Application Of New Methodologies In Organic Reactions

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Abstract: In the past decade, the field of organic synthesis has witnessed tremendous advancements in the areas of photoredox catalysis, electrochemistry, C–H activation, reductive coupling and flow chemistry. While these methods and technologies offer many strategic advantages in streamlining syntheses, their application on the process scale is complicated by several factors. In this Review, we discuss the challenges that arise when these reaction classes and/or flow chemistry technology are taken from a research laboratory operating at the milligram scale to a reactor capable of producing kilograms of product. We discuss how these challenges have been overcome through chemical and engineering solutions. Specifically, this Review will highlight key examples that have led to the production of multi-hundred-gram to kilogram quantities of active pharmaceutical ingredients or their intermediates and will provide insight on the scaling-up process to those developing new technologies and reactions.
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Introduction

In the last decades, transition-metal-catalyzed coupling reactions have emerged as a powerful tool to form C–C and C—X (X = O, N, Si, halogens, S, B, among others), intending to achieve compounds employed in various industries such as food [1], medicine [2], petroleum [3], petrochemical [4], electrochemical [5,6] and polymers [7]. The orientation of the new C–C bond is affected by different factors which the catalyst is the most important one. Several studies have been conducted on various catalysts of C–H activation fields. The value of this technique, in comparison to the traditional cross-coupling reactions, is due to step economy and the elimination of difficult stages and steps to give pre-functionalized reactants. On the other hand, in the first the use of the C–H functionalization system required catalysts that was made via noble metals such as Pd [8], Rh [9], or Ru [10]. Therefore, there is highly desirable to provide a new methodology for using earth-abundant first-row transition-metal alternatives with comparable catalytic activities [11].

Cost-effective catalysts have been recently developed very fast, and the cobalt catalyst has achieved a specific position. This particular position in C–H functionalization for cobalt is because of its features, such as low cost, low toxicity, and the specific reactivity of cobalt complexes. It is possible to offer new logical paths to reach nucleophilic organometallic cobalt intermediates, according to the difference between electronegativity in 4d transition metals and the 3d transition metal cobalt [2].

Cobalt salts were developed as effective catalysts to explore more efficient synthetic methodologies, for example, for the homo-coupling of Grignard reagents by Kharasch and Fields [3]. About ten years later, Aller reported Raney cobalt-catalyzed hydrogenation of 3,4-methylene dioxybenzyl cyanide to give homo-piperonylamine [4]. In 1979, Tsutomu et al. reported the methanol carbonylation catalyzed by cobalt in the presence of hydrogen to provide mainly acetaldehyde. Its hydrogenation was easily occurred to ethanol during the period of carbonylation on a catalytic amount of $Ru_3 (CO)_{12}$. The difference between the effect of iodide ions on methanol carbonylation catalyzed by Co-, Rh-, or Ir-catalyst was displayed [5]. About sixteen years later, Malacria et al. reported free ligands and η4 -cobalt complexes, which was catalyzed cyclization reactions of 1,7- and 1,8-enynes derivatives through selective cobalt allylic C–H activation [16]. In the first decade of the 21st century, an impressive number of efficient pathways and novel methodologies have been offered that the formation of Csp-Csp [7], Csp^2-Csp^2 [8], Csp^3-Csp^3 [9] bonds, the connection of Csp-H [2], Csp^2-H, and Csp^3-H bonds with each other or heteroatoms is possible [1]. Notably, Gao and co-workers suggested a series of ternary catalytic systems containing cobalt salts, phosphine ligands, and Grignard reagents to promote the addition of arylpyridines and imines to inactivated internal alkynes to give high regio- and stereoselectivities [2].

In recent years, the trend of several cobalt catalysts, especially cobalt-catalyzed C–H activation for forming C–C and C–H heteroatom bonds, was growing [2]. Ackermann [3], [4], [5], Yoshikai [6], and Nakamura [7] are among the pioneers of the preparation of efficient and selective Co-catalysts for

C–H activation/coupling reactions with a wide range of substrates fields. The apparent parameter showing the distinction between weak and strong catalysts is the presence of reactive Grignard reagents [8], additives [9], or ligands [3]. Thus, removing each of these reagents leads to developing a catalyst system for cobalt in organic reactions and provides an easier way to accomplish the reaction [3].

