

## Preface

Professor Barry Trost's many fundamental and broad ranging contributions have made a major impact on organic chemistry. Trost's work has been characterized by a remarkable combination of imagination, innovation and scholarship. He has ranged over the entire field of organic synthesis, introducing novel methodology that has simplified the construction of many complex targets, including many natural products of biological interest.

In a seminal paper, Trost pointed out that, beyond stereochemical control, "atom efficiency" and minimum waste production must be considered. Thus, his goal became to combine synthetic building blocks to produce complex targets with a minimum of byproducts. He has made considerable progress in that context by the careful design of remarkably specific catalysts.

Trost's early activities focused around the organic chemistry of sulfur. He introduced a number of novel reactions such as cyclobutanone and lactone annulations, and, of even more general significance, he designed a fundamentally new way of forming olefinic bonds in organic compounds through the introduction and removal of sulfur. The methodology, subsequently much used, is illustrated by the identification of one of his papers in this area as a "Science Citation Classic" by the Institute for Scientific Information.

Important as these and a number of other sulfur based methods have proved, it is the invention of new fundamental bond formation processes by the use of homogeneous catalysis which has been Trost's most spectacular contribution. He played a major role in developing the organic chemistry of palladium by being first to demonstrate and greatly expand an original observation by Jiro Tsuji, and making it into a major general method for the formation of a new bond between an allylic carbon center and carbon, oxygen, nitrogen, sulfur, hydrogen, etc. under catalysis by homogeneous complexes of palladium. Trost's fundamental mechanistic studies in that area demonstrated that these new bond formation proceed with retention of configuration at the carbon center undergoing substitution. Another remarkable

feature contributed by his laboratory is the ability of the methodology to achieve macrocyclizations even at high concentrations (0.1–0.5M) with polymeric catalysts. Notably, eight- and nine-membered rings were formed preferentially, even in competition with six- and seven-membered rings. The power of the methodology was highlighted by facile syntheses of numerous naturally occurring macrocycles, including aspochalasin B, antibiotic A26771B, phoracantholides, and recifeiolide. On the 50<sup>th</sup> anniversary of the first synthesis of morphine, Trost reported a short asymmetric synthesis of both codeine and morphine based upon that key reaction. An intermediate in his synthesis also served for an efficient 10 step synthesis of galanthamine, viewed by some as a clinically promising agent for the treatment of Alzheimer's disease. Trost has developed a new paradigm for the synthesis of nucleosides that constitute the basic building blocks of both RNA and DNA, and this has been extended to unnatural nucleosides as well. Practical asymmetric syntheses of the antitumor agent pancratistatin and the glycosidase inhibitors allosamizoline and mannostatin were also produced in his laboratory. The power of the methodology for asymmetric synthesis is highlighted in their use in kinetic resolutions: racemic vinyl epoxides were converted regio- and enantioselectively into basic building blocks like vinylglycidols and vinylglycinols, some of which are being developed into commercial processes. Practical asymmetric syntheses of the powerful PKC antagonist LY333531 and of the anti-AIDS agent tipranavir evolved from this new type of deracemization. The establishment of the relative and absolute stereochemistry of the alkaloid broussonetine G by the synthesis of all possibilities became feasible by the double use of this deracemization. A very short asymmetric synthesis of vitamin E analogues, and of the aflatoxin system evolved from these developments. The ability of these chiral catalysts to control both regio- and enantioselectivity has led to a practical synthesis of calanolide A, an HIV reverse transcriptase inhibitor that is under development for clinical trials, as well as to a flexible synthetic strategy that allowed the syntheses of furaquinocins A, B, and E. These enantioselective catalytic reactions, unlike most asymmetric transition metal catalyzed reactions that form only one type of bond, allow asymmetric formation of many bonds including, but not limited to, C-C, C-N, C-O, and C-S.

