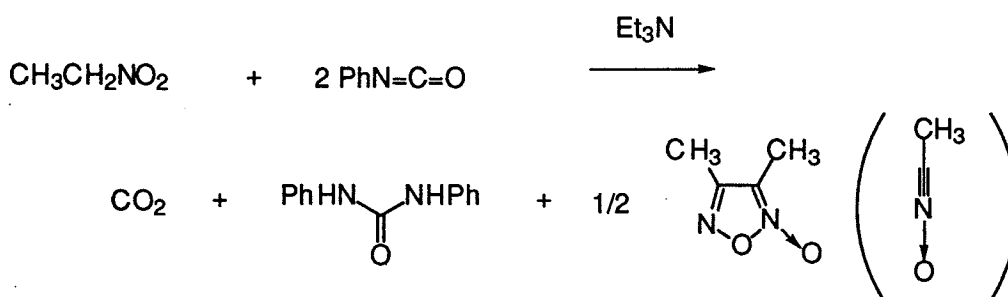


CONTRIBUTIONS OF PROFESSOR MUKAIYAMA IN ORGANIC SYNTHESIS

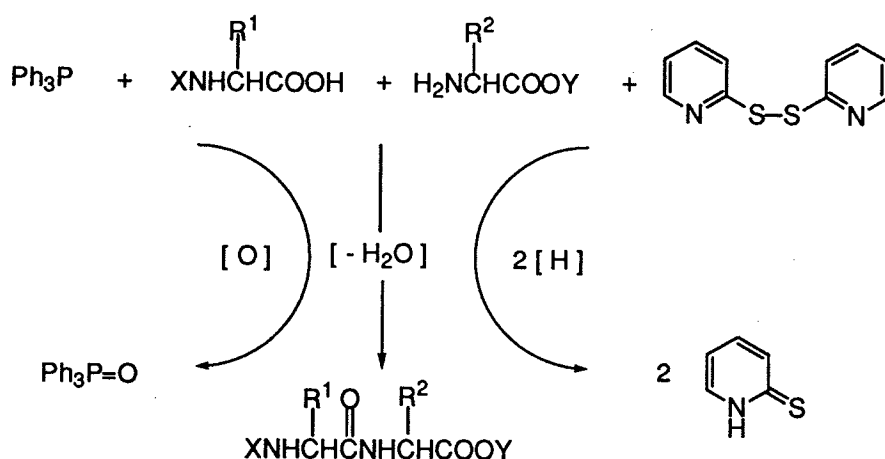
It is my great honor to introduce accomplishments of Professor Mukaiyama's research in this special issue of Heterocycles. Professor Mukaiyama was invited to serve in several universities as Gakushuin University (1953–1958), Tokyo Institute of Technology (1958–1975), The University of Tokyo (1974–1987), Science University of Tokyo (1987–present), or Research Center of Mitsui Petrochemical Company (1987–1995), while most Japanese professors of that time generally spent their academic career confining one or two universities or institutes. Here is briefly summarized his contributions accomplished in those places.

There are two approaches to the research of synthetic organic chemistry: One is to study fundamental subjects and the other is to study targeted subjects. The former is represented as new reaction chemistry, where observation of unexpected phenomena brings important new seeds. The latter, on the other hand, is the orthodox total syntheses of complex molecules, which are completed by repeated discussions and experiments on the unexpected results confronted. In both approaches, Professor Mukaiyama has made great contributions to synthetic organic chemistry.

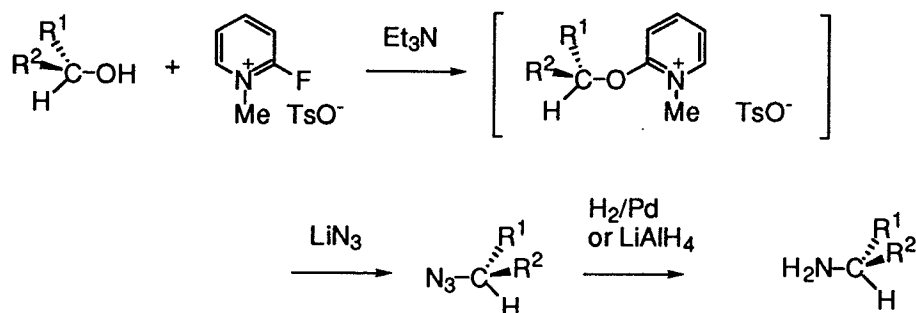
In new reaction chemistry, the key issue is how to find a valuable seed from countless experimental results. Professor Mukaiyama's research on new reaction chemistry started from the intramolecular dehydration of nitroalkanes which was found by chance. During his study on the reaction mechanism of thermal dissociation of urea and urethanes, he came across an unexpected phenomenon. That is, vigorous evolution of CO₂ and rapid precipitates of diphenylurea were observed along with the third product, dimethylfuroxane formed by the dimerization of acetonitrile oxide, when he tried to prepare α -nitropropionanilide by the addition reaction of nitroethane to phenyl isocyanate with a catalytic amount of triethylamine. Based on this finding, a simple method for the generation of alkanenitrile oxides, typical 1,3-dipoles, was established by the dehydration of nitroalkanes with phenyl isocyanate (1960).



With a cue he obtained from this dehydration reaction, he studied extensively the deoxygenation reactions by using trivalent phosphorus compounds after the idea gotten from unexpectedly observed results that trivalent phosphorous compounds acted as strong deoxygenation reagents (1963). Then, the unique oxidation–reduction condensation was developed by the combined use of triphenylphosphine as a reductant and 2,2'-bipyridyl disulfide as an oxidant, where H₂O was removed as 2[H] and [O]. It is completely different from the conventional dehydrating reactions in which H₂O is removed in the form of [H] and [OH] (1970). This condensation has found a wide application to the syntheses of peptides, nucleosides, and macrolides (1972–76).



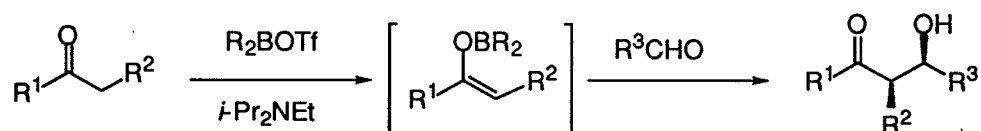
Furthermore, various onium salts of azaaromatics such as 2-halo-1-methylpyridinium salts were designed to carry out the dehydration reaction under neutralizing conditions. Due to their mildness and efficiency, the onium salts have been successfully employed for intra- and inter-molecular dehydration reactions (1975–78).



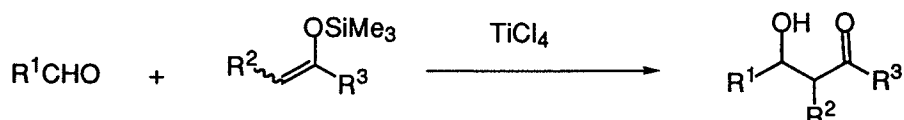
Professor Mukaiyama has established a series of basic methodologies for the construction of carbon-skeletons, particularly for aldol and Michael reactions. In those days, these reactions were generally

performed under basic conditions where "enolate species" were generated as reactive intermediates. In contrast to these commonly employed carbanion chemistry, he developed practical methods in which "enol species" were employed as key intermediates.

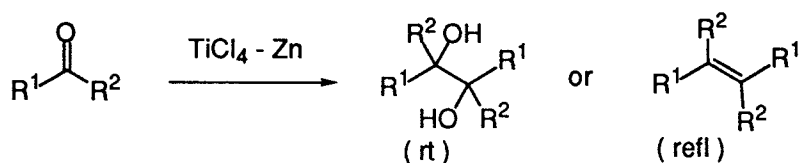
His aldol reaction using vinyloxyboranes was found again through the unexpected phenomena during the study on the reaction of organo-thioboranes and carbonyl compounds. He discovered that vinyloxyboranes generated from alkylthioboranes and ketene reacted with carbonyl compounds under neutral conditions (1971). The alternative convenient procedure was established for the generation of vinyloxyboranes directly from common ketones by treatment with dialkylboryl triflates and tertiary amines. Thus generated vinyloxyboranes reacted smoothly with carbonyl compounds to afford the corresponding aldols in high yields (1976). This method has been widely employed in organic synthesis as a stereoselective C–C bond forming reaction in acyclic systems.



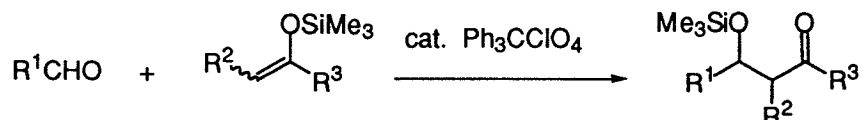
The crossed-aldol and the Michael reactions have been developed by using TiCl_4 as a Lewis acid and vinyloxysilanes as stable enol equivalents (1972–76). These facts demonstrated that, in contrast to the common belief at that time, the reactions under acidic conditions can provide highly selective synthetic schemes.



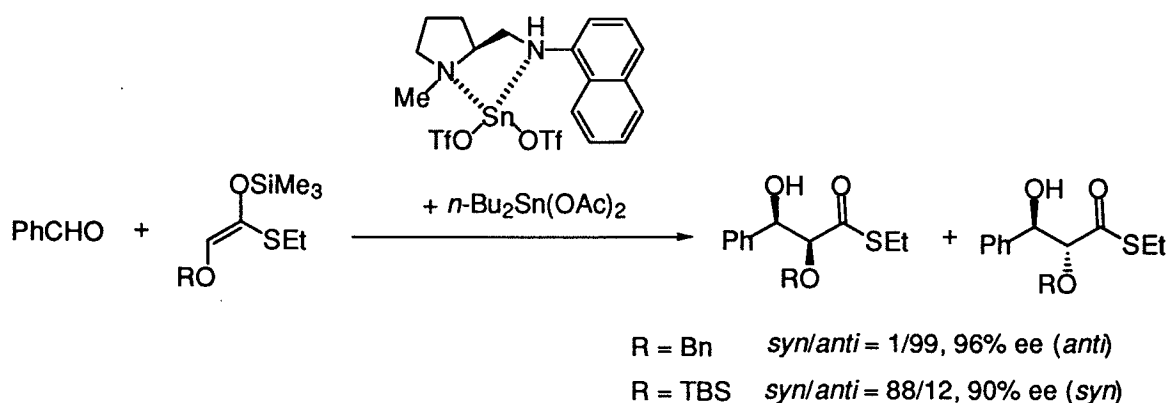
These results stimulated wide interests in the Lewis acid nature of the titanium compounds which are commonly used in current organic synthesis. These studies also made vinyloxysilanes popular as readily available and isolable enol derivatives, and established them as effective carbon nucleophiles indispensable for a variety of modern synthetic activities. Furthermore, several useful functional group interconversions by using TiCl_4 and low valent titanium compounds were also developed (1973).



Subsequently, he showed that trityl salts, represented by triphenylmethyl cation (trityl) perchlorate, can be used as an efficient catalyst in such an aldol reaction of vinyloxysilanes and aldehydes. While the original aldol reaction required a stoichiometric amount of titanium tetrachloride, a catalytic amount of a trityl salt was sufficient to drive the reaction to completion (1984).