Among what matters the most is matter itself. It is, therefore, not a surprise that chemistry, the science of matter, is considered by many as the central science lying between physics and biology. Its power derives from its ability to analyse and synthesize molecules from atoms and other, more or less complex, molecules. The latter practice, synthesis, is of paramount importance to our well-being, for through it we create new chemical entities (i.e. molecules) from which we derive our most precious material items. A subdiscipline of synthesis is organic synthesis, the art and science of constructing substances, natural or designed, whose primary element is carbon. The flagship of organic synthesis is total synthesis, the endeavour of synthesizing the molecules of living nature in the laboratory. The ability of man to replicate the molecules of living creatures, and create other molecules like them, is a remarkable development in human history. Its birth goes back to 1828, when German chemist Friedrich Wöhler, a Foreign Member of the Royal Society (ForMemRS), synthesized urea, an example of a naturally occurring substance from the living world [**1**]. Such molecules are commonly known as natural products, a term usually referring to secondary metabolites. The creative nature of total synthesis earned this discipline the privilege of being called a fine art and a precise science. Technologies derived from it, and organic synthesis in general, have led to an impressive host of benefits to society, including useful products ranging from pharmaceuticals, dyes, cosmetics and agricultural chemicals to diagnostics and high-technology materials used in computers, mobile phones and spaceships [**2**].

Organic synthesis in perspective

The world has changed dramatically in the last two centuries as a result of scientific discoveries and their applications. One of the most profound of these discoveries is the advent of organic synthesis as marked by Wöhler's synthesis of urea. And although its foundations go back before that era, this initial event, together with developments in structural theory and analytical techniques, gave momentum to its advancement and application in several fields. But what were the conditions and foundations that allowed this science to emerge? And from where did they come?

To answer these questions, we must go back to ancient times, when humans were practising transformations of matter as a means to prepare food, medicines, dyes, tools and weapons. The artefacts left behind from ancient civilizations like those of the Egyptians, Babylonians, Greeks, Romans and Chinese provide evidence for such endeavours, although there was no significant understanding of the nature of these transformations. The curiosity about nature, however, drove the Ancient Greeks to think and speculate about matter, a practice that led to Democritus' atomic theory.

The latter served as the basis from which the more precise atomic theory of the English chemist and physicist John Dalton, a Fellow of the Royal Society (FRS), emerged at the dawn of the nineteenth century. Dalton's theory was one of the most influential theoretical developments in science of all time and gave enormous momentum to further the advancement of chemistry [**3**]. But before we move forward in time, we must mention the alchemists and their practices that can be traced back to thousands of years ago in the Middle East and the Orient, and prevailed later on during the Middle Ages in Europe. From these endeavours, modern chemistry emerged slowly in the eighteenth century. Among the main protagonists responsible for the transition to modern chemistry from alchemy was Irish-born Robert Boyle (FRS), who was both an alchemist and a modern chemist. He exposed his philosophies in his book *The Sceptical Chymist*, which was published in 1661, one year after the Royal Society was founded. Boyle promoted experimentation based on purity, precision and data.

Experimentation and quantitative analysis were moved to a higher level by French chemist Antoine-Laurent de Lavoisier (ForMemRS), who many consider as the father of modern chemistry, with Boyle viewed as the grandfather. Lavoisier described his chemical philosophy and methods in his *Traité Élémentaire de Chimie* that provided the foundation for the emergence of modern chemistry. His chemistry was primarily inorganic and was based on combustion and elemental analysis. Lavoisier published a list of chemical elements but had no means to distinguish between them and atoms; the latter had to await Dalton's atomic theory and subsequent developments that took hold in the nineteenth century. Among these developments was the emergence of organic chemistry, the branch of chemistry dealing with organic compounds, those made of carbon and a few other elements, most commonly hydrogen, oxygen, nitrogen, sulfur, phosphorus and halogens.

