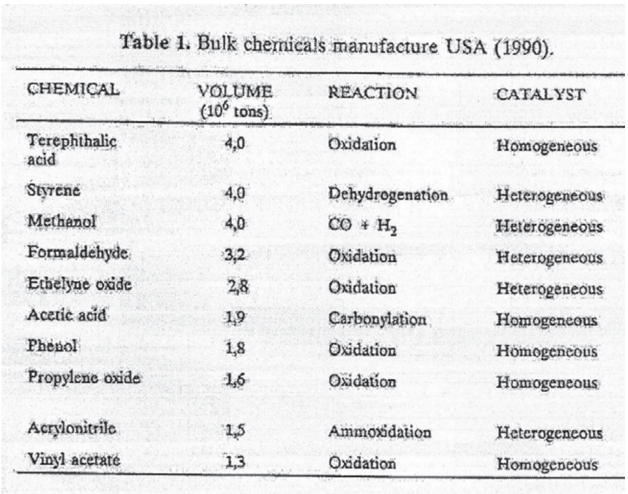


Table 1. Bulk chemicals manufacture USA (1990).

CHEMICAL	VOLUME (10^6 tons)	REACTION	CATALYST
Terephthalic acid	4,0	Oxidation	Homogeneous
Styrene	4,0	Dehydrogenation	Heterogeneous
Methanol	4,0	$CO + H_2$	Heterogeneous
Formaldehyde	3,2	Oxidation	Heterogeneous
Ethelyne oxide	2,8	Oxidation	Heterogeneous
Acetic acid	1,9	Carbonylation	Homogeneous
Phenol	1,8	Oxidation	Homogeneous
Propylene oxide	1,6	Oxidation	Homogeneous
Acrylonitrile	1,5	Ammoxidation	Heterogeneous
Vinyl acetate	1,3	Oxidation	Homogeneous

chemicals." Sheldon then provided his Table 1 of examples, also reproduced above. Additional examples of other such existing large volume chemical processes will soon be described in more detail this author's manuscript currently in preparation.

But Sheldon also noted that in smaller volume segments of the chemical industry (Fine Chemicals and Pharmaceuticals) the environmental performance was much worse, at least as measured in terms of the estimated ratio of the kg of waste products produced per kg of desired product. See Sheldon's Table 2, reproduced below.

This "Sheldon" ratio, "kg of waste to kg of desired product", was originally intended as a much broader metric for the Real-World waste / environmental performance of actual commercialized processes, considered as a commercialized final whole, as compared to Trost's concept of an "Atom Economy" measure of a theoretical 100% efficiency of a hypothetical chemical equation on paper, while contemplating future chemical reactions.[17]

Table 2. From Sheldon 1992a. Byproduct formation in chemicals production.

Industry Segment	Product Tonnage	Kg byproduct / Kg product
Oil Refining	10^6–10^8	ca. 0.1
Bulk Chemicals	10^4–10^6	<1–5
Fine Chemicals	10^2–10^4	5–>50
Pharmaceuticals	10–10^3	25–>100

Initially in this 1992 paper, and more prominently in his later papers, Sheldon named this ratio of wastes to desired product (in a Real-World functioning process) the "E-factor." This "E-Factor" has subsequently become a widely known and routine chemical metric, adopted and used by many others for evaluating the "Greenness" of actual industrial chemical processes.

But in 1992 Sheldon also publicly pointed out that the nature of and/or the toxicity or dangers from the waste also needed to be evaluated. Sheldon accordingly formulated an "equation" to incorporate the E-Factor" and also an "Unfriendliness Quotient" as well, to evaluate "Environmental Acceptability" as shown below.

Environmental =	**E**	**x**	**Q**
Acceptability	"Environmental factor" (kg waste / kg product)	x	"Unfriendliness Quotient"

Sheldon then commented that "For example, if innocuous salts such as NaCl or Na_2SO_4 were arbitrarily given an unfriendliness factor of 1, then chromium salts could be assigned a factor of say 100, and toxic metals e.g. Pb, Cd a 1000. Obviously, these figures are debatable and will vary from one company or production unit to another, being partly dependent on the ability to recycle a particular stream."

This author agrees that assigning numerically precise and non-subjective "Q" values is extremely difficult. But this author also agrees that "unfriendliness" should be carefully contemplated by scientists and engineers at the same time they evaluate the "E-Factor," as they imagine future processes and products, as well as later for the final commercial processes, even if "unfriendliness" can't be rigorously defined mathematically.

Professor Sheldon, after having emphasized the importance of catalysis to already existing industrial processes, then turned toward a historical explanation for the good environmental performance of the oil refining and commodity chemical industries, as compared to much worse environmental performance of the fine chemical and pharmaceutical industry segments. In a discussion of "Development of Organic Synthesis and Catalysis." Professor Sheldon stated:

> Another reason why catalysis has not been widely applied in the fine chemical industry is the more or less separate development of organic chemistry and catalysis (See Fig-

---

[17] This author was coached that as much of the starting materials as possible be incorporated into the product by his Celanese supervisor, Pr. Adolfo Aguiló, in 1983. Aguiló advocated the concept be used when imagining new chemical reactions and products, as well as used to evaluate a final process. I had no impression that Aguiló believed these concepts to be either his, or new, but only an established part of practice in the commodity chemicals industry. In another manuscript currently under preparation, an explicit example from the 1970's literature illustrating the use of the "E-Factor" concept will be described.

ure 8) since the time of Berzelius, who coined both terms, in 1807 and 1835, respectively.

See Sheldon's Figure 8 reproduced below. Sheldon commented that;

> In the late nineteenth and early twentieth century catalysis developed largely as a subdiscipline of physical chemistry. Following the advent of the petrochemicals industry, catalysis was widely applied in oil refining and bulk chemicals manufacture. Industrial organic chemistry on the other hand, really began with Perkin's serendipitous synthesis of aniline purple (mauveine) in 1856….The present-day fine chemicals and pharmaceuticals industries developed largely as spinoffs of this activity.