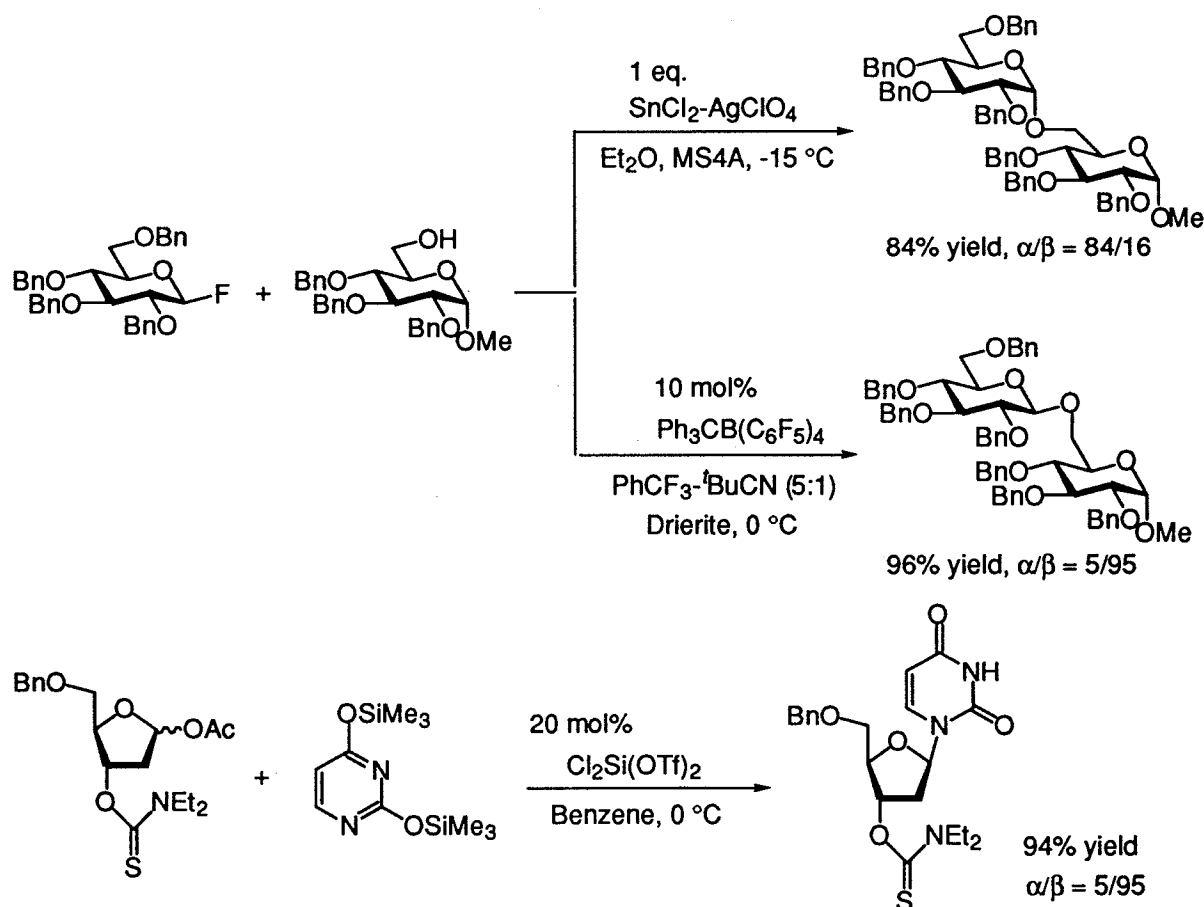


In the area of asymmetric synthesis, he has developed various highly selective and practical asymmetric reactions controlled by metal-coordinated chiral ligands (1977–present). Particularly successful results based on this concept have been found in the stannous triflate-mediated aldol and Michael reactions. Almost complete stereochemical control in both relative and absolute outcome is achieved in these reactions even with the catalytic use of chiral diamines as ligands, starting from both achiral aldehydes and vinyloxysilanes (1991). The enantioselective aldol-type reactions have been successfully extended to the synthetic method of various *natural* and *unnatural* monosaccharides (1991–1994).



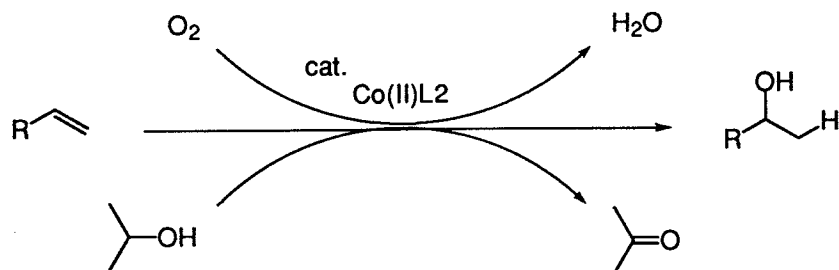
Professor Mukaiyama has pursued fresh approaches toward the exploration of various stereocontrolled reactions. For example, concerning glycosylation reactions, the stereoselective formations of both 1,2-*cis* and *trans* glycosides have been achieved. Especially, introduction of 1-fluoro sugars as stable glycosyl donors has realized an efficient method for the preparation of 1,2-*cis*-glycosides (1981), and since then, 1-fluoro sugars have been commonly used for the development of the modified glycosylation reactions. He succeeded in developing new catalytic and stereoselective glycosylation of silyl ethers with 1-*O*-acyl carbohydrates by using the combined-catalyst system (for example, $\text{SnCl}_4 - \text{AgClO}_4$), in which the stereoselectivity is well controlled by the choice of the catalysts, solvents, and

neighboring groups (1992–present).