The chemistry of natural products was born in the eighteenth century, primarily from the work of the apothecaries, the pharmacists of the time, among whom Swedish Carl Wilhelm Scheele was the most prominent. He, besides being credited with the identification of oxygen, discovered several naturally occurring organic acids, including citric, gallic, malic, lactic, oxalic and uric acids. Scheele also developed important practical laboratory techniques such as distillation and crystallization.

By the dawn of the nineteenth century, the stage was set for the arrival of organic chemistry in general and organic synthesis in particular. Thus, in addition to the advancement of Dalton's atomic theory, a number of other important discoveries and ideas emerged and eventually gave rise to the understanding of the structure of the molecule and the art of its synthesis. Included among the initial prominent contributions to the establishment of the foundations of modern chemistry are those of English chemist Humphry Davy (FRS and President of the Royal Society), Swedish chemist Jöns Jakob Berzelius (ForMemRS), English chemists Alexander Williamson (FRS) and William Odling (FRS), and French chemist and physicist Joseph Gay-Lussac (ForMemRS). Their theories and discoveries served as the foundation from which further advancements occurred, including the distinction between atomic and equivalent weights, the structural theory and the tetrahedral nature of carbon. Among the protagonists of these developments were French chemists Jean-Baptiste André Dumas (ForMemRS), Auguste Laurent, Charles Gerhardt, Joseph Le Bel and C. Adolphe Wurtz (ForMemRS), German chemist Friedrich August Kekulé (ForMemRS), Italian chemists Amedeo Avogadro and Stanislao Cannizzaro (ForMemRS), Russian chemist Dmitri I. Mendeléev (ForMemRS), French physicist, chemist and mathematician Jean-Baptiste Biot (ForMemRS), French chemist and microbiologist Louis Pasteur (ForMemRS) and Dutch chemist Jacobus van't Hoff (ForMemRS) [**1**,**3**].

3. Emergence and evolution of organic synthesis and total synthesis

The development of experimental methods for practical chemistry and the discoveries of naturally occurring substances such as urea, quinine, morphine and strychnine in the late eighteenth and early nineteenth centuries laid the foundations and provided the impetus for the emergence of organic synthesis [**1**].

. This momentous event, albeit a serendipitous discovery, meant that man could construct organic compounds, the molecules of living nature, in the laboratory and without the aid of living creatures or their organs. This important singularity led to the downfall of vitalism, the understanding of the phenomenon of isomerism, and to a revolution in science that came to be known as organic synthesis. As urea was a naturally occurring organic compound, the milestone of its synthesis also marks the birth of total synthesis, the subdiscipline of organic synthesis dealing with the construction of nature's organic molecules. The achievement of the synthesis of urea by Wöhler was followed by the total synthesis of acetic acid, a natural product containing two carbon atoms (as opposed to urea's one), by German chemist Hermann Kolbe (ForMemRS) in 1845.

Soon after its occurrence, the advent of organic synthesis gave birth first to the dye industry and then to the pharmaceutical industry with the synthesis and commercialization of mauve (or mauveine) and acetylsalicylic acid (aspirin), respectively, triggering these industrial revolutions. The first discovery was made, also serendipitously, by English chemist William Henry Perkin (FRS) during his attempts to synthesize quinine (the miracle natural product used as medication to treat malaria), employing an erroneous recipe. At the time, Perkin was a student of German chemist August Wilhelm von Hofmann (FRS), who founded and directed the Royal College of Chemistry in London upon invitation by Queen Victoria. The second discovery was made by German chemist Felix Hoffmann at the Bayer company and was based on the isolation and structural elucidation of salicin, the active pain-relieving ingredient of the willow bark, whose medicinal properties were known from ancient times [**2**].

Indeed, natural products played a crucial role in the emergence and advancement of organic synthesis from its birth to the present day. Thus, from the early days of elemental analysis of natural products, these substances fascinated and challenged organic chemists, first with their structural elucidation and then with their total synthesis. By the dawn of the twentieth century, chemists had synthesized, besides urea and acetic acid, numerous natural and designed molecules, including indigo, alizarin, glucose, coniine and salicylic acid, the precursor of acetylsalicylic acid. They had also discovered several new reactions and applied them to the synthesis of a wide range of organic compounds, including many derivatives of benzene, collectively known as aromatic compounds [**1**–**3**].

