

# Chemoselective Boron-Catalyzed Nucleophilic Activation of Carboxylic Acids for Mannich-Type Reactions

*J. Am. Chem. Soc.* **2015**, *137*, 7075–7078

The carboxyl group (COOH) is a ubiquitous chemical function present in a very large number of compounds essential for life itself – such as amino acids and fatty acid derivatives – as well as in countless bioactive molecules, natural compounds and drugs. The development of efficient methods for achieving the structural modification and homologation of carboxylic acid derivatives without requiring the use of protecting groups continues to attract a great deal of interest in organic chemistry. In particular, novel carbon–carbon bond-forming reactions allowing for a stereocontrolled and direct functionalization of carboxylic acids are in great demand.

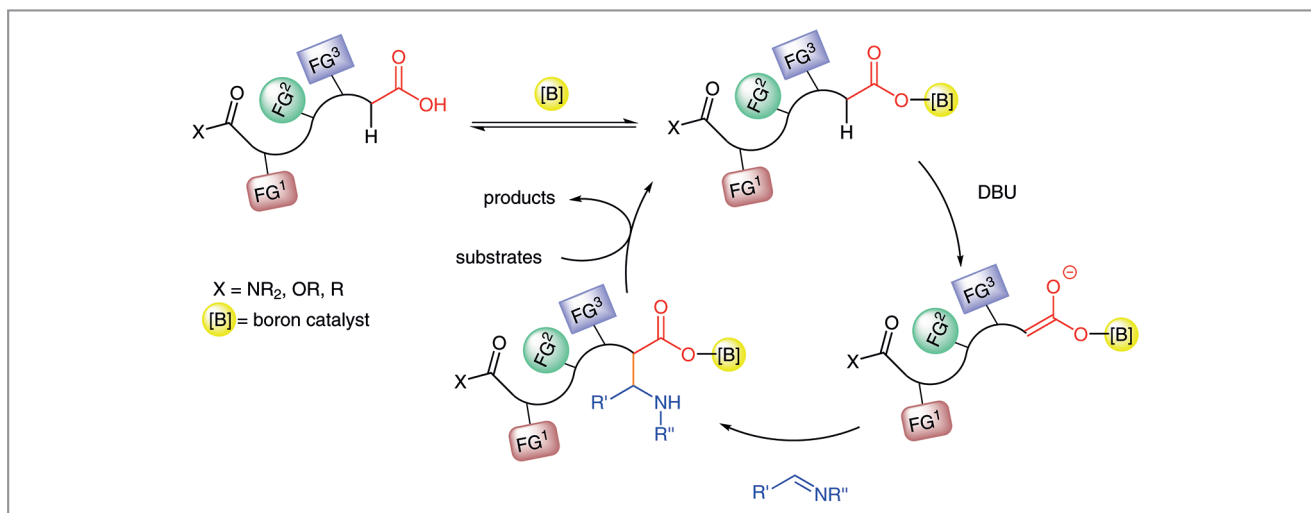
Recently, the group of Professor Motomu Kanai at The University of Tokyo's Graduate School of Pharmaceutical Sciences (Japan) has developed a method for generating carboxylic acid derived enolates under mild conditions, and extended this method to the first carboxylic acid selective catalytic Mannich-type reaction. "The carboxyl group is ubiquitous in organic molecules, especially in biologically active lead drug molecules," said Professor Kanai. "Its Brønsted acidity is among the highest in naturally occurring molecules. Therefore, carboxyl groups can be chemoselectively recognized by a Brønsted base catalyst even in the presence of multiple functional groups. However, use of carboxylic acids as carbon

nucleophiles has been limited due to the difficulty in generating dianionic enolates."

