Unique Physicochemical and Catalytic Properties Dictated by the B_3NO_2 Ring System

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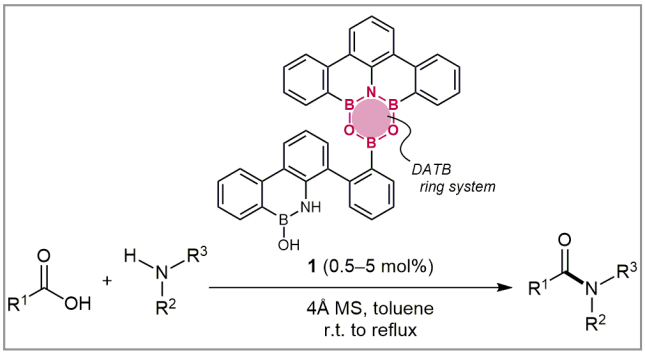
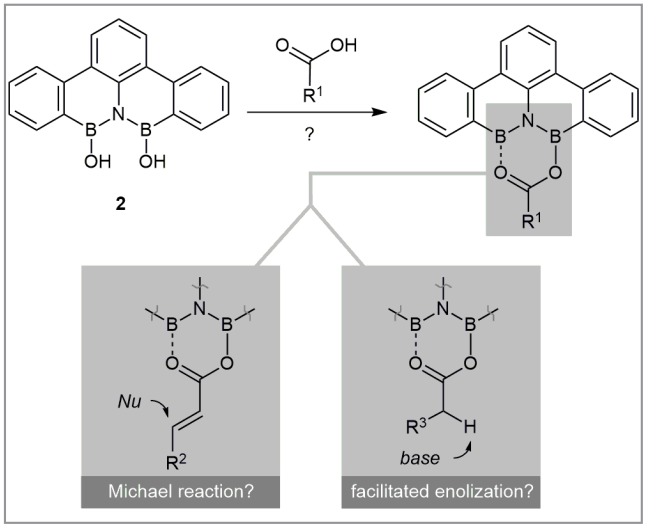
Amidation is one of the most used organic transformations for the synthesis of pharmaceuticals, functional polymers (e.g. nylon, Kevlar), and agrochemicals. However, there remains much scope for improvement of state-of-the-art amidation methodology. Although reagent-driven amidation has been well advanced to reliably access a myriad of amide-functionalized molecules, this methodology contains an inherent drawback, namely the co-production of unwanted reagent-derived waste. The development of a catalytic alternative is an obvious solution but has witnessed slow progress and suffers from severely limited substrate generality and insufficient catalytic activity. An amidation catalyst powered by broad and general scope, as well as featuring high catalytic activity, would have the potential to be widely adopted in academia and industry.



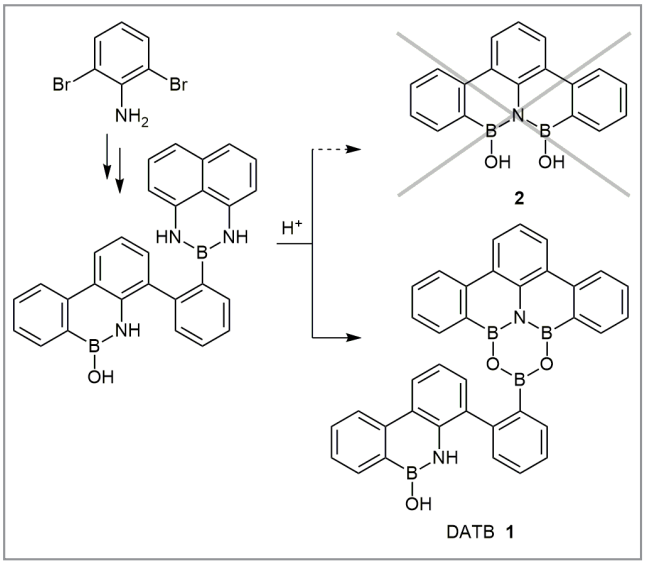
Scheme 1 Catalytic dehydrative amidation promoted by DATB catalyst **1**

Recently, a Japanese team led by Professor Masakatsu Shibasaki and Dr. Naoya Kumagai at the Institute of Microbial Chemistry (Tokyo, Japan) discovered a non-metallic catalyst **1** characterized by a six-membered B_3NO_2 heterocyclic core coined DATB (1,3-dioxa-5-aza-2,4,6-triborinane), which proved to be a highly effective catalyst for dehydrative amidations (Scheme 1). Dr. Kumagai said: "Originally, we were not specifically aiming to develop an amidation catalyst, but rather were eager to synthesize a powerful activator for the carboxylic acid functional group. It was serendipitous that we identified DATB catalyst **1** and got deeply involved in its chemistry, as is the case for a number of fascinating discoveries. We envisioned that a compound having two boron atoms in a suitable spatial arrangement, as in compound **2**, could doubly activate carboxylic acids via two-fold B–O interactions, anticipating that the Michael reaction or facilitated enolization could proceed (Scheme 2). A postdoctoral fellow – Dr. Makoto Furutachi – tackled the synthesis of **2**, but the compound he managed to isolate was a frustratingly insoluble material with a complicated ^{1}H NMR spectrum in DMSO-d_6, which made it impossible to elucidate the structure. Being a highly dedicated experimentalist who remained devoted to the task, Dr. Furutachi was eventually rewarded with a crystal structure revealing the pseudodimeric structure of DATB **1** (Scheme 3)." Dr. Kumagai continued: "However, we were not crafty enough to find any utility of this peculiar heterocyclic compound, as it is not soluble in common organic solvents and all attempts at opening the B_3NO_2 ring system to achieve the initial target (compound **2**) met with failure."