A few paragraphs later, Sheldon added that:

> Fine chemical manufacture has, to this day, remained primarily the domain of the synthetic organic chemist who, generally speaking, clings to the use of stoichiometric methods… Indeed, the fine chemicals industry, with its roots in coal-tar chemistry, is rampant with classical stoichiometric technologies that generate large quantities of inorganic salts. Examples include sulfonation, nitration, halogenation, diazotization, Friedel Crafts acylations, and stoichiometric oxidations and reductions…Many of these technologies are ripe for substitution by catalytic low-salt technologies.

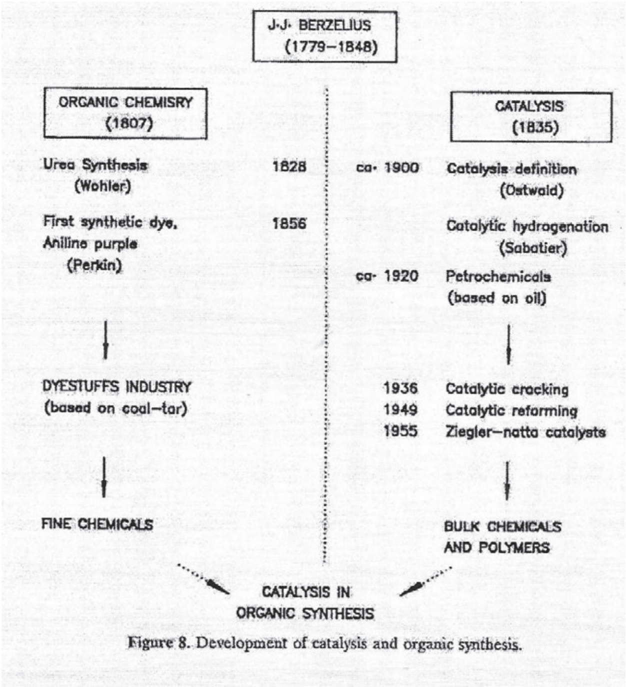


Figure 8. From Sheldon 1992a.

In subsequent paragraphs, Sheldon highlighted the BHC Ibuprofen Process (as he also did again in many of his subsequent papers) as an already existing example of the applications of catalysis and Atom Economy and the E-Factor in the Fine Chemical / Pharmaceutical industries. This author was the person who initially conceived the BHC Ibuprofen Process in 1984. That process was developed by a multi-disciplinary team at Celanese at Corpus Christi Texas, and then commercialized by BHC in Bishop Texas in 1992.[6] This author will review Sheldon's 1992 description of the BHC Ibuprofen Process, then add some comments below.

Sheldon's 1992 Texas A&M paper first discussed "Ibuprofen Manufacture" in terms of Ibuprofen's relatively high production volumes (for a Fine Chemical / Pharmaceutical), and how sales of the prescription drug converted to "generic" status in many countries after Boot's compound patent[18] expired. Then Sheldon commented regarding his Figure 14, reproduced on the next page:

> Two routes for the production of ibuprofen are compared in Figure 14. Both routes proceed via a common intermediate, p-isobutylacetophenone. The classic route, used by the Boots company (the discoverers of ibuprofen) involves a further five steps, relatively low atom utilization, and substantial inorganic salt formation.
> The elegant alternative, developed by Hoechst Celanese [*] involves only two (catalytic) steps from the common intermediate, 100% atom utilization, and negligible salt formation.

In 1992a Sheldon had broadly mentioned solvent waste and toxicity issues in his Figure 1 but did not directly comment on solvent usage / waste issues for any of the steps of the Boots process. But Sheldon[19] and many others have since explicitly recognized that solvents were and still are the major source of waste and/or pollution in many processes for producing pharmaceuticals.

Sheldon mentioned the similarity of the acylation steps of both synthetic routes shown in Figure 14, which both react iso-butylbenzene with acetic anhydride to produce p-isobutyl-acetophenone. The Boots acetylation reaction used a traditional batch process, solvents, and at least stoichiometric quantities of $AlCl_3$ as a co-reagent for the acetylation reaction, which resulted in the stoichiometric quantities of Aluminum wastes, also produced a mole of acetic acid waste, though its solvent waste production was not publicly known.

---

[18] See U.S. Patent #3,385,886 to Nicholson and Adams, issued May 28, 1968, claiming priority to a British patent application first filed February 2, 1961. Nicholson was a chemist and Adams was a pharmacist.

[19] See Sheldon 1996, and Sheldon 2020, and several of his other articles.

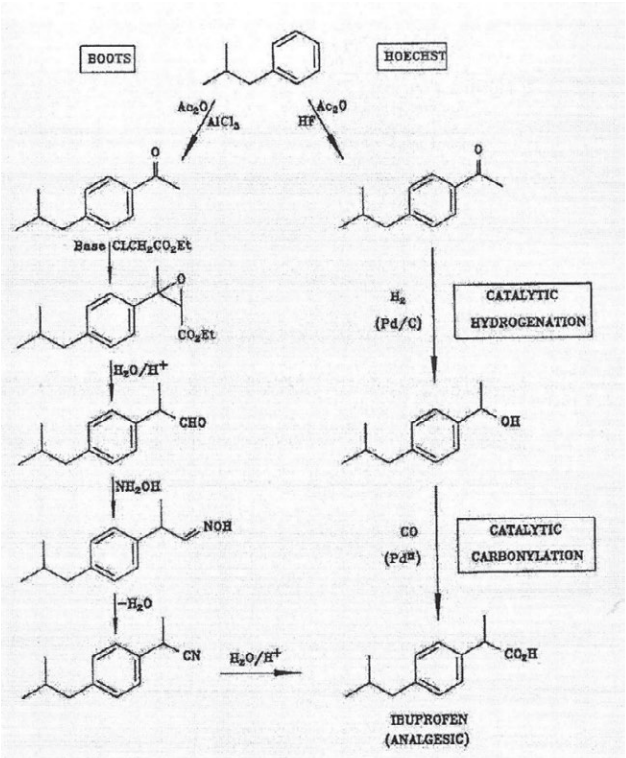


Figure 14. Two routes to ibuprofen.