There have been numerous attempts to generate asymmetric catalysts for allylic alkylation, but the generality of the Trost catalysts appears unsurpassed. Remarkably, the ability to control enantioselectivity has extended even to the pronucleophile, which has resulted in a practical asymmetric synthesis of quaternary

$\alpha$ -amino acids, a class of biologically important non-natural amino acids, that cannot be synthesized asymmetrically by asymmetric hydrogenation. The sphingofungins which represent a class of highly complex amino acids yield to a simple synthesis by taking advantage of this reaction. The benzomorphans, clinically important analgesics minimizing addictive properties, become readily accessible, enantiomerically pure, for the first time, by combining asymmetric induction in an enolate alkylation with a novel alkene migratory hydroamination. These catalytic procedures are practical and, I understand, are being developed for commercial applications. These catalysts extend their effects beyond enantioselectivity. Notably, they impart rate enhancements, regioselectivities, and diastereoselectivities, including control of olefin geometry. Trost demonstrated that by rationally changing the electronics of the transition metal complex, for example by changing the central transition metal to molybdenum and tungsten, the rules of selectivity can be further altered. The molybdenum allylic alkylation nicely establishes one of the two stereogenic centers of tipranavir, while the remote second one is established by the palladium reaction (*vide supra*), to provide a short practical approach to this important anti-AIDS drug.

Trost developed a new insight into acid-base chemistry when the acid is a proton and the base is a low valent metal. The resulting protonated metal opens up a new class of reactions. In one such process, cyclizations that mirror the related Alder ene reaction can be catalyzed in a fashion that previously was not possible. As a result, not only can reactions be performed as much as 200° lower in temperature, but processes that previously failed, now occur and, most importantly, new pathways become possible by capitalizing on the nature of the intermediates in the catalytic process. For example, 1,3-dienes, not accessible in a thermal process, now become readily available. Streptazolin, a novel antimicrobial and antitumor agent, possesses a very unstable 1,3-diene unit that hampered virtually all of the previous syntheses. The palladium based approach provided the most effective one. Creation of polycyclic systems becomes highly "atom economical" by palladium-catalyzed cycloisomerization followed by Diels-Alder cycloaddition. This metal catalyzed reaction also set the stage for the development of catalytic asymmetric Alder ene type reactions. A new process initiated by this catalyst involves addition of pronucleophiles to allenes. Intramolecular versions provided a remarkably efficient macrocyclization to medium and large rings without resorting to particularly high dilution. A totally new type of process also evolved from this catalyst, in which

coumarins are formed in one step from phenols and acetylenic esters under much milder conditions than classical methods such as the Pechmann reaction. In this case, the carboxylic acid catalyzes the addition of the much weaker acid, the phenol, to palladium(0) to initiate the cycle. One major outgrowth of this concept has been the invention by Trost of a new synthesis of analogs of vitamin D, a process being implemented for a synthesis of one such analog for the treatment of psoriasis.

Trost has established new frontiers for the organic chemistry of ruthenium in the synthesis of organic compounds, and supplied the first examples of catalytic processes involving vinylidene and allenylideneruthenium intermediates. Using cyclopentadienyl-bis-(triphenylphosphine)ruthenium chloride, an allyl alcohol and a terminal alkyne add to each other to form  $\beta,\gamma$ -unsaturated ketones. Switching the catalyst to cyclopentadienyl-1,5-cyclooctadieneruthenium chloride changes the mechanism and the nature of the product. The product is now a  $\gamma,\delta$ -unsaturated ketone that forms via a ruthenacyclopentene intermediate. This latter process becomes the equivalent of a ruthenium catalyzed intermolecular Alder ene type reaction. The outstanding chemical selectivity makes this reaction particularly suitable for the synthesis of complex organic compounds, as illustrated by concise and efficient syntheses of the biologically important acetogenins. The power of this simple, highly atom economical process, is specially notable in complex synthesis. It was used, along with the palladium catalyzed alkyne-alkene addition, in an efficient synthesis of callipeltoside A, and provided the basis for the construction of amphidinolide P in which a conjugated enyne gave exclusive branched regioselectivity to generate a 1,3-disubstituted-butadiene moiety. The process served as a critical part of a synthesis of the antitumor and antiviral mycalamides. The predictability of the synthetic methodology led to the demonstration of the incorrectness of the assumed structure of amphidinolide A, as well as to the deduction of the correct structure, and its ultimate synthesis. Mechanistic reasoning led Trost to combine sequential ruthenium catalyzed alkene-alkyne coupling with palladium catalyzed AAA, five and six membered rings result. The mutual compatibility of the two catalytic reactions allow them to be performed in a single pot. Trost manipulated the ruthenacycle chemistry to develop simple one-step syntheses to important 1,5-dicarbonyl building blocks. In one version, a propargyl alcohol and a vinyl ketone combine to form 2-alkylidene-1,5-dicarbonyl compounds. In another version, a three-component coupling of an alkyne, water, and a vinyl ketone add to each other to form 2-alkyl-1,5-dicarbonyl compounds. From the same ruthenium complex, Trost