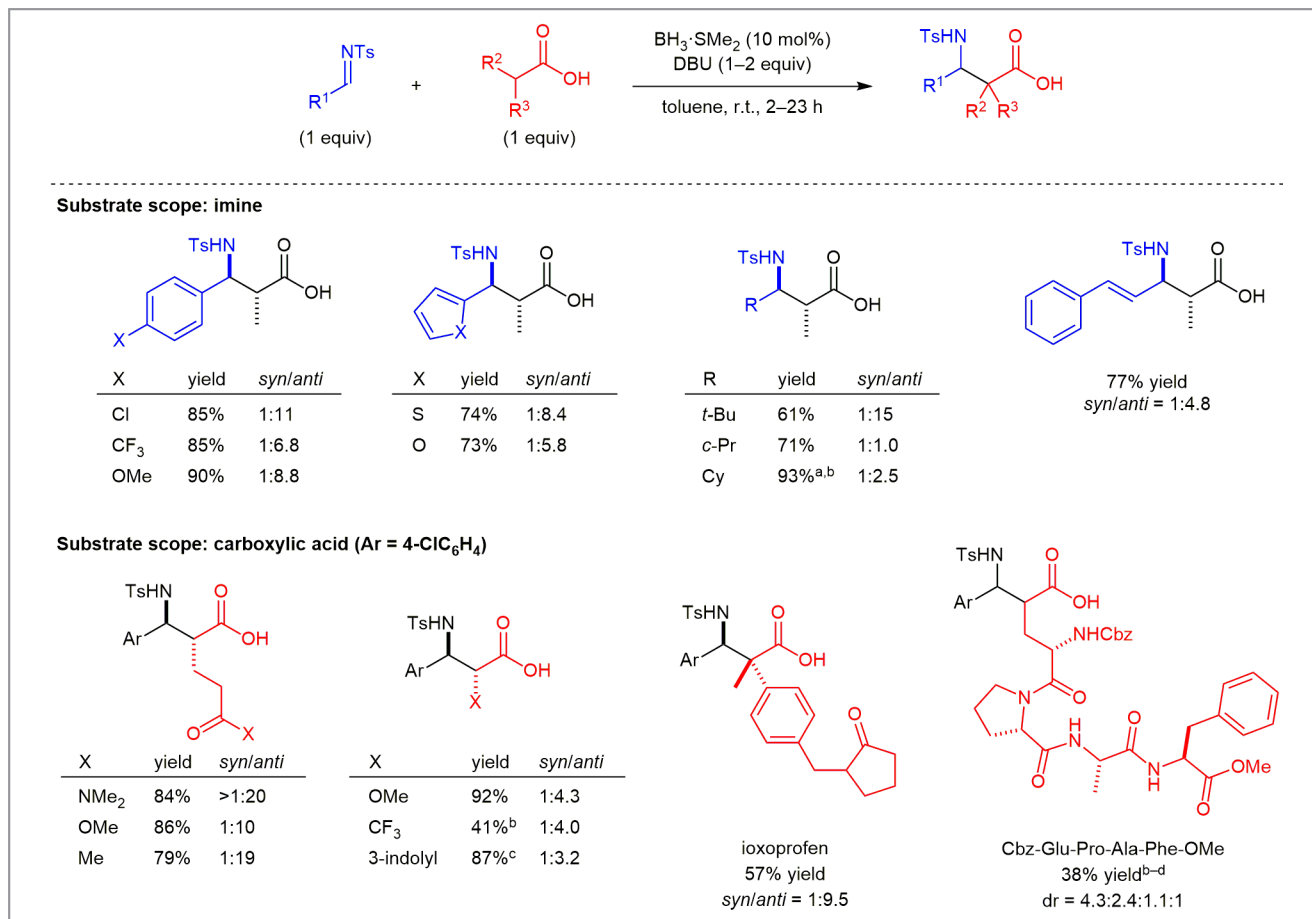
Professor Kanai explained: "A reversible acid/base covalent interaction between carboxylic acids and a simple boron catalyst (precatalyst =  $\text{BH}_3\cdot\text{SMe}_2$ ) acidified the  $\alpha$ -protons, so that a mild organic base, DBU, was able to deprotonate the activated substrate, thus generating the corresponding carboxylic acid enolates." He continued: "The catalytically and chemoselectively generated enolates from carboxylic acids were trapped by *N*-tosyl imines through Mannich-type reaction."

According to Professor Kanai, there are two main aspects worthy of note in this catalysis: (1) chemoselectivity (Scheme 1), since carboxylic acid enolates were generated even in the presence of intrinsically more enolizable ketone, ester, and amide functionalities; an impressive entry in this aspect is a successful application to side-chain modification at a glutamic acid residue of a tetrapeptide, and (2) enantioselectivity (Scheme 2), as shown by the fact that introduction of a BINOL-derived chiral ligand to the boron catalyst afforded a highly enantioselective Mannich-type reaction of carboxylic acids.

Professor Kanai said: "We now know that chemoselective (chiral) enolate formation is possible from carboxylic acids by action of a boron catalyst and an organic base. Thanks to



**Figure 1** Plausible catalytic cycle of boron-catalyzed Mannich-type reaction of carboxylic acids



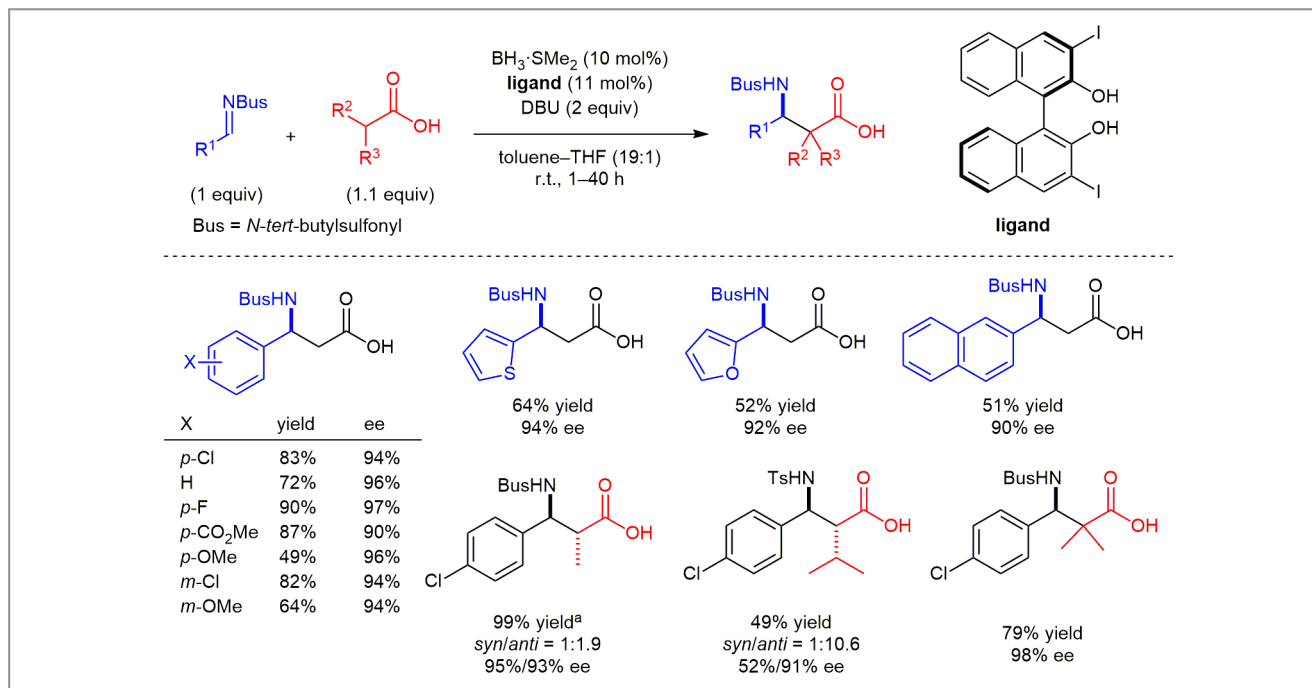
**Scheme 1** Representative examples of the boron-catalyzed Mannich-type reaction of carboxylic acids. Isolated yields and diastereomeric ratios were determined after conversion of the Mannich products into methyl esters. <sup>a</sup> 20 mol% of BH<sub>3</sub>·SMe<sub>2</sub> was used. <sup>b</sup> 2.0 equiv of imine were used. <sup>c</sup> THF was used as solvent. <sup>d</sup> 33 mol% of BH<sub>3</sub>·SMe<sub>2</sub> was used.

the wide scope of enolate chemistry, our catalytic method can find many extensions.” He continued: “As a future direction, we are especially interested in the late-stage catalysis to diversify complex molecule structures at their carboxyl groups, including biologically active peptides and functional proteins, by taking advantage of the high chemoselectivity of the boron catalysis.”

For many conceivable future directions, however, elucidation of the active enolate structure is the first priority for the group. “This will allow us to design more sophisticated catalysts for expansion of potential applications,” explained Professor Kanai. “More broadly, we need to develop more comprehensive protecting-group-free catalytic processes as well as isolation processes.” In Schemes 1 and 2, the Tokyo-based researchers isolated the products after protection of the carboxylic acids as esters. However, Professor Kanai remarked:

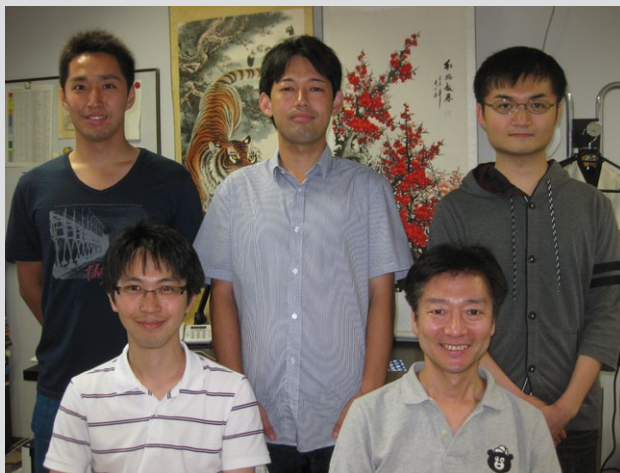
“We feel uneasy on this point. Our dream is streamlining complex molecule synthesis by minimizing non-productive protection/deprotection processes by developing new catalysts that can recognize and selectively activate each functional group. The boron catalysis is the starting point for us,” he concluded.

*Matthew Farnish*



**Scheme 2** Representative examples of the boron-catalyzed asymmetric Mannich-type reaction of carboxylic acids. Isolated yields, diastereomeric ratios, and enantiomeric excess values were determined after conversion of the Mannich products into methyl esters. <sup>a</sup> 1.0 equiv of propionic acid was used.

## About the authors



Back row, from left: H. Nagai, Y. Morita, T. Yamamoto;  
front row, from left: Prof. Y. Shimizu, Prof. M. Kanai

**Motomu Kanai** was born in Tokyo (Japan) in 1967. In March 1991 he obtained his MSc from the Graduate School of Pharmaceutical Sciences, The University of Tokyo (Japan) under the supervision of the late Professor Kenji Koga. In April 1992 he was appointed as Assistant Professor at ISIR, Osaka University (Japan) and in June 1995 he was awarded a PhD from ISIR, Osaka University under the supervision of Professor Kiyoshi Tomio-ka. From January 1996 to August 1997 he was a postdoctoral researcher at the University of Wisconsin (USA) in Professor Laura L. Kiessling's laboratory, and from September 1997 to April 2010 he worked in Professor Masakatsu Shibasaki's laboratory at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, firstly as Assistant Professor (September 1997 to July 2000), then as a Lecturer (July 2000 to January 2003), and finally as an Associate Professor (February 2003 to March 2010). Since then he has been a Full Professor. From October 2011 to present, he has been the principal investigator on the JST-ERATO Kanai Life Science Catalysis Project. His research interests lie in the design and synthesis of molecules that have functions, such as catalytic or biological activities.

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**Yohei Shimizu** – who in this work conceived and designed the experiments together with Professor Kanai – was born in Nagano (Japan) in 1984. He gained his MSc in March 2008 from the Graduate School of Pharmaceutical Sciences, The University of Tokyo under the supervision of Professor Masakatsu Shibasaki, and his PhD in March 2011 from the same institute, under the supervision of Professor Shibasaki initially and then Professor Kanai. He has been an Assistant Professor in Professor Kanai's lab from April 2011 to present. From July 2012 to September 2012, he was a visiting scientist at the Department of Chemistry, University of Cambridge (UK), under the supervision of Professor Matthew J. Gaunt. His main research interests are the development of novel reactions which enable easier synthesis of complex molecules, and application of the reactions to total synthesis.

**Yuya Morita** – who in this work found the BH3 catalyst conditions and developed the catalytic asymmetric reaction – was born in Osaka (Japan) in 1989 and gained his MSc from the Graduate School of Pharmaceutical Sciences, The University of Tokyo in March 2014, under the supervision of Professor Kanai. Since April 2014 he has been a PhD student in Professor Kanai's lab. His research interests include methodology development and total synthesis.

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