RETROSPECTIVE

Ei-ichi Negishi 1935–2021: The carbon–carbon bond-maker

James M. Tour[a,1]

Prof. Ei-ichi Negishi, winner of the 2010 Nobel Prize in Chemistry, died on June 6, 2021 at age 85. He died of pneumonia following surgery. He was surrounded by his two daughters and their families, his caregiver, and a minister. As his daughter, Charlotte Negishi East, wrote to me, "It was a beautiful time. . .read[ing] scripture from [the] Japanese Bible and. . . such meaningful songs and prayers, many stories about our father- . . .some were very funny, and we were able to laugh during this extremely sad time. . .until he died peacefully surrounded by loved ones."

Prof. Negishi was born July 14, 1935, in what is now Changchun, China, while at the time of his birth it was called Hsinking. That was the capital of the Japanese occupied territory of Manchukuo. His family eventually moved to a town outside Tokyo after World War II, where his parents were farmers raising their five children. Although academically unmotivated as a child, Negishi's abounding competitive spirit caused him to battle for the top academic spot in his school, just out of his passion to excel over others. That opened the door for him to attend the University of Tokyo. Negishi was then awarded a Fulbright scholarship in 1958 to study at the University of Pennsylvania, where he received his doctorate in 1963 doing organosulfur chemistry. Negishi was a postdoctoral fellow at Purdue University under Prof. H. C. Brown, who later received the 1979 Nobel Prize in Chemistry for the hydroboration reaction. Brown was the only mentor that Negishi ever mentioned. The two became close friends and Negishi modeled his own chemistry around the methodical approach that he learned from Brown.

Negishi received his first academic appointment at Syracuse University. I met him in the fall of 1978 when he was designated to teach my sophomore undergraduate organic chemistry class. And that is where I was convinced that I would no longer seek a career in forensic science, but would become a synthetic organic chemist. Prof. Negishi, whom I would never dare to call by his first name, was like the guide holding my hand as I beheld the Grand Canyon for the first time. From his first lecture, starting with "CHONXS," the elements of organic chemistry, through the second semester of synthesis, I loved that class. I found myself working every problem, just for fun, at the end of each chapter in Ternay's *Contemporary Organic Chemistry* (1).

Ei-ichi Negishi receiving the news that he had won a share of the 2010 Nobel Prize in Chemistry. Image credit: Purdue University.

As a young professor at Syracuse University in 1977, Negishi discovered the palladium-catalyzed cross-coupling reaction to join two carbon atoms together. While the reaction was kinetically optimal when using an organozinc reagent as the nucleophile (referred to now as the "Negishi reagent" or the "Negishi reaction"), he was also the first to explore the use of organo-boron, tin, aluminum, magnesium, and more, as the nucleophiles in these reactions. This discovery in his years at Syracuse became the basis for his receipt of the 2010 Nobel Prize in Chemistry. Around the same time, he also discovered the zirconium-catalyzed carboalumination reaction, which placed an angular methyl group across a terminal alkyne with high regio- and stereoselectivity. These were then nicely activated by the resulting alkenylaluminum reagent to participate in the palladium-catalyzed cross-coupling to generate the terpenoid series of natural products. Terpenes are a very broad class of natural products and they constitute portions of many pharmaceuticals. Negishi then moved to Purdue University in 1979, where he would spend the remainder of his career, mapping out the scope of these

[a]Department of Chemistry, Rice University, Houston, TX 77005

Author contributions: J.M.T. wrote the paper.
The author declares no competing interest.

[1]Email: tour@rice.edu.

Published August 27, 2021.

carbon–carbon bond-forming reactions. Before leaving Syracuse, Prof. Negishi asked me to consider working for him in graduate school at Purdue upon my graduation from Syracuse. I did, joining his group in 1981.

The power of this palladium-catalyzed cross-coupling chemistry is immense. One would be hard-pressed to find a natural product synthesis or conjugated polymer synthesis that does not have a palladium-catalyzed cross-coupling step in it. This opened the door to the delivery of many new molecules that were formerly inaccessible. Natural products and compounds of pharmaceutical interest started to be made by the dozens based upon this carbon–carbon coupling method. Palladium, being nontoxic, was an especially welcomed catalyst in the pharmaceutical industry. Like a craftsman, Negishi mapped out the detailed methods needed to join all the pairs of coupling partners that a synthetic chemist might seek: aryl-aryl, aryl-alkenyl, aryl-alkynyl, and so forth. That is what provided such generality to the use of this Negishi methodology.

Prof. Negishi was a demanding advisor. I recall one day near the end of my time in graduate school. I asked him when I could cease laboratory work and start writing my thesis because my post doctorate would be starting soon. Negishi told me that "A good student should not need more than two weeks to write their thesis." I was shocked and visibly upset. He looked at me (although I did not look back at him) and said, "Jim, I assure you that life will only get harder." In this day where our comments to students need to be more tactful, it is enlightening to reflect on the value of that intense training. Prof. Negishi was unapologetic in his driving of a graduate student. It was good training. And yes, life often got harder.

At the same time, Prof. Negishi had an amazingly open door. When I would go to his office to ask a question, as brief as it might be, he would always invite me to sit down for longer than I had planned. Then he would analyze the state of my doctoral pursuits while giving me his thoughts on career and life. On one occasion, he told me that it would be hard to have a well-funded academic career making natural products and that I should redirect my future independent career to using my synthetic skills for either bioorganic chemistry or the chemistry of materials science. I listened, making a dedicated effort to pursue the latter.

Prof. Negishi would often take the group out to dinner at a local Chinese restaurant or to dinner gatherings at his home. We were greeted most warmly by him and his wife. His competitive streak was apparent in everything, from croquet to ping pong to karaoke singing; he was a good singer. He wanted to win in everything. That, too, was good training. I learned much from him. We all did.

When it came to chemistry, Prof. Negishi would tell us that we had to work fast lest we "get scooped." He would say that, "If you're thinking about something, be sure that someone else in the world is thinking about it also. So, you'd better work fast." Competition was part of the lifeblood in the group. To that end, he would often reflect upon the Nobel Prize and what it would take to receive that high honor. He mused and strove for it. He talked about it, worked toward it, and eventually received it.

Upon receipt of the Nobel, he shared that joy with all. I recall at a dinner in 2011 shortly after his receipt of the prize, Negishi opened up his wallet and protruding was the actual Nobel medallion. It was not the copy, but the actual award in solid gold. He passed it around the table in the restaurant for all the guests to hold. It had an obvious dent on the edge, and he said that the last time he passed it around somebody dropped it on the ground and it bent. But he laughed it off. We all laughed.

I miss him. But his training and intensity remains with me, and I pass those on to my students.

1 A. L. Ternay, *Contemporary Organic Chemistry* (W. B. Saunders, 1976).