Optimization in Organic Synthesis

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"Art is always a bonus to synthesis . . . . the artistic aspect of synthesis, beautiful and marvelous as it is, should not be a justification for carrying out a total synthesis. If your problem is truly essential then you don't care about the elegance. The more essential your first E is, the less important your last E becomes."[1]

"Will we be able to recapture the many millions of presumed 'transient' natural products that were evolutionarily de-selected along the paths that eventually led to the natural products synthesized on Earth today? . . . I cannot imagine that in a young synthetic chemist's lifetime, it will not be accomplished." [2]

Organic Synthesis, *quo vadis*?[3] has been a phrase, perhaps in a more modern language, on the lips of the practitioners of this demanding science-art, undoubtedly from the earliest times[4] but more vigorously in the last two decades.[5] Comparison of achievements of yesterday[6] and today[7] suggests progress in our abilities to construct molecules of complexity, with higher stereocontrol, faster analysis, and greater prediction of eventual success. However, the practical aspects, on any scale, of brevity, efficiency, safety, eco-consciousness, and energy- and resource-frugality remain, as noted by a major synthetic craftsman,[8] crudely addressed. The Y2K symbolism is perhaps also appropriate for urgently dedicating our efforts to making headway in the solution of these interrelated goals.

Our central science[5a] progresses on fronts of method development and total synthesis with a great deal of cross-talk and interdependency (see Fig. 1). The burgeoning literature of new methods suggests that 70% are not repeated, perhaps even in the original laboratories, a situation with dire consequences for ascertaining true yield ranges and reproducibility a la the *Org. Syn.* religion. Furthermore, as judged from a cursory glance of tables in recent journals, much is left to be desired in giving confidence to the user that a method has generality (substrate diversity, FG and steric tolerance, catalyst or reagent minimization, and temperature and solvent optimization). Although the beauty of judiciously modeled use of PGs is to be applauded,[9] FG protection is a continuing embarrassment and annoyance. Synthetic chemists are challenging the dogma by daring the multi-FG molecules to behave in the manner desired. Ugi multicomponent reactions[10] and combinatorial synthesis[11] will undoubtedly soon influence the PG-expediency problem. In industry, statistical programs[12] at times drive optimization of reactions thus meeting the normal intense time constraints to produce mulit-kg of commercial substances.

Atom-economy, a term coined by another influential synthetic chemist,[13] has brought awareness of an issue to academic scientists which their industrial process and development colleagues un-

Medicinal Research Reviews, 19, No. 5, 342–347, 1999

CCC 0198-6325/99/050342-06

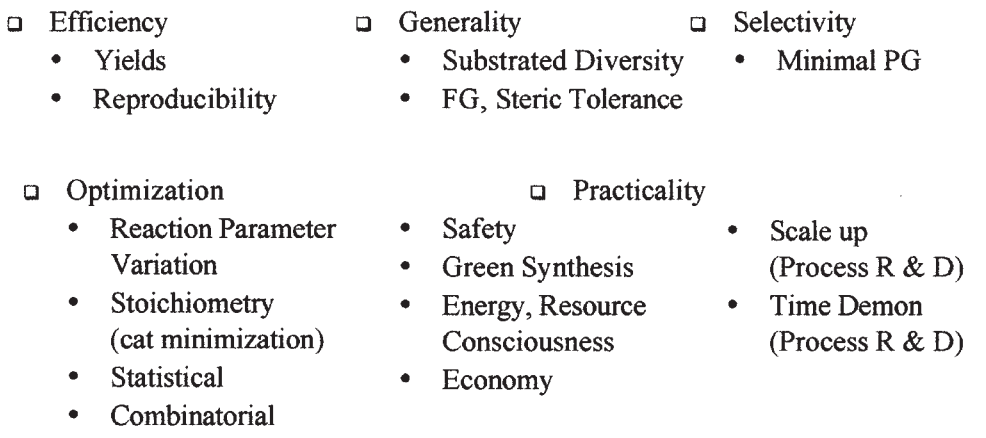

Figure 1. Method development.

