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Tamae Seo

# Palladium-Catalyzed Mechanochemical Cross-Coupling Reactions

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Tamae Seo

# Palladium-Catalyzed Mechanochemical Cross-Coupling Reactions

Doctoral Thesis accepted by  
Hokkaido University, Sapporo, Hokkaido, Japan

 Springer

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# Supervisor's Foreword

Mechanochemistry is a reaction method using mixing or grinding machines, such as ball mills, in the absence or presence of small amounts of organic solvents believed to be necessary for carrying out organic synthetic reactions. Due to the rapid development of the field in the last decade, mechanochemistry has been recognized as an innovative and efficient method for organic synthesis because of its environmental friendliness, reaction acceleration, and ease of operation. In addition, mechanochemistry can provide a novel method for the synthesis of compounds that are not amenable to use in conventional solution-based organic synthesis.

Mechanochemistry has a long history, and many examples have been reported for a long time. However, because many organic synthesis researchers believed that the use of solvents was necessary to perform organic reactions, the active development of practical mechanochemical reactions has only recently emerged. Since 2018, our group has been demonstrating the usefulness of mechanochemical reactions through the development of mechanochemical organic synthesis reactions with the use of ball mills.

Dr. Tamae Seo's Ph.D. thesis focuses on developing new mechanochemical organic reactions that exhibit higher or unique reactivity compared to conventional solution-based reactions. In this research subproject, she has achieved a number of research results. All of them will make significant contributions to the field. In Chap. 1, she developed a novel catalytic system for mechanochemical, Pd-catalyzed C-N cross-coupling reactions. The addition of olefins as activation of the active catalytic species significantly increased the catalytic efficiency. Solid-state Suzuki-Miyaura cross-coupling reactions using the olefin addition strategy were successively developed in Chap. 2. In Chap. 3, mechanochemical Suzuki-Miyaura cross-coupling was explored for insoluble aryl halides, which cannot be used in organic synthesis, by taking advantage of the no-solvent conditions. The results of this work are a new approach to the use of insoluble materials in organic synthesis. In Chap. 4, the author studied the effect of polymers for insoluble on the mechanochemical Suzuki-Miyaura cross-coupling for insoluble aryl halides. In Chap. 5, she studied mechanochemistry-directed ligand design for mechanochemical Suzuki-Miyaura cross-coupling, which

represents a new guiding concept for the design of new mechanochemical reactions. Chapter 6, nickel(II)/mechanoredox cocatalyst system, is a combined catalytic system using Ni catalyst and piezoelectric materials.

In the thesis, the author not only developed novel mechanochemical organic synthetic reactions but also demonstrated a new concept for the rational design of new catalysts suitable for mechanochemical reactions. These results are a guide for the identification of the effective design of the new mechanochemical reactions.

Sapporo, Hokkaido, Japan  
December 2023

Prof. Hajime Ito

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# Chapter 1

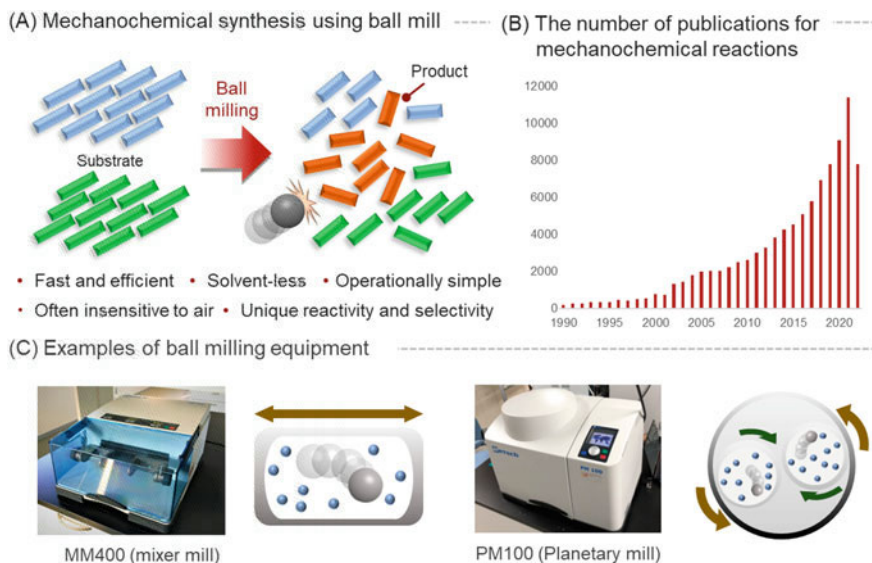
## General Introduction



### 1.1 Mechanochemistry for Organic Synthesis

In the past two decades, mechanochemistry has become increasingly popular among a wide range of researchers as an environmentally friendly and highly efficient method. This method has been extensively exploited in material science, polymer chemistry, and inorganic and organic synthesis [1–20]. In the early days of mechanochemistry, many published papers relied on the traditional method of conducting mechanochemical reactions, especially in the field of crystal engineering by using a mortar and pestle [21]. Recently, automated ball mills have been used to carry out the solvent-free mechanochemical reactions with precise control over the mechanical energy input (Fig. 1.1) [1–20]. The advantages of mechanochemical reactions using ball milling include the avoidance of potentially harmful organic solvents, shorter reaction times and simpler operational handling. In addition, mechanochemical reactions are particularly useful for the poorly soluble substrates in organic solvents [22–24]. Apart from these practical benefits, mechanochemical reactions using ball milling can potentially provide exciting opportunities to access large areas of unexplored chemical space that have different reactivities and selectivity different from those in solution-based conditions [25–40]. Given these attractive features of mechanochemical synthesis, the number of published papers has significantly increased year after year (Fig. 1.1B). The International Union of Pure and Applied Chemistry (IUPAC) selected mechanochemistry in 2019 as one of the 10 chemistry innovations that will most likely change the world, highlighting the recent increased interest in mechanochemistry among researchers in a variety of research areas [41].