The major achievements in organic synthesis and total synthesis of the last decades of the nineteenth century were widely recognized and appropriately hailed, as acknowledged by two Nobel Prizes in Chemistry

awarded during the first 5 years of the Prize's existence [**4**]. The first went to German chemist Emil Fischer (ForMemRS) in 1902 'in recognition of the extraordinary services he has rendered by his work on sugar and purine syntheses', and the second to German chemist Adolf von Baeyer (ForMemRS) in 1905 'in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds'. Many more Nobel Prizes would follow with notable frequency and regularity, reflecting the impressive advances made continuously in these fields throughout the twentieth century, underscoring their importance to science and society. These advances were made possible not only by discoveries and inventions within the field of organic synthesis in terms of new synthetic reactions, methods and strategies, but also by the improvement of analytical techniques and instrumentation, as well as theories that led to better understanding of the nature of the chemical bond [**5**] and chemical reactivity. The isolation and structural elucidation of novel molecular architectures from natural sources provided fuel and inspiration to the practitioners of total synthesis. Among the most important new reactions to be discovered in the first part of the twentieth century were the catalytic hydrogenation reaction of unsaturated carbon–carbon bonds by French chemist Paul Sabatier (ForMemRS) and the Grignard reaction for the formation of carbon–carbon bonds by French chemist Victor Grignard. Sabatier and Grignard shared the 1912 Nobel Prize in Chemistry for their pioneering and influential discoveries. Another highly influential discovery of that era was the Diels–Alder reaction (4+2 cycloaddition for constructing six-membered ring compounds) made by German chemists Otto Diels and Kurt Alder in 1928. Their work was recognized in 1950 with the Nobel Prize in Chemistry. A number of relatively complex alkaloid natural products were synthesized, including tropinone, quinine, morphine and strychnine. The total synthesis of strychnine was accomplished by American chemist Robert Burns Woodward (ForMemRS), a major figure who led a revolutionary movement in the field in the 1950s and 1960s that culminated in his recognition by the Royal Swedish Academy of Sciences with the 1965 Nobel Prize in Chemistry 'for his achievements in the art of organic synthesis' [**6**]. By then, in addition to strychnine, he had synthesized quinine (formal total synthesis), reserpine, chlorophyll and cephalosporine, and then went on to complete the total synthesis of vitamin B_{12}, the most complex natural product to be replicated in the laboratory at the time, in collaboration with Swiss chemist Albert Eschenmoser (ForMemRS) [**7**]. Woodward's contributions also included the adoption of modern instrumentation for structural purification and elucidation purposes, as well as theoretical aspects of organic chemistry, for example the Woodward–Hoffmann rules.

In the meantime, the spectacular success of penicillin as a life-saving antibiotic generated impetus for the discovery of a wide range of new biologically active natural products from microorganisms, a surge at the helm of which were initially the pharmaceutical companies, soon to be joined by academic institutions. Many of these compounds became clinical agents to treat disease and some are in use even today. Their allure attracted the attention of synthetic organic chemists of the second half of the twentieth century and resulted in major achievements in the field of total synthesis. Human hormones such as the steroids and the eicosanoids (e.g. prostaglandins, thromboxanes and leukotrienes) played similar roles to those natural products derived from plants and microbes in challenging and inspiring young practitioners entering the field. One of these practitioners was American chemist Elias J. Corey (ForMemRS), whose legendary contributions helped shape organic synthesis in decisive ways during the second half of the twentieth century. His achievements included the introduction of the theory of retrosynthetic analysis, the development of several new synthetic methods, reagents and catalysts and the total synthesis of numerous bioactive naturally occurring substances, including several members of the prostaglandins, leukotriene and macrolide classes, ginkgolide B, maytansine and ecteinascidin 743. Corey was awarded the Nobel Prize in Chemistry in 1990 'for his development of the theory and methodology of organic synthesis' [**8**–**10**].

The latter part of the twentieth century witnessed impressive advances in the area of new synthetic methodology, which propelled the art of organic synthesis to higher levels of elegance, practicality and efficiency. These new methods facilitated discovery research, product development and manufacturing of pharmaceuticals and other fine chemicals that benefited society. Among the most powerful of these useful reactions are the Wittig reaction for constructing carbon–carbon double bonds, developed by German chemist Georg Wittig, and the hydroboration reaction, developed by American chemist Herbert C. Brown. Brown and Wittig shared the 1979 Nobel Prize in Chemistry 'for their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis'. The contributions of English chemist Sir Derek H. R. Barton (FRS) and Norwegian chemist Odd Hassel to conformational analysis played a major role in shaping our understanding of molecular structure that facilitated

chemical reactivity and selectivity. Barton's discoveries extended well beyond stereochemistry and into other domains of organic synthesis such as biomimetic oxidative coupling reactions and radical chemistry. His pioneering studies in the latter field included deoxygenation and oxygenation methods (C−H activation/functionalization) that proved highly useful and inspiring to synthetic organic chemists of his and later generations. Barton and Hassel shared the 1969 Nobel Prize in Chemistry 'for their contributions to the development of the concept of conformation and its application in chemistry'. American chemist Gilbert Stork (ForMemRS) and Albert Eschenmoser made pioneering contributions to organic synthesis of theoretical and practical importance. Thus in 1955, they independently proposed the so-called Stork–Eschenmoser hypothesis stating that polyunsaturated molecules possessing all *trans* olefinic bonds (e.g. squalene oxide, the biosynthetic precursor of steroid hormones) should undergo stereospecific cyclization to furnish a polycyclic system with all *trans* ring fusion stereochemistry (e.g. *trans*, *trans*, *trans* for dammaratienol, the product of squalene cyclization). This hypothesis was later verified experimentally by W. S. Johnson, who achieved the first biomimetic total synthesis of progesterone in 1971. Stork made several other seminal contributions to organic synthesis, including stereocontrol, cascade radical reactions and total synthesis. Eschenmoser's contributions to organic synthesis are equally impressive and include regio- and stereocontrol reactions, method development, corrin chemistry and the aforementioned landmark total synthesis of vitamin B_{12}. Other important reactions include phosphate and amide bond forming processes, discovered by Indian-born American biochemist H. Gobind Khorana (ForMemRS; 1968 Nobel Prize in Physiology or Medicine, shared with American biochemists Robert W. Holley and Marshall W. Nirenberg) and American biochemist R. Bruce Merrifield (1984 Nobel Prize in Chemistry), for the synthesis of oligonucleotides and peptides, respectively. In the meantime, catalytic asymmetric reactions for oxidation, reduction and a variety of other important processes (2001 Nobel Prize in Chemistry awarded to American chemist K. Barry Sharpless, Japanese chemist Ryoji Noyori (ForMemRS) and American chemist William S. Knowles), metathesis reactions (2005 Nobel Prize in Chemistry awarded to American chemists Robert H. Grubbs and Richard R. Schrock (ForMemRS) and French chemist Yves Chauvin) for the construction of olefinic bonds and cyclic structural motifs and polymers, and palladium-catalysed cross-coupling carbon–carbon bond-forming reactions (2010 Nobel Prize in Chemistry awarded to American chemist Richard F. Heck and Japanese chemists Ei-ichi Negishi and Akira Suzuki) changed the way synthetic chemists were thinking about and practising their science.

The impact of organic synthesis on science and technology does not stop with biology and medicine. It encompasses many other scientific and technological endeavours and facilitates their improvement, scope and reach. Among the most prominent fields that benefited enormously from applications of organic synthesis are those of molecular recognition and supramolecular chemistry, materials science and nanotechnology and chemical biology. Indeed, the universe of compounds synthesized by organic synthesis, natural and designed, is very large and could be almost infinite. Reflective of the progress made in organic synthesis in recent years are the numerous elegant total syntheses of biologically and medically important molecules achieved in laboratories around the world [**11**].