flinchingly face in their task to produce a commercial drug or agrochemical within defined cost constraints. Actuality is a multidimensional term which embodies efficiency, economy, of course, but as justly demanded by society, safety, energy and resource sentience, and enviro–compassion. The greening of synthesis is a timely subject,[14] at the basic levels of hazardous organic solvent and waste byproduct (organic, inorganic) curtailment is receiving attention in initiatives in fluorous phase,[15] supercritical fluid,[16] and ionic liquid[17] research. Metal catalysis, both heterogeneous and homogeneous, advancing to a competitive position with natural enzyme rates, has exceptionally influenced how we conceptualize C&bond;C bond formation[18] and now require increase in turnover number,[19] in addition to the continuing discovery and mechanistic understanding of new catalytic systems. Stimulated by availability of such catalytic processes, sequential/tandem/domino/cascade reactions[20] are increasingly noted[21] and may constitute new horizons in industrial practice. Although still considered as intrusions into chemical synthesis by some, biotransformations[22] should be welcomed into our armementarium, especially in view of exciting new developments in modular enzymes.[23]

To extrapolate to industrial process operation again,[24] the trouble with scale-up synthesis includes, in addition to factors of academic or industrial drug discovery labs mentioned above, the more often-than-not divergence from the method established in a mg-scale route, impurities, chromatography, engineering, and clock-ticking, among other factors, play demonic roles.[25] In all of our trials and tribulations, the definition of a perfect chemical reaction is still far from our grasp.

In the realm of multistep (total[26]) synthesis, the oft-cited definition of an ideal synthesis attributed to a cutting-edge synthetic chemist[27] will also remain a challenge in Y2K. In initiating a synthesis, the economic and "ready" availability of starting materials and reagents requires more than lip service; at the end, the number of steps and overall % yield demands cold-daylight realism and a thought on future credibility.[28] In setting out on the expedition for a challenging multistep synthesis, the retrosynthetic analysis paradigm (disconnection approach, synthetic "trees") all of us learned from Corey[29] and the pointers of convergent/linear, relay (also in the new dimension of to/from biotransformation-derived material), and the arithmetic demon vividly taught to some of us by Ireland[30] are our constant guideposts (see Figs. 2 and 3). To this conceptual tool box, Corey added computer-assisted design (CAD)[31] which spawned great activity that continues today.[5b] The scribbling of retrosynthetic arrows are prevalent wherever synthetikers gather but it would appear that the impact of the actual mechanics of CAD on research and teaching on our art has been modest. Nevertheless, these contributions have more recently spawned attempts to devise semiquantative graphical representations of topology, connectivity,[33] and molecular complexity[34] and relate them to the disconnection approach and chemical intuition "measures." And at the conclusion of a multistep synthesis

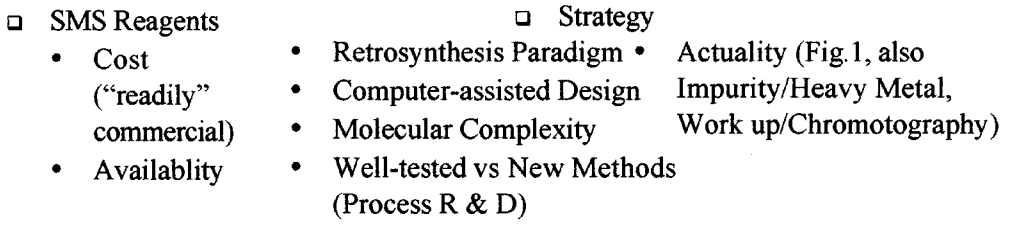

Figure 2. Multistep synthesis.

of a complex target? Aside from the well-deserved euphoria, shared by university and industrial chemists alike, the cost, engaged personpower,[35] and environment and energy impact should receive close scrutiny. This is (or is becoming) a *sine qua non* for an industrial process which must go on stream (the ultimate reproducible *Org. Syn.* prep); it is incompletely practiced in small-scale synthesis whether it be in university or industrial labs but this is destined to change. Of course, the academic researcher must answer to the ultimate question: what have we learned?[36] and thereby contribute in some way to advances in our discipline.

Quo vadis? Chemical synthesis, being only a recent component of human evolution, will continue to respond to the solution of societal problems in health, food, environment, and material requirements. Furthermore, the logic and technologic of our science assures that it will impact surrounding disciplines.[37]

Since prognosis is always dangerous,[38] only certain progressive elements on the horizon may be mentioned. In asymmetric synthesis, enantioenrichment and amplification[39] constitute some of the new conceptual elements in evolutionary stages. Biotransformations, practiced since the advent of penicillin drugs, are increasingly applied in industry where prejudice and inhibition are overridden by business considerations.[40] Aside from development of new effective and ecofriendly reaction media,15–17 solid support, microencapsulated, and aqua-stable reagents are being devised.[41]

As part of the combinatorial chemistry surge, ancillary areas of analytical chemistry, robotics, and informatics are forcing a closer chemist–engineer interface.[42] Indubitably, combichem is becoming part of the common practice of a synthetic lab for optimization of new methods,[43] and screen-

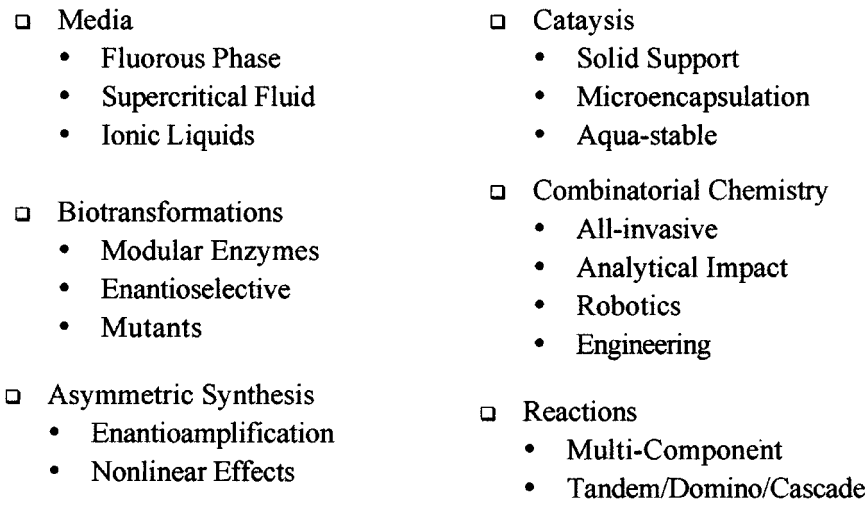

Figure 3. Evolving concepts and technology.

ing of new ligands and catalysts.[44] No combinatorial magic bullets as yet exist and the field is changing from the numbers game to focused biological relevant diversity with, as always, chemistry being the limiting factor. Such an approach essentially admits that we cannot make all the molecules and therefore should focus on simplest ones.[45]

In industry, the Discovery Chemist is now leaning over the shoulder of the process chemist.[46] Together, with ingenuity, practical savy, and with the help of the blossoming custom synthesis cottage industry,[47] the high-pressure time lines to the go/kill phase of the potential drug are being met more rapidly.

Optimization in Organic Synthesis, the title of the symposium held during the 3rd Winter Conference on Medicinal and Bioroganic Chemistry in Steamboat Springs, CL, January 22–28, 1998, encompasses the content of this Introduction and defines some of the components addressed by the invited speakers. Carsten Bolm illustrates how design of new enantioselective catalytic systems advances our utility of the classical (Baeyer–Villiger) reaction; Gilbert Stork instructs all of us on the origin and the significance of selectivity in organic synthesis with illustrations, now textbook, of work from his laboratories; Paul Wender shows how complex biological activity of natural products drives the invention of new synthetic reactions; and Matthias Beller demonstrates the importance to focus on the need for simple building blocks and to develop new regioselective catalytic reactions.

The many facets of *Optimization in Organic Synthesis* and our responsibility to its achievement justifies continuing meetings under this or similar titles[48] to bring home the message which, by the nature of the vitality of the field, is a moving target.

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