There are two types of commonly used ball mill machine for mechanochemical reactions in the laboratory. One is a mixer ball mill and the other is a planetary mill (Fig. 1.1C). In a mixer mill, the reaction jar was mounted horizontally and rapidly shaken from side to side at the desired frequency causing the enclosed balls bearing to shear and grind the chemical together. On the other hand, in a planetary mill, the reaction jars are spun at high speed in the reverse direction to that of the main sun



**Fig. 1.1** Mechanochemical synthesis using ball mill. **A** Representative image of mechanochemical reactions. **B** Number of publications on mechanochemical synthesis in recent years. **C** Examples of ball milling equipment

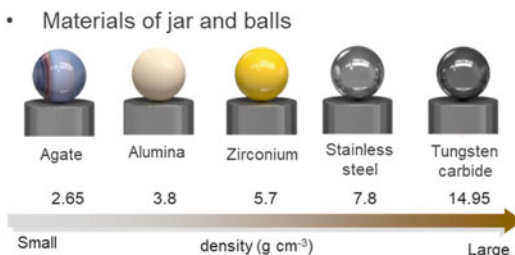
wheel, which results in the balls grinding the solids in the jars. Importantly, the main mechanical energy applied to the reaction mixture is impact force in a mixer ball mill, while the main type of force applied in the planetary mill is shear force.

Mechanochemical synthesis has many different parameters from solution synthesis using organic solvents (Fig. 1.2). The key factors are adjustment of the milling jar size and milling frequency and selection of the milling material. The jars and balls can be made from a variety of materials, such as stainless steel, tungsten carbide, zirconia, etc. The mechanical impact and mixing of reactants are changed by using different materials of jar and balls. The reactivity in mechanochemical reactions strongly depends on the reactant state (i.e., solid substrates are less reactive than liquid substrates under solvent-free ball milling reactions) [1–20]. There is another critical parameter for mechanochemical reactions. The addition of a small amount of liquid sometimes enhances the reaction efficiency and/or reaction kinetics. This is termed “liquid-assisted grinding (LAG)”. The parameter of LAG was defined as the ratio of liquid to the total weight of solid reactants [42, 43].

Under solution-based conditions, the techniques required to carry out reactions often involve high-vacuum Schlenk lines and glove boxes. These are expensive and users need special operational skills. However, mechanochemical synthesis using ball milling typically does not require such precautions and can synthesize a wide range of valuable organic molecules in air [1–20]. A representative procedure of the mechanochemical reactions using a mixer mill is shown in Fig. 1.3. First, one grinding ball was loaded in a milling jar. Then reactants were added to the jar. After the ball

### 1. Control of impact and mixing

- Jar size and reaction scale
- Grinding speed (Hz or rpm)
- Size and number of balls
- Ball to reagent ratio



### 2. Character of reactants : Solid, liquid, gas, rheology, melting point

### 3. Grinding additive

Grinding with a small amount of liquid additive (Liquid-Assisted-Grinding)

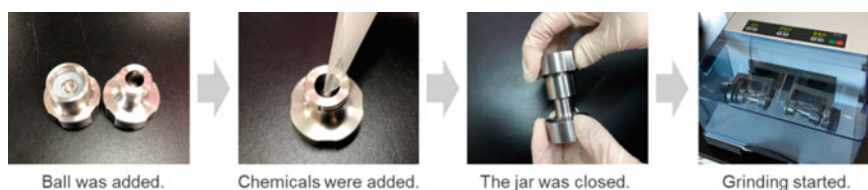
$$\eta = \frac{\text{Volume of liquid additive } [\mu\text{L}]}{\text{Total mass of solid reactants } [\text{mg}]}$$

$\eta = 0$  : neat grinding  
 $0 < \eta \leq 1$  : LAG  
 $1 < \eta < 10$  : slurry  
 $10 \leq \eta$  : homogenous solution

**Fig. 1.2** Key parameters for mechanochemical reactions

milling jar was closed, the jar was placed in the ball mill. The mechanochemical reaction can be performed without the requirement of special operating conditions, such as glove box operation in inert gas. The low diffusion efficiencies of gaseous water and oxygen in crystalline or amorphous solid-state reactions are the main reason for the low effect on the presence of atmospheric water and oxygen on chemical reactions conducted in a ball mill [44–47].

A variety of organic transformations have been carried out under mechanochemical conditions as an environmentally friendly alternative to conventional solution-based reactions. Among these, the development of mechanochemical palladium-catalyzed cross-coupling reactions has attracted particular attention because these reactions in solution have long been used as the most powerful, versatile, and well-established bