HETEROCYCLES, Vol. 97, No. 1, 2018, pp. 4 - 6. © 2018 The Japan Institute of Heterocyclic Chemistry
DOI: 10.3987/COM-18-S(T)Foreword_2

PREFACE TO HETEROCYCLES ISSUE HONORING THE 70TH BIRTHDAY OF PROFESSOR DR. KIYOSHI TOMIOKA: LIFE-LONG APPRECIATION FOR CHEMICAL BOND FORMATIONS

It is truly my great honor and pleasure to contribute this short essay to celebrate Professor Tomioka's 70th birthday. I first encountered Professor Tomioka in the Department of Pharmaceutical Sciences at the Hongo campus of The University of Tokyo when I was an undergraduate student 30 years ago. I still remember very clearly what he said in the first lecture of the fundamental organic chemistry course: although it is simple to draw a single chemical bond on the blackboard, remember how difficult it is to actually create a chemical bond and that an enormous number of people have worked tirelessly to achieve chemical bond-formation. Now I have a much deeper understanding of what he meant. At that time, I never imagined that he would become my life-long mentor. Today, I often quote the same phrase to my students in the remodeled lecture hall in the same department.

As an undergraduate student, I intended to enter a biology lab. The biology labs were very popular, however, and I was forced to enter the laboratory of the late Professor Koga in which Professor Tomioka was *the* associate professor. At the time, I thought myself very unfortunate because I had not studied organic chemistry very hard before entering the lab. It proved to be the most fortunate turning point in my life! Professor Tomioka was very strict in every sense of the word. My project through my undergraduate and master courses was the total synthesis of dolastatin 10,[1] a peptidic anticancer agent containing unnatural amino acids isolated by Pettit and coworkers in 1987.[2] Everyday we discussed my progress based on the raw data, including ^{1}H NMR and TLC. Specifically, it was extremely difficult to create an O–CH_3 bond from the γ-amido-β-hydroxy ester units in dolastatin 10 (Dil and Dap units). β-Elimination proceeded easily to afford γ-amido-α,β-unsaturated esters under all of the previously reported *O*-methylation methods. Indeed, it was the first and last time I used thallium ethoxide, which is extremely toxic, and the synthesis using the reagent was a total failure. During this project, I realized that successfully creating a chemical bond in the real world, and not just on the blackboard, is really a kind of magic. Finally, we solved the problem by using a highly reactive methylating reagent, MeOTf. Rapid trapping of the lithium alkoxide anion of the starting materials by the highly reactive methylating reagent in the presence of HMPA at precisely –20 °C was critical. In this method, the *O*-methylated products did not coexist with

the starting alkoxide acting a base, leading to suppression of the problematic β-elimination. Professor Tomioka termed the method "rapid methylation". Although I was not fully satisfied with this ordinary name, I learned a lot from this single step. Professor Tomioka was patient enough to give me the time required for discovery, while always reminding me to run the frontline optimization studies in milligram scale in parallel with the scaled-up synthesis of the frontline materials in kilogram scale.

In addition to learning practical experimental techniques and how to promote specific research projects, I also learned from Professor Tomioka that science is an activity to construct new concepts. He conceived and proposed the concept of *pseudo*-chirality of heteroatoms in chiral ligands for organolithium reagents and lithium enolates.[3] With Professor Shindo, the ace student in Professor Tomioka's subgroup at that time, he developed a dimethoxyethane-analog chiral ligand and various asymmetric C–C bond formations using the ligand. The chiral ligand is very simple and beautiful. People might think that the ligand structure reflects Professor Tomioka's intelligence. I believe that the ligand design is due not only to his deep intelligence, but also to his thorough and complete dedication to chemistry–24 h a day, 365 days a year. He designed and studied a very potent anti-cancer agent, aza-podophyllotoxin, containing a nitrogen atom that substituted for a chiral carbon atom.[4] The synthesis and biologic evaluation of those natural product analogues should be considered a foundation for the design of the chiral ligand. In this sense, his life-long research is a symphony masterpiece comprising several elements that harmonize with each other.

Professor Tomioka will celebrate his second retirement this year—his first was from Kyoto University and his second is from Doshisha Women's College. I sincerely congratulate him on his life-long success as a researcher and a mentor. My wish is that he maintains both his health and humor far into the future.

REFERENCES

1. K. Tomioka, M. Kanai, and K. Koga, *Tetrahedron Lett.*, 1991, **32**, 2395.
2. G. R. Pettit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczynskyj, K. B. Tomer, and R. J. Bontems, *J. Am. Chem. Soc.*, 1987, **109**, 6883.
3. K. Tomioka, M. Shindo, and K. Koga, *J. Am. Chem. Soc.*, 1989, **111**, 8266.
4. K. Tomioka, Y. Kubota, and K. Koga, *Tetrahedron Lett.*, 1989, **30**, 2953.

Motomu Kanai
Professor
The University of Tokyo

Motomu Kanai was born in 1967 in Tokyo, Japan, and received his bachelor degree from The University of Tokyo (UTokyo) in 1989 under the direction of the late Professor Kenji Koga. In the middle of his PhD course in UTokyo (in 1992), he obtained an assistant professor position in Osaka University under the direction of Professor Kiyoshi Tomioka. He obtained his PhD from Osaka University in 1995. Then, he moved to University of Wisconsin, USA, for postdoctoral studies with Professor Laura L. Kiessling. In 1997, he returned to Japan and joined Professor Masakatsu Shibasaki's group in UTokyo as an assistant professor. After doing lecturer (2000~2003) and associate professor (2003~2010), he is currently a professor in UTokyo (since 2010). He acted as the PI of ERATO Kanai Life Science Project (2011~2017) and is acting as the PI of "Hybrid Catalysis" Grant-in-Aid for Scientific Research on Innovative Areas by JSPS (2017~2022). He has received The Pharmaceutical Society of Japan Award for Young Scientists (2001), Thieme Journals Award (2003), Merck-Banyu Lectureship Award (MBLA: 2005), Asian Core Program Lectureship Award (2008 and 2010, from Thailand, Malaysia, and China), Novartis Lecturer in Organic Chemistry (2011), and Thomson-Reuters The 4th Research Front Award. His research interest is the development of catalysts.