Figure 14. From Sheldon 1992a.

In contrast, the BHC acetylation step[20] used HF as a liquid catalyst, in a continuous two-phase countercurrent and organic solvent-free process, which very efficiently carries out the acylation reaction, and also very efficiently recycles the corrosive and toxic HF and minimizes the HF inventory required. Because of the relatively high production volumes needed, the sophisticated engineering and high capital cost of the BHC custom continuous process was economically and environmentally justified. But had the volume of desired product been a good deal lower, a batch process might have been selected for economic reasons. Finally, the mole of stoichiometric acetic acid waste from the acylation step of the BHC Process is recovered, but the acetic acid "waste" is inexpensive, relatively non-toxic, bio-degradable, and could have been reasonably waste treated biologically at plant sites unsuited for reclaiming the acetic acid.

Because the p-isobutyl-acetophenone is a low-melting liquid, the BHC hydrogenation of the acetophenone was and is a solventless, but otherwise is a conventional, low pressure batch hydrogenation over Raney nickel, to produce the racemic liquid 1-phenylethanol required for the 3d carbonylation step. The hydrogenation step is perfectly atom economical in theory, and gives very good real yields, so can be viewed as being highly "Environmentally Acceptable". Many such hydrogenations of ketones to alcohols had been previously known. However, had either the starting acetophenone or the 1-phenylethanol been substantially higher melting substances, or had it been necessary to produce only one enantiomer of the 1-phenylethanol (or ibuprofen), a different and more difficult reduction strategy and/or reaction scheme would very likely have been required, both for the hydrogenation and/or subsequent carbonylation steps, unless a final optical resolution step was added that could have "wasted" 50% of the final product.

In his 1992a Texas A&M paper, Sheldon did not comment directly on the final carbonylation step, i.e. the carbonylation of (4'-isobutyl-)1-phenyl ethanol to give racemic ibuprofen. But Sheldon remedied that omission in his subsequent 1992b *Chemistry & Industry* paper, which stated:

> This example is a striking illustration of the benefits to be gained by catalytic thinking….the fact that the **key** carbonylation step bears a striking resemblance to the modern technology for acetic acid manufacture is no mere coincidence." (Bolding added)

Sheldon also commented in 1992b that "Catalytic conversions, on the other hand, are generally more direct: the acetic acid and ibuprofen syntheses via catalytic carbonylation are illustrations of such brevity." Sheldon, (unlike many subsequent Academic commentators who mostly ignored the carbonylation step in favor of praising the HF acylation step, and failed to cite either the Celanese patent or name the authors) actually understood the BHC Ibuprofen Invention, and that the carbonylation step was both the most patentably novel and strategically key step in the BHC scheme.

This author will now add some brief comments about that final strategic "key" carbonylation step. The primary Celanese technical disclosures were published in U.S. Patent # 4,981,995, issued to Elango, Murphy, Smith, Davenport, Mott, Zey (all chemists) and Moss (an engineer), and later assigned to Hoechst Celanese. U.S. Patent # 5,166,418, and a European Patent Application EP 0 337 803 published in 1989 named Hendricks, Mott and Zey as inventors. This author also described some of the other non-technical influences and events preceding and during the conception and development of the BHC Ibuprofen Process in Murphy (2018).

---

[20] See U.S. Patent # 5,068,448 to Lindley, Curtis, Ryan, de la Garza, Hilton, and Kenneson, "Process for the Production of 4'-Isobutylacetophenone", assigned to Hoechst Celanese Corporation.

Dr. Veraderaj Elango carried out the early exploratory laboratory work on all three steps, and discovered the combination of palladium, triphenylphosphine, and aqueous HCl as catalyst for the key carbonylation step (initially in the presence of solvents, at modest pressures of carbon monoxide) that looked very promising and highly "atom economical"[21]. Mott and Zey then developed an organic-solventless two-phase version of the batch carbonylation reaction, in which the 1st phase is a molten combination of the 1-(4'-isobutyl)-phenyl ethanol, palladium, and triphenylphosphine, and the 2nd phase is aqueous HCl, then the two phase are strongly mixed together under carbon monoxide to produce the final racemic ibuprofen with good rates and in very good yield. In EP 0 337 803 Mott and Zey disclosed a method for efficiently separating active chloro-palladium / triphenylphosphine catalyst complexes from the ibuprofen product, and recycling them into the next carbonylation cycle. Joel Hendricks (an engineer) and Mott (a chemist) also discovered that including some ibuprofen with the starting materials substantially increases the reaction rates and selectivities, see U.S. Patent # 5,166,418. In his 2010 paper, Sheldon estimated that the carbonylation reaction proceeded to 99% conversion, 96% selectivity to racemic ibuprofen, at a catalyst turnover frequency of 375 per hr. A team of chemists, engineers, technicians, and operators managed by Dr. Larry O. Wheeler piloted the process at Corpus Christi and built and commercialized the process at Bishop Texas in 1992.

One early publication that described the BHC Process was a February 8, 1993 article in *Chemical & Engineering News*, titled "Custom Chemicals", which stated that "Environmental issues are the engines that drive the fortunes of the custom chemical manufacturing industry today." The article discussed the many technical, economic, and regulatory difficulties the chemical manufacturers were encountering while addressing the environmental issues, and featured a version of Sheldon's Figure 14 describing the BHC Process as one prominent example of a solution to the problems.

The BHC Ibuprofen Process then won Chemical Engineering Magazine's bi-annual Kirkpatrick Award for "Pioneering Chemical Engineering Innovation" in December 1993. The opening three sentences of the article stated: "Increasing the efficiency of a process is an ongoing directive in chemical process industries (CPI). Minimizing its impact on the environment is another. Traditional bulk-pharmaceutical manufacturing could use some help on both counts," then went on to describe the BHC Ibuprofen Process.