discovered an unprecedented type of [2+2+2]cycloaddition of alkynes to 1,5-cyclooctadiene to generate energy rich tricyclo [4.2.2.0]decenes. A second generation ruthenium catalyst expands the scope of these reactions. For example, the addition of an allene and a vinyl ketone provides a synthesis of substituted 1,3-dienes which sets the stage for ring formation by Diels-Alder reactions. A [5+2] cycloaddition to create seven-membered rings proceeds under unusually mild conditions and opens new strategic insights into numerous biological important natural products.

Cycloisomerizations of diyne diols and diyne monools provide easy chemoselective conversions to dienones. A synthesis of the neuroexcitatory amino acid kainic acid which nicely sets all the stereocenters and a simple synthesis of the cylindracenes C, D, and E resulted.

Trost opened a new door in hydrometalation chemistry by the discovery of a direct *trans* hydrosilylation that occurs by a novel mechanism. Complementary selectivities to those seen in the normal *cis* hydrometalation protocol are now obtained in reactions ranging from cross-coupling to cycloadditions. Novel asymmetric approaches to aldol, homoaldol, and bis-homoaldol-type additions via alkyne additions became possible. This hydrosilylation approach to a homoaldol reaction was used in a short synthesis of the alkaloid spectraline.

Trost recently developed a new area of dinuclear zinc catalysts by designing a ligand that leads to such complexes spontaneously. Such bifunctional complexes provide a new dimension in catalyst design – notably for asymmetric catalysis. Direct aldol and Mannich-type reactions proceed chemo-, regio-, diastereo-, and enantioselectively without the need to preform enolates or their equivalents stoichiometrically. For the first time, methyl vinyl ketone has been shown to function in direct asymmetric aldol additions to provide particularly versatile adducts. Methyl alkynyl ketones also function well, and this led to a concise synthesis of the antitumor agent fostriecin. In both cases, other strategies for direct aldol additions of such unsaturated donors fail. The utility of the method, which succeeds when other strategies are unavailable or fail, is illustrated by a short synthesis of the antibiotic boronolide, and demonstrated by an eight step synthesis of a fragment of the proposed structure of amphidinolide A that previously required eighteen steps using asymmetric dihydroxylation. These dinuclear catalysts also effect the asymmetric addition of nitromethane to aldehydes. with very high selectivity.

Barry Trost has had a major impact on our ability to convert simple structures to complex ones, with high selectivity. His wide ranging contributions have

expanded, modified, and even reversed traditional reactivity patterns. These achievements certainly relate to the ability of his group to have contributed many total syntheses (more than 135, I understand) ranging from peptides and nucleosides to terpenes and alkaloids. It is no wonder that his superb and broad ranging accomplishments have placed Barry Trost, according to Thompson ICI, among the most cited chemists in the world. He certainly is one of the most important.

A handwritten signature in black ink that reads "Gilbert Stork". The signature is written in a cursive style with a long, sweeping underline that extends to the left.

Gilbert Stork