Dr. Kumagai recalled: "Roughly one and a half years had passed since the first identification of **1** before we discovered a particular use for the compound. At that time, Dr. Furutachi had already left to continue his academic career at a different institution. Taking notice of a paper introducing direct

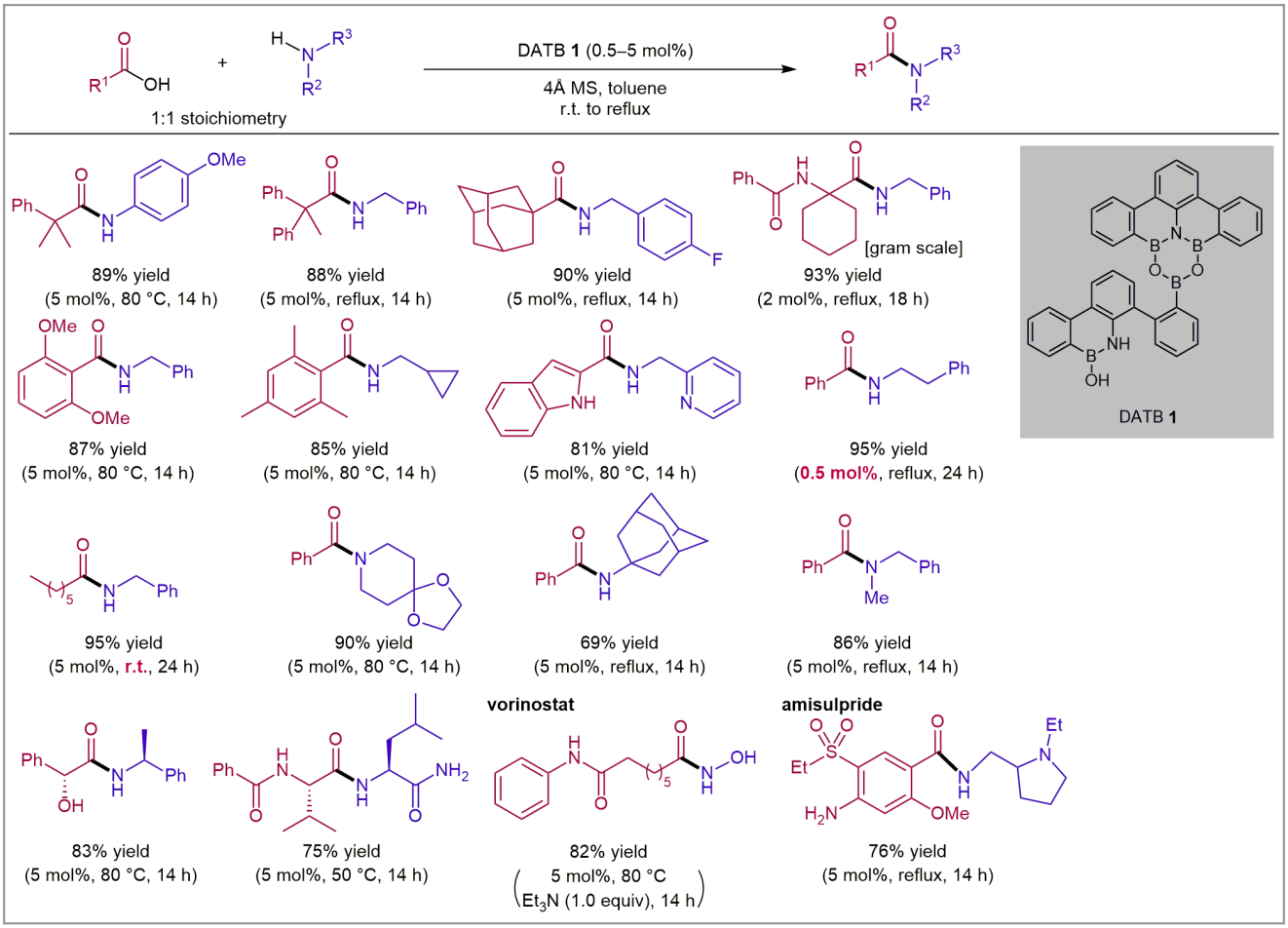


Scheme 2 Initial blueprint of the utility of diboronic compound **2**



Scheme 3 Unexpected formation of DATB **1**

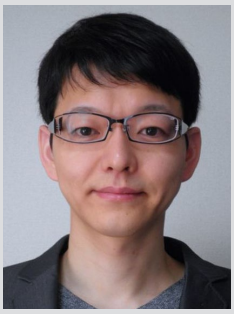
dehydrative amidation in a cooperative catalytic system led us to re-evaluate compound **1**, which lay dormant in a freezer. Back then we were mainly working in the field of C–C bond-forming reactions, thus amidation was a bit out of our focus. But we anticipated that a small fraction of **1** might have a chance to open up to **2** in the reaction mixture, giving a template to strongly activate carboxylic acids for amidation. We selected a bulky acid for the initial trial, which was considered an intractable substrate for catalytic amidation, and this initial trial just worked beautifully." He remarked: "With this finding in hand, a postdoc – Dr. Hidetoshi Noda – and a skilled technician – Ms. Yasuko Asada – conducted a series of experiments, which clearly demonstrated that DATB **1** outperformed other known amidation catalysts in terms of substrate generality and high catalytic activity (Scheme 4). True mechanistic pathway is still under intense investigation; however, we are at least sure that the DATB core of **1** does not open during the reaction – again, the initial expectation was incorrect."



Scheme 4 Selected examples of direct amidation promoted by DATB **1**

Dr. Kumagai concluded: “We keep actively working on this catalytic system. Detailed DFT calculations and kinetic experiments are shedding more light on the distinct mode of action operative in DATB catalysis, where multiple boron atoms are likely to be involved. Better mechanistic understanding will lead us to rationally design a second-generation DATB catalyst with enhanced catalytic activity. We envision that these continuing studies will lead to practical catalytic alternatives, eventually replacing the conventional reagent-driven amidation protocols, covering the synthesis of a wide variety of amide-containing compounds including peptides.”

About the authors



Dr. H. Noda

Hidetoshi Noda was born and raised in Tokyo (Japan). He graduated from The University of Tokyo (Japan), where he conducted his bachelor's and master's research in the group of Professor Masakatsu Shibasaki. After three years of experience in industry, he moved to Switzerland to pursue his doctorate with Professor Jeffrey W. Bode at ETH Zurich. In 2015, he obtained his Dr. Sc. and joined the Institute of Microbial Chemistry, Tokyo (Japan) as a JSPS fellow. In 2017, he obtained tenure at the same institute.

Dr. M. Furutachi

Makoto Furutachi was born in Saga (Japan) in 1985. He received his bachelor's degree from Fukuoka University (Japan) in 2008 with Professor Junei Kinjo, his master's degree from The University of Tokyo (Japan) in 2010 with Professor Masakatsu Shibasaki, and his PhD from the same university in 2013 with Professor Motomu Kanai. He was a postdoctoral fellow at the Institute of Microbial Chemistry, Tokyo (Japan) in 2013 – 2015 with Professor Masakatsu Shibasaki, and has been an assistant professor at Fukuoka University since 2015 with Professor Kunihiro Sumoto. His current research interest is medicinal chemistry.

Y. Asada

Yasuko Asada graduated from Kitasato University (Japan) in 1994 and worked as part of the technical staff in research laboratories at Sagami Chemical Research Center (Japan). With her expertise in organic synthesis, she joined several research units to support and facilitate research activities in both academia and industry. From 2014, she settled in the Institute of Microbial Chemistry, Tokyo (Japan) where she is currently working as a technician.

Prof. M. Shibasaki

Masakatsu Shibasaki received his PhD from The University of Tokyo (Japan) in 1974, under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University (USA). In 1977, he returned to Japan and joined Teikyo University as an associate professor. In 1983, he moved to Sagami Chemical Research Center (Japan) as a group leader, and in 1986, he assumed a professorship at Hokkaido University (Japan) before returning to The University of Tokyo as professor in 1991. He is currently Director of the Institute of Microbial Chemistry, Tokyo (Japan). He has received several prestigious awards, including the Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (Tetrahedron Chair, 1998), the Pharmaceutical Society of Japan Award (1999), the ACS Award (Arthur C. Cope Senior Scholar Award, 2002), the National Prize of Purple Ribbon (2003), the Japan Academy Prize (2005), the ACS Award for Creative Work in Synthetic Organic Chemistry (2008), the Centenary Medal and Lectureship (2008), the Prelog Award Medal (2008), the Special Award, the Society of Synthetic Organic Chemistry, Japan (2010), the Noyori Prize (2012), and others. His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.

Dr. N. Kumagai

Naoya Kumagai was born in 1978 and raised in Ibaraki (Japan). After receiving his PhD in pharmaceutical sciences at The University of Tokyo (Japan) in 2005, under the supervision of Professor Masakatsu Shibasaki, he pursued postdoctoral studies in the laboratory of Professor Stuart L. Schreiber at Harvard University (USA) in 2005 – 2006. He moved back to Professor Shibasaki's group at The University of Tokyo as an assistant professor in 2006. He is currently a Chief Researcher at the Institute of Microbial Chemistry, Tokyo (Japan). He is a recipient of the Pharmaceutical Society of Japan Award for Young Scientists (2010), Banyu Chemist Award (2012), and Mitsui Chemicals Catalysis Science Award of Encouragement (2014). His research interests include the development of new methodologies in catalysis and their application to bioinspired dynamic processes.

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