Another later example of a prominent publication that praised the BHC Ibuprofen Process was Cann & Connelly's 2000 ACS-supported book intended for students, "*Real-World Cases in Green Chemistry*". The book devoted a chapter to the BHC Ibuprofen Process example, as an example of the importance of catalysis and Atom Economy. It stated that the overall BHC Ibuprofen Process had a theoretical "Atom Economy" of 77% but noted that the lost mass / atoms attributable to the acetic acid produced in the first acylation step "is recycled", implying that the Real-World Atom Economy and Environmental Acceptability of the BHC Ibuprofen Process was very high. In Real-World practice the yields and efficiencies of each of the steps are in fact all very high, so that viewed together as a whole, the BHC Ibuprofen Process was a good deal unexpectedly better than the prior Boots process, and much better than just "the sum of the parts".

In the first moments and days of conception, this author clearly understood that there was potential for such good future outcomes, but there were many uncertainties. It took the further contributions and teamwork of the many subsequent Celanese chemists, engineers, management, and business-people, as well as a joint venture with Boots, to turn that potential into a commercial Reality that actually improved the Environment.

4. PROFESSOR SHELDON'S CONCEPT OF "CATALYTIC RETROSYNTHESIS"

Later in his 1992 Texas A&M paper Sheldon introduced into the Academic literature his concept of "Catalytic Retrosynthesis". Sheldon stated:

> The example of ibuprofen perfectly illustrates the benefits to be gained by paying attention to the atom utilization in different routes and for being catalysis-minded. Indeed, organic chemists should be urged to integrate these aspects into their retro-synthetic thinking. Thus in planning an organic synthesis, a 'catalytic retrosynthesis' could be constructed, identifying catalytic pathways to the desired product… Such a catalytic retrosynthesis for ibuprofen is shown in Figure 16.

Sheldon's Figure 16 "catalytic retrosynthetic" analysis of Ibuprofen is reproduced below. Retrosynthetic analysis was of course a standard part of traditional synthetic organic chemistry strategies, originated by E.J. Corey of Harvard University in the 1960s, a concept for which Corey won the Nobel Prize in 1990.

---

[21] The words "atom economy" had not yet been coined at that time (in the mid-1980s), but the workers at Celanese (and likely many other industrial chemists of those times) were very familiar with the concept that as much of the weight of the starting materials as possible should be incorporated into the product.

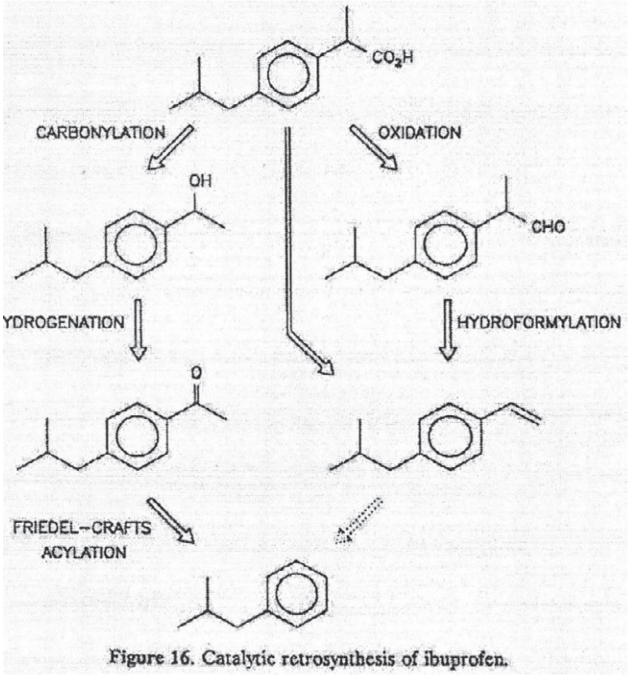


Figure 16. Catalytic retrosynthesis of ibuprofen.

Figure 16. From Sheldon 1992a.

This author did in fact, in May of 1984, consider both sides of the retro-synthetic analysis of racemic ibuprofen illustrated by Sheldon's Figure 16, and also intentionally used catalytic reactions, (as previously described in detail in Murphy (2018).[22] In 1984 I was working in a small Celanese team that was making major improvements in commercial rhodium-catalyzed methanol carbonylation technology.[23] I attended the 10th Annual meeting of the Organic Reactions Catalysis Society in Williamsburg Virginia in May 1984, where Professor John Stille of Colorado State University gave a talk on attempts (with modest results) to hydroformylate styrene asymmetrically.[24] Stille briefly showed a slide of structures of several known "profen" drugs, including Ibuprofen, that could be a target for a "hydroformylation" synthetic strategy. In my conference hotel room that night, I conducted a retrosynthetic analysis of Ibuprofen (and several other "profen" drugs whose structures Stille had revealed [6]) and considered both branches of the retrosynthetic analysis illustrated by Sheldon's Figure 16. I did not know that first night which of the "profen" drugs Stille had shown would have to be single enantiomers, or which ones would have credible / viable commercial markets.

I concluded quickly on that night that the "hydroformylation" strategy shown (for ibuprofen) along the right of Sheldon's Figure 16 was too long, uncertain, and incomplete to be especially attractive for Celanese, though I did not totally discount it.

Because I was actively working on methanol carbonylation, it seemed obvious to consider the "carbonylation" strategy illustrated on the left of Sheldon's Figure16. The synthetic scheme would have looked much more difficult had a single enantiomer of the Ibuprofen been required. Fortunately, it turned out (after I got home to Celanese) that only racemic Ibuprofen was needed. I shared my ideas for the "carbonylation" synthetic scheme with a separate Celanese research group in Corpus Christi exploring new routes to Fine Chemicals and Pharmaceuticals. Veraderaj Elango, who worked in that group, later found the Pd / PPh$_3$ / HCl catalyst combination that very efficiently carried out the key carbonylation step, to yield the racemic Ibuprofen, in good rates and yields.

Looking backwards another step, my intuition that night in Williamsburg was that a ketone hydrogenation to produce a racemic benzylic alcohol was reasonably likely to succeed in good yields, as many examples of such ketone hydrogenations were known.

Looking backward another step, I had reasonable initial confidence that a Friedel-crafts acylation of isobutyl-benzene to produce the needed acetophenone could succeed, something the literature (including the Boots patents) rapidly confirmed when I got home. But I did not know that night what volume of ibuprofen production would be needed, and whether or not it could justify an anticipated high capital cost to build a custom commercial plant to handle the dangerous and corrosive HF, and thereby avoid the use of AlCl$_3$ in the acylation step. That question was only answered a good deal later at the end of development, by the team of Celanese engineers who did the economic / market estimates and process design work.

Overall, the three-step BHC synthetic strategy produced by the "catalytic retro-synthetic analysis" seemed to have uncertain but very interesting potential "Quality"[4,25]. But a GREAT deal of inter-disciplinary teamwork was needed to resolve the initial uncertainties.

As commercialized in 1992, the BHC Ibuprofen Process directly illustrated six of the "12 Principles of Green Chemistry" (only published years later); 1) prevention of waste rather than treatment or cleanup, 2)

---

[22] This author never considered (until years later) the combination of the two well-known techniques of catalysis and retro-synthetic analysis to constitute a new "Principle", a proposition this author still considers debatable.

[23] See Smith et.al, (1987).

[24] See Stille, J.K. (1985).

[25] See Murphy (2020b)

catalysis, 3) Atom Economy, 4) minimization of solvents, 5) energy efficiency, and 6) avoidance of protecting groups). Two more of the "12 Principles" had been used by Nicholson and Adams at Boots in the 1960s, during the discovery of Ibuprofen (designing safer chemicals and designing for degradation). It violated two of the "12 Principles", (less hazardous chemical synthesis and inherently safer chemistry), primarily because of the use of HF in the acylation step, but use of HF was much later determined to be both environmentally and economically superior to the use of stoichiometric quantities of $AlCl_3$ in the original Boots acylation step. The last two of the later published "12 Principles of Green Chemistry" (use of renewable feedstocks and "real time analysis to prevent pollution") were irrelevant to the BHC Ibuprofen process.

Looking back from a different perspective, there were indeed many benefits from a retro-synthetic analysis for Ibuprofen, using catalytic reactions. It "automatically" routed the analysis toward shorter, and highly atom efficient routes that avoided waste / pollution production and protecting groups, and toward raw material and energy efficiency.

Ibuprofen was a relatively simple target molecule for a pharmaceutical, but many uncertainties remained after the retro-synthetic analysis in the earliest moments and days of conception. Again, the teamwork of many people from many disciplines was required to address and overcome the uncertainties and turn the initial conception into a commercial reality that actually "Prevented Pollution". Many pharmaceuticals are more complex molecules than Ibuprofen, and therefore require more complex analysis, and Real-World compromises and teamwork, from the many subsequent scientists, engineers, and businesspeople required to turn original ideas into commercial realities.

In the remainder of his 1992 Texas A&M article, and in many of his subsequent articles over the following years (See appended Reference List for citations to many of Sheldon's subsequent publications), Sheldon described and/or predicted many applications and examples of the uses of catalysis in the fine chemical and pharmaceutical industries, to achieve waste and pollution reduction.

In Sheldon's later papers he also repeatedly discussed the importance of considering positive economic outcomes to the Real-World development and commercialization of environmentally superior commercial processes. Improved economic performance was a very important but far too often unrecognized driver of what was termed "Pollution Prevention" in Industry in the 1980s.[4,5]

Recently, Sheldon, Bode, and Akakios summarized thirty years of the subsequent evolution and application of concepts related to Green Chemistry metrics (Sheldon et. al. (2022)). Sheldon noted that "The ideal E-factor is zero conforming to the first principle of green chemistry: 'It is better to prevent waste than to treat or clean up waste after it is formed.'" Sheldon also later noted "An important driver for the widespread introduction of green chemistry in chemicals manufacture was always waste prevention at source [4], not only for its environmental benefits but also for its economic competitiveness through efficient and cost-effective use of raw materials."

Sheldon noted the E-Factor calculations have subsequently undergone some evolution, broadening, and refinements since his earliest paper 30 years ago, to explicitly include solvent losses and water utilization. Sheldon now defines the E-Factor as "the actual amount of waste, defined as 'everything but the desired product' produced per kg of product," but somewhat later remarked that:

> …current thinking is to calculate E-factors both with and without water [8,9]. This has led to the use of simple Efactors (sEF), that disregard solvents and water in early route scouting, and complete E-factors (cEF) that include solvents and water with no recycling [5]. The true commercial E factor will fall between the sEF and cEF, and can be calculated when reliable data for recycling and solvent losses are known.

This author agrees with Sheldon that "simple" E-factors which do not initially address solvent issues can be useful during the conception and exploratory scouting stages of a Real-World commercial project. At the stage of conception and early scouting experiments in the Ibuprofen project, we were uncertain if the basic catalytic chemistry would function adequately, so we initially and consciously but temporarily ignored the solvent issues (as being totally unpredictable until the basic chemistry and promising catalysts had been demonstrated). Consideration of solvents and/or process water questions was delayed until development began, and then it turned out then that solvents were unnecessary during the synthetic chemistry, but necessary during the separation of the expensive Pd catalyst from the ibuprofen product, and final purification of the ibuprofen!

Sheldon also noted in 2022 that "The pharmaceutical industry accepted the challenge and has spent the last 2-3 decades cleaning up their manufacturing operations[3]. However, in the intervening years APIs have become increasingly complicated molecules, compared with 40 years ago, thus requiring longer syntheses for their production." One of many new sources of information and tools, to address such large challenges, can be found on the website of the ACS Pharmaceutical Roundtable.[26] Trost's Bryostatin total synthesis provided a wonderful example of such challenges, and the use of homogeneous catalysts to shorten very long and complex total synthesis schemes in order to make them practical, and simultaneously improve the final E-Factor and environmental impacts as well.

5. CHANGE, EVOLUTION, AND THE FUTURE OF "GREEN CHEMISTRY"

Some larger perspectives are needed, about the scope and purposes of "Green Chemistry". Having a "Green Chemistry" idea, or following a set of "Principles", or even running a few experiments in the lab is only a beginning, toward a much larger goal and/or purpose.

In this author's opinion and experience, the primary goal and/or purpose of "Pollution Prevention / Green Chemistry" is not to try to discover or make a new "Science". In this author's opinion and experience, the goal and/or purpose of "Green Chemistry" has always been to use already known "Science", Engineering, and Technology to try to make new and improved Real-World processes and products, for the needs of the Real-World and its people, also while preventing the formation of waste and pollutants, so as do less damage to the natural World and its environment and ecology. Fortunately, a good deal of new "Science" has developed along the way.

Addressing that broader but primary goal, and transforming that goal into Real-World reality, has always required consideration of, and contributions from other "Sciences" outside Chemistry, including Biology, Ecology, Engineering, Economics, Business, and even Politics and Policy. For example, pharmaceutical research has always been interdisciplinary, with chemists making molecules for biological testing for activity, toxicity, etc., all for the use of doctors and patients. With the growing use of the techniques of modern biotechnology, to make antibody drugs and RNA vaccines, the pharmaceutical industry trend is now toward the increasing importance of biology, and also the engineering techniques necessary for Real-World production of such biotechnology drugs. Interdisciplinarity is now increasingly important.

Furthermore, the efforts of Trost and Sheldon as described above were only a limited (and very "Chemistry focused") part of the much earlier, broader, international, and interdisciplinary efforts at "Pollution Prevention" that developed in Industry in the 1970s and 1980s.[4,5] Those much broader "Pollution Prevention" efforts were a "paradigm change" that embraced everything from the mining of minerals, oil drilling and refining, to end use issues including toxicity, formulations, packaging, coatings, recycling, disposal, and degradability. Many industrial chemists were involved in the "Pollution Prevention" efforts of the 1970s and 1980s, but few Academic chemists became involved in such efforts until the 1990s.

Professors Barry Trost and Roger Sheldon were among the earliest "chemical" Academics to become involved. Sheldon brought a wealth of knowledge about and experience in the Chemical Industry with him when he moved to Academia in 1991.

Sheldon's Tables 1 & 2, and Figure 8 recognized some of those prior developments in industry, over the prior decades. Sheldon recognized that those developments contrasted with, and in some ways conflicted with, the different goals and techniques that had evolved in traditional synthetic organic chemistry, a "Field" largely dominated by Academic perspectives, goals, and the peer reviewed Scientific literature. But with the growth of research in both organometallic chemistry and homogeneous catalysis in both Industry and Academia in the 1960s and 1970s, the two previously largely separate fields of synthetic organic chemistry and catalysis began to merge, as Sheldon's Figure 8 correctly suggested.

Both Trost and Sheldon then made substantial contributions to the early evolution of methods for more cleanly synthesizing and manufacturing fine chemicals and pharmaceuticals in the early 1990s, years before the words "Green Chemistry" were used in public, or the "12 Principles of Green Chemistry" were published in 1998. Their later contributions are also indisputable, as are the later contributions by many other Scientists, from many "disciplines", in both industry and in Academia.

Unfortunately, with the publication of the "12 Principles of Green Chemistry" in 1998, too much of the Academic and government "worlds" began to narrow the focus toward chemistry only, while largely ignoring the much earlier and much broader interdisciplinary approaches that had produced many environmentally favorable commercial processes in the 1970s and 1980s. In this unfortunate "paradigm change" many Academics began to conduct research and teach students based on an inaccurate "narrative" that "Green Chemistry" had originated at the EPA, and could be "guided" by the wildly incomplete and highly Academic perspectives of the "12 Principles".

---

[26] See the ACS Pharmaceutical Roundtable website, at https://www.acsgcipr.org/

This author has a very different perspective on, and has published (see Murphy 2020a), a very different interpretation of the history of the origins and emergence of "Green Chemistry", namely that:

> …Real-World Industrial "Green Chemistry" emerged as a holistic final outcome from an extremely varied and complex set of parallel evolutionary "random tinkering" sub-processes that began about the time of World War II, and that evolutionary process accelerated in the 1970s … That overall evolutionary process was the product of very complex interactions of very many internal and external events, carried out by many human investigators from multiple disciplines and countries, who were individually driven by many different goals, motivations, influences and input factors, including customer / societal needs and desires, economics, the environment, the legal / statutory / regulatory pressures, as well as the constantly evolving state of the underlying sciences of Chemistry, Biology, and Engineering, over decades. Many of the resulting individual inventions were also the direct product of individual human creativity, thought, and logic, as aided by intercommunications between the investigators, as well as the constraints of the laws of Nature, local circumstances, and elements of chance.[4]

This author believes that such an evolutionary and multi-disciplinary view of the history of "Green Chemistry" can have many implications for the directions "Green Chemistry" should go in the future. Fortunately, in the last ten years or so, some prominent "Green" Academic practitioners (including Professor Anastas) and their approaches seem to be broadening and evolving again, toward interdisciplinarity, "Sustainability", and "Circular" technologies and economics.[27] This author very much approves of and supports returning toward such broader interdisciplinary contributions and perspectives in the future.

Moving back toward such interdisciplinary and teamwork-based approaches is quite a "paradigm change". Deep knowledge, experience, and "expertise" in each of the relevant sub-disciplines is still required, but is clearly not enough. The interdisciplinary subject matter is far too Vast and/or infinite for any one person to understand completely, and a good deal of unpredictability is built into such Vastly complex evolutionary processes. Yet interdisciplinary teams can address and solve many very complex Real-World problems, by focusing on the scope of the specific Real-World problem they are attempting to address, and using interdisciplinary teamwork and iterative, evolutionary approaches.[28]

Lastly, this author is concerned that over the last 25 years hundreds of thousands of university students have been taught that the "12 Principles of Green Chemistry" were the primary cause of the much of the environmental progress of the last 25 years. Those narratives neglect the primary early role that Industry played, and have left hundreds of thousands of students with a false belief that the US government and Academia were primarily responsible for the "Green" progress that has been achieved. They also propagate a very questionable belief that top-down "command and control" legal/political governmental mandates were a primary cause the progress over the last 25 years, and neglect consideration of inherently interdisciplinary evolutionary developments that were actually responsible for much of the progress.

While such oversimplified narratives may be difficult to avoid when introducing K-12 and undergraduate students to Science, this author believes such narratives are somewhat destructive to the understanding and futures of Science and Engineering graduate students preparing to go out into a profoundly interdisciplinary and evolutionary Real-World. This author believes graduate students interested in inherently interdisciplinary fields such as "Green Chemistry" and "Green Engineering" should be exposed to and consider evolutionary and interdisciplinary perspectives about Science, and their relationships to the extremely complex external and evolutionary technical, social, and legal phenomena that are ubiquitous in the Real-World. This author believes such graduate students should be allowed to participate in interdisciplinary graduate coursework and/or seminars addressing environmental problems and solutions. This author is heartened by the indications that both "Green" R&D in general, and Science and Engineering education, seem to be evolving back toward such interdisciplinary approaches, and that these developments may represent another new "paradigm change" in Academic Education.

Mark A. Murphy Ph.D., J.D. is a retired industrial chemist and patent attorney, writing "Pro-Bono." He thanks his many prior colleagues from Science, Engineering, and Law, and the authors of the references cited herein, and his wife Mary Bertini Bickers (a woman of many very unusual talents in her own right) for her many forms of support. The opinions stated in this article are solely those of the author and were not induced or financially supported in any way by any other person, business, or legal entity.

Sheldon's Figure 1, Table 1, Table 2, Figure 8, and the several text passages quoted herein from Sheldon 1992a are being reproduced in this article with the permission of Springer Nature, current owner of Plenum Press's original copyrights.

---

[27] See for example Mulvihill et.al. (2011), Iles and Mulvihill (2012), Constable (2021), and Ncube et.al. (2023).

[28] See Murphy (2020b).

REFERENCE LIST

Anastas, PT., and Warner, J. C., (1998) "Green Chemistry Theory and Practice", Oxford University Press, New York.

Anastas, P.T. and Beach, E.S., (2009) "Changing the Course of Chemistry," Chapter 1, in "*In Green Chemistry Education*," Anastas, P.T., Levy, I.J., and Parent, K.E., editors, ACS Symposium Series Volume 1011, Washington DC 2009, available at https://pubs.acs.org/doi/abs/10.1021/bk-2009-1011.ch001 .

Cann, M.C. and Connelly, M.E. (2000) *Real-World Cases in Green Chemistry*, published by the American Chemical Society, Washington DC. A copy is available at https://www.amazon.com/Real-world-cases-green-chemistry-Michael/dp/0841237336 .

Constable, D.J.C., 2021, "Green and sustainable chemistry – The case for a systems-based, interdisciplinary approach", *iScience*, 24, 103489, December 17 2021, see https://www.sciencedirect.com/science/article/pii/S2589004221014607

"Custom Chemicals", (1993) article by Stephen C. Stinson in *Chemical & Engineering News*, February 8, 71, 6, 34-59, see https://pubs.acs.org/doi/10.1021/cen-v071n006.p034

Howard-Grenville, J., Nelson, A.J., Earle, A.G., Haack, J.A., and Young, D.M., "If Chemists Don'tDo It, Who Is Going To? Peer Driven Occupational Change and the Emergence of Green Chemistry," *Administrative Science Quarterly*, 2017, Vol 62(3) 524-560. https://journals.sagepub.com/doi/abs/10.1177/0001839217690530

Kirkpatrick Chemical Engineering Achievement Award, *Chemical Engineering Magazine*, December 1993, pages 94-95, "The Award Goes To….", see https://www.chemengonline.com/kirkpatrick-award/

Illes, A., Mulvihill, M.J., 2012, "Collaboration Across Disciplines for Sustainability: Green Chemistry as an Emerging Multistakeholder Community", *Environ. Sci. Technol*. 46, 11, 5643-5649. See https://pubs.acs.org/doi/10.1021/es300803t

Mulvihill, M.J., Beach, E.S., Zimmerman, J.B., and Anastas, P.T., 2011, "Green Chemistry and Green Engineering: A Framework for Sustainable Technology Development", *Annu. Rev. Environ. Resour*., 36, 271-293, see https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1955060

Murphy, M.A., (2020a), "Early Industrial Roots of Green Chemistry – II : International "Pollution Prevention" Efforts During the 1970's and 1980's" *Substantia*, 4(2), 2020; see https://riviste.fupress.net/index.php/subs/article/view/894

Murphy, M.A., (2020b), "Exploring the Vastness of design space for greener solutions using a Quality Approach," *Physical Sciences Reviews*, 20200001, see https://www.degruyter.com/document/doi/10.1515/9783110669985-002/html?lang=de

Murphy, M.A., (2021), "Early Industrial Roots of Green Chemistry : International "Pollution Prevention" Efforts During the 1970's and 1980's", *Chemistry International*, January – March 2021, pgs 23-25, https://www.degruyter.com/document/doi/10.1515/ci-2021-0105/html

Murphy, M.A., (2018), "Early Industrial Roots of Green Chemistry and the History of the BHC Ibuprofen Process Invention and Its Quality Connection", *Foundations of Chemistry*, 2018, 20: 121-165m; https://doi.org/10.1007/s10698-017-9300-9

Ncube, A., Mtetwa, S., Bukhari, M., Fiorentino, G., and Passaro, R.,2023, "Circular Economy and Green Chemistry: The Need for Radical Innovative Approaches in the Design for New Products", *Energies* 2023, 16(4), 1752; see https://www.mdpi.com/1996-1073/16/4/1752

"*Non-Waste Technology and Production*, Proceedings of an international seminar organized by the Senior Advisors to ECE Governments on Environmental Problems on the Principals and Creation of Non-waste Technology and Production, Paris, 29November – 4 December 1976", published in 1978 by Permagon Press on behalf of the United Nations as copyright holder. See https://www.sciencedirect.com/book/9780080220284/non-waste-technology-and-production

Royston, M.G., "*Pollution Prevention Pays*", Permagon Press, 1979, currently available from Elsevier Science Direct at https://www.sciencedirect.com/book/9780080235974/pollution-preventionpays

Sheldon, R.A., (1987) "Catalytic Oxidation and Fine Chemicals", *Catalysis Today*, 1, 351-355.

Sheldon, R.A., (1992a), "Catalysis, The Atom Utilization Concept, and Waste Minimization", Chapter 10, pp 99-119, in "*Industrial Environmental Chemistry*" edited by D.T. Sawyer and A.E. Martell, Plenum Press 1992, in Proceedings based on a March 1992 Symposium sponsored by the Texas A&M IUCCP (Industry-University Cooperative Chemistry Program). currently available at https://link.springer.com/chapter/10.1007/978-1-4899-2320-2_9, used with permission of the current copyright holder, Springer Nature.

Sheldon, R.A., (1992b), "Organic Synthesis – Past, Present, and Future," *Chemistry & Industry*, 7 December 1992, 903-906.

Sheldon, R.A., (1993), "The Role of Catalysis in Waste Minimization", in *Precision Process Technology*, Weijnen, M.P.C., Drinkenburg, A.A.H. (eds) *Precision Process Technology*. Springer, Dordrecht. https://link.springer.com/chapter/10.1007/978-94-011-1759-3_10

Sheldon, R A. (1994), "Consider the environmental quotient", *Chemtech*, 24:3, pages 38-47. see https://www.osti.gov/biblio/7109196

Sheldon, R.A., Dakka, J, (1994), "Heterogeneous catalytic oxidations in the manufacture of fine chemicals", *Catalysis Today*, 19 (2) (1994) 215-246, see https://www.sciencedirect.com/science/article/abs/pii/092058619480186X

Sheldon, R.A., (1996), "Selective catalytic synthesis of fine chemicals: opportunities and trends", *J. Mol. Mol. Catal. A.*, 107, May 1996, 75-83, see https://www.sciencedirect.com/science/article/abs/pii/1381116995002294

Sheldon, R.A., (1997), "Catalysis and Pollution Prevention", *Chemistry & Industry*, Jan 6 1997, 12-15

Sheldon, R.A., (1997), "Towards Environmentally Friendly Chemical Processes", In: Swift, K.A.D. (eds) *Current Topics in Flavours and Fragrances*. Springer, Dordrecht. https://doi.org/10.1007/978-94-011-4022-5_4

Sheldon, R.A., (1997), "Catalysis: The Key to Waste Minimization", *J. Chem Tech. Biotechnol.* 68, 381-388, https://doi.org/10.1002/(SICI)1097-4660(199704)68:4%3C381::AID-JCTB620%3E3.0.CO;2-3

Sheldon, R.A., (2000), "Atom efficiency and catalysis in organic synthesis", *Pure and Applied Chemistry*, vol. 72, no. 7, 2000, pp. 1233-1246. https://doi.org/10.1351/pac200072071233

Sheldon, R.A., (2010), "Introduction to Green Chemistry, Organic Synthesis and Pharmaceuticals", Chapter 1 in *Green Chemistry in the Pharmaceutical Industry*, Editor(s): Dr. Peter J. Dunn, Dr. Andrew S. Wells, Dr. Michael T. Williams, Wiley-VCH Verlag GmbH & Co. KGaA, see https://onlinelibrary.wiley.com/doi/10.1002/9783527629688.ch1

Sheldon, R.A., Bode, M.L., and Akakios, S.G., (2022), "Metrics of green chemistry: Waste minimization", in *Current Opinion in Green and Sustainable Chemistry*, Volume 33, February 2022, 100569, see https://www.sciencedirect.com/science/article/abs/pii/S2452223621001255

Smith, B.M., Torrence, G.P,. Murphy, M.A., and Aguiló, A., (1987), "The Rhodium-Catalyzed Methanol Carbonylation To Acetic Acid at Low Water Concentrations: The Effect of Iodide and Acetate on Catalyst Activity and Stability", *J. Mol. Cat.* 39, 115-136.

Stille, J.K.: (1985), "Asymmetric hydroformylation via polymer supported chiral catalysts". In: Robert, L. (ed.) Volume 22 of the "*Catalysis of Organic Reactions*" Series. Augustine, Marcel Dekker Inc, New York.

Trost, B.M., (1991), "The Atom Economy- A Search for Synthetic Efficiency," *SCIENCE*, 6 Dec, Vol 254 no. 5037, pp. 1471-1477.

Trost, B.M., (1995), "The Atom Economy- A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way," *Angewante Chemie International Edition in English*, Volume 34, Issue 3, p. 259-281. https://doi.org/10.1002/anie.199502591

Trost, B.M., (2002), "On Inventing Reactions for Atom Economy": *Acc. Chem. Res.*, 35, 9, 695-705. https://pubs.acs.org/doi/10.1021/ar010068z

Trost, B.M., Dong, G., (2008), *NATURE*, November 27; 456(7221): 485–488. https://doi.org/10.1038/nature07543