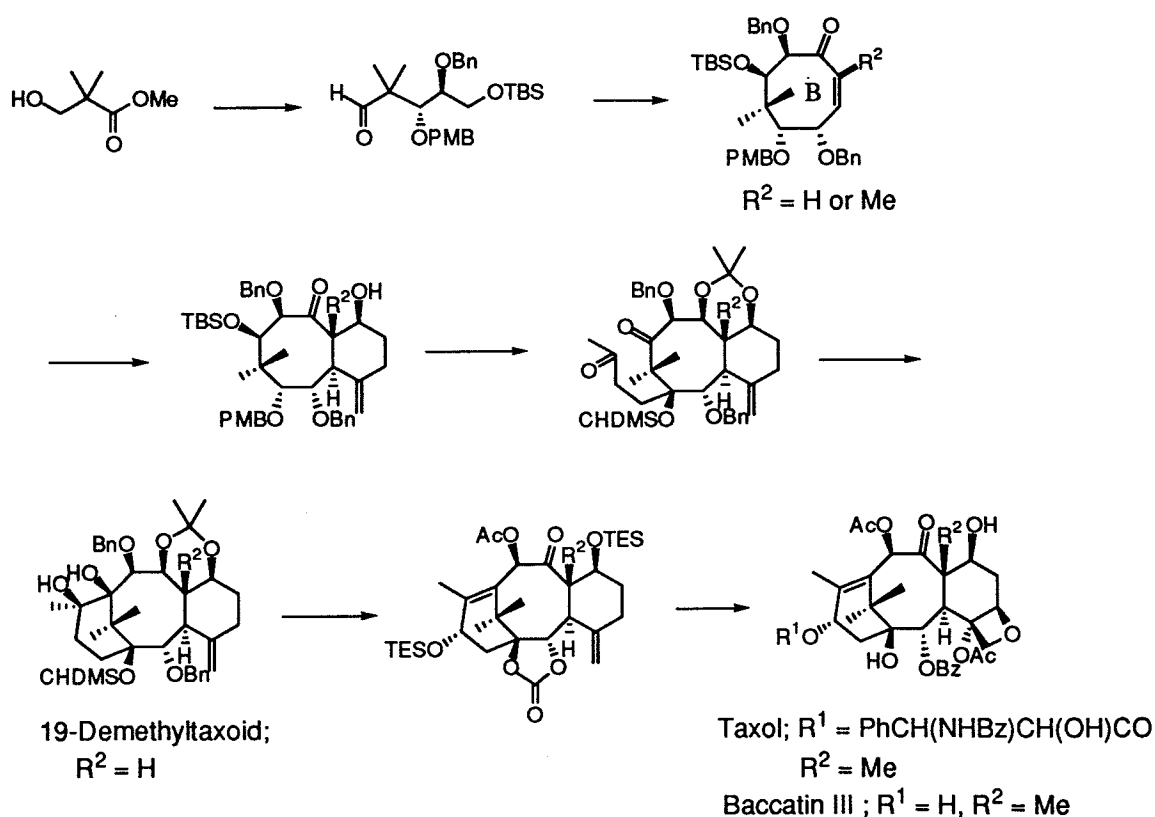


A quite new-type of glycosylation reaction was also exploited starting from both glycosyl donors and alcohols with free hydroxy groups to afford the corresponding glycosides in high yield with high selectivity. For example, each of α and β furanosides can be prepared stereoselectively by using triphenylmethylm tetraakis(pentafluorophenyl)borate as a catalyst in nitropropane and with $\text{LiN}(\text{Tf})_2$ in dichloromethane, respectively.

The study of metal-complex catalysts that allow one to control reactivity and regioselectivity by the judicious choice of their ligands would be of particular interest. Therefore, he initiated the study on the oxygenation of olefins with molecular oxygen using a catalytic amount of metal complex containing 1,3-diketone ligand, leading to the development of cobalt(II)-catalyzed oxidation–reduction hydration, catalytic peroxygenation, and nickel(II)-catalyzed epoxidation (1987–1995).



Recently, for the first time in over 40 years of his research on the exploration of new synthetic methods, Professor Mukaiyama turned his eyes on the targeted subject, the asymmetric total synthesis of taxol, an antitumor agent currently most anticipated and calls attention of many synthetic chemists. Based on the strategy of constructing the taxol skeleton in the order of B(8-membered)-C-A rings, he succeeded in synthesizing the skeleton by using his own asymmetric and stereoselective aldol reactions and the titanium-mediated coupling reaction. After the arrangement of functional groups, baccatin III having the basic taxol structure was prepared. He also developed an efficient method to introduce *N*-benzoyl-phenylisoserine to baccatin III and completed the total synthesis of taxol within five years (1992–97).



Thus Professor Mukaiyama has undoubtedly created many original and useful synthetic methods through his unique approaches based on his intuitive concepts. Because of their versatility, many reactions developed by him have found wide applications in organic synthesis and have been successfully employed by a number of organic chemists as key steps in the syntheses of complex molecules. More importantly, his pioneering contributions have stimulated further developments of useful synthetic methodologies and have been refined by many chemists, which clearly indicate his strong influence in the sphere of synthetic organic chemistry.



Koichi Narasaka

Department of Chemistry, School of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan