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Author(s)	Pang, Yadong
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博士の専攻分野の名称 博士（工学） 氏名 Pang Yadong

審査担当者	主査	教授	大熊 毅
	副査	教授	伊藤 肇
	副査	教授	澤村 正也
	副査	准教授	石山 竜生

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Development of Synthetic Methods for Organoboron Compounds Using
Transition-Metal-Catalysis and Mechanochemistry
(遷移金属触媒とメカノケミストリーによる有機ホウ素化合物の合成法の開発)

Mechanochemistry, which uses mechanical energy to facilitate chemical reactions by grinding, stretching, shearing, or other types of mechanical action, has experienced an explosive growth in the past two decades. It is re-emerging as a technique for organic synthesis which was well known in the area of crystal engineering and polymorphism. Advantages of this mechanochemical synthesis using ball milling include the avoidance of potentially harmful organic solvents and external heating, shorter reaction times, simpler operational handling, and improved or new selectivity. Given these benefits, in 2019, the International Union of Pure and Applied Chemistry (IUPAC) selected mechanochemistry as one of the ten chemistry innovations that will most likely change the world, highlighting the recent increased interest in mechanochemistry among researchers in a variety of research areas.

Despite the recent significant progress, the scope of mechanochemical approach using ball mill is still quite limited. To expand the scope of mechanochemical organic synthesis as well as the discovery of new reactivity under the mechanochemical conditions, the author decided to focus on the development of new organic transformations using ball milling technique.

This thesis consists of three chapters and the background of this study was described as an introduction.

Chapter 1 describes the first mechanochemical method for an iridium(I)-catalyzed C–H borylation using a diboron reagent. Recently, chemists have developed numerous organic transformations using mechanochemistry. However, transition-metal-catalyzed C–H bond functionalizations using mechanochemistry have remained underdeveloped. Mechanochemistry has been also applied to the transition-metal-catalyzed halogenation, amination, olefination, arylation, allylation, alkynylation, and oxidative cyclization of C–H bonds. However, to the best of the author's knowledge, a mechanochemical C–H borylation has not been reported to date, even if the development of such a catalytic C–H borylation would be particularly attractive from an industrial perspective. In this study, the author developed the first C–H bond borylation using mechanochemistry. This reaction can be applied to a variety of heteroaromatic compounds, furnishing the corresponding arylboronates in good-to-high yields with excellent regioselectivity. Notably, this mechanochemical C–H borylation does not require the use of inert gas and/or harmful organic solvents. To demonstrate the synthetic utility of this protocol, a one-pot mechanochemical C–H borylation/Suzuki–Miyaura cross-coupling sequence was developed.

Chapter 2 describes the first example of arylation and borylation reactions using mechanical force and piezoelectric materials. Up to date, mechanical force provided by ball milling has been used primarily to mix substrates, reagents and catalysts in the mechanochemical synthesis. If mechanical force can be used to promote chemical reactions, new reactivity and selectivity could be discovered. Visible-light photoredox catalysis represents a key recent development

in contemporary organic synthesis. Inspired by the unique profile of photoredox systems, the author hypothesized the redox activation of small organic molecules could be achieved through a mechanistically distinct approach using mechanical energy. In particular, the author envisioned that the agitation of piezoelectric materials via ball milling could generate temporarily highly polarized particles that might act as strong reductants to transfer electrons to small organic molecules, followed by oxidative quenching of a donor, thus inducing the selective formation of bonds in a manner analogous to photoredox catalysis. In this study, the author discovered that the mechanoredox system reduces aryl diazonium salts to generate the corresponding aryl radicals. This process can be applied to the arylation and borylation using mechanical force. Notably, these mechanoredox transformations can be carried out on gram scale without organic solvents in air, and do not require special operating conditions. This operational simplicity suggests that the present approach may complement existing photoredox transformations in a practical and environmentally friendly manner. Beyond the immediate benefits of this protocol, this strategy could be applicable to light-sensitive or light-absorbing substrates that cannot be subjected to conventional photoredox systems.

Chapter 3 describes the first example for the synthesis of (Z)-1-bromo-1-alkenylboronate esters via copper(I)-catalyzed stereoselective debromoborylation of aliphatic 1,1-debromo-1-alkenes with bis(pinacolato)diboron in the presence of a copper(I) catalyst. The borylation reaction exhibits a wide substrate scope, good functional group compatibility and affords a variety of (Z)-brominated borylation products in moderate to good yields. At the same time, this study is the first example of the selective debromoborylation of 1,1-dibromo-1-alkenes, which is expected to become a powerful synthetic approach to construct a broad range of intermediates and materials.

Therefore, the author acknowledges that he is qualified to receive a Ph.D. degree from Hokkaido University.