4. Endeavours in total synthesis

The selection of the target molecule from the myriad natural products for total synthesis by the practitioner of the art depends on the novelty of its molecular structure, biological activity and natural scarcity, among other criteria. Thus, some synthetic chemists may wish to use the structure of the molecule as an opportunity to discover and develop new reactions for unmet needs in organic synthesis in order to construct its unusual or sensitive structural motifs. Others may be interested to investigate and develop a scarce biologically active natural product, or a variation of it, as a biological tool or a pharmaceutical drug candidate for development as a clinical agent to use against disease. And yet others may wish to undertake a total synthesis campaign for the intellectual challenge and sheer excitement that it provides. To these reasons must be added the education and training of young students and the problem-solving skills they acquire during such endeavours, as well as the value of the fundamental discoveries that are often made whether through logical reasoning or serendipity.

Endeavours in total synthesis can be more or less challenging depending on the complexity of the molecular structure targeted. Simple and chemically stable molecules yield to synthesis more easily than those possessing complex and labile architectures. However, complexity does not always equate with size when it comes to molecules and their construction. Thus, a smaller molecule with unusual atom connectivities and structural motifs is always more challenging to synthetic organic chemists than one possessing a larger, but repetitive structure such as a polymer, a polypeptide or a polynucleotide.

The more challenging the total synthesis appears to be, the more chances it has to offer opportunities to discover and invent new synthetic strategies and technologies. And the higher the importance of the biology and medicine of the target molecule, the richer the harvest of the benefits and rewards of the endeavour is likely to be. Such campaigns often turn into interesting chemical biology studies and drug discovery programmes through molecular design and synthesis of analogues of the natural product.

5.The total synthesis of calicheamicin

Calicheamicin is a fascinating molecule whose intrigue stems from not only its phenomenal cytotoxic properties and potential as an anti-cancer agent but also its stunning molecular architecture and fascinating mechanism of action. At the time of its isolation from *Micromonospora echinospora* ssp. *calichensis* in the 1980s, neither its structure nor its mechanism of action was precedented. Particularly striking were the 10-membered enediyne, oligosaccharide and trisulfide structural motifs of the molecule of calicheamicin, all three of which are involved in its mode of action that leads to lethal double-strand cuts of the genetic material (double-helix DNA). This mechanism can be compared to that of a guided missile in which the enediyne moiety acts as the explosive payload (generating reactive benzenoid diradicals through Bergman cycloaromatization), the oligosaccharide domain as the delivery system (binding to the minor groove of DNA) and the trisulfide unit as the triggering device (initiating, upon activation, the Bergman cycloaromatization reaction). With all these exquisite features in place, the stage was set for what we expected to be an exciting adventure ahead as we embarked on the journey to the total synthesis of calicheamicin in the late 1980s. Indeed, we had no idea at the outset whether we could ever arrive at our destination, for the challenges facing us were formidable and unpredictable, owing to the demonic complexity of the molecule and its potential chemical instability.

Arduous and difficult as the sail was, it led us, 5 years later, triumphantly to calicheamicin, our molecular 'Ithaca'. Most importantly, we arrived there much wiser and quite content with the bounty of discoveries and inventions we collected on the way. These rewards came in the form of new synthetic methods and strategies, designed analogues of calicheamicin that exhibit similar biological properties despite their simpler structures, and a final confirmation of the originally assigned structure of the natural product.

The total synthesis of Taxol

The legendary cancer curative properties of Taxol (paclitaxel) are matched by the intrigue of its discovery and development as an anti-cancer drug in the latter part of the twentieth century. Originally isolated from *Taxus brevifolia* (Pacific yew tree) and structurally characterized in the early 1970s, Taxol remained a scientific curiosity until its antimitotic mechanism of action as an anti-tumour agent was recognized in the early 1980s. The latter discovery gave momentum to its clinical development, and it became an approved drug in the early 1990s. Taxol is currently one of the most effective and widely used anti-cancer drugs for a variety of cancers, administered to patients either alone or in combination with other drugs. The natural scarcity of the molecule in its original source, coupled with the anticipated demand for the drug, created an urgency for its laboratory synthesis in the 1980s, one that was frustrated by the formidable challenge of the task owing to its molecular complexity. Indeed, numerous groups around the world embarked on its total synthesis at the time, and others continue to be intrigued to this day by its structure as a synthetic target. The importance and lure of Taxol did not escape us, and, in the early 1990s, we initiated a campaign to synthesize it, an endeavour that ended with the first published total synthesis of Taxol in 1994 [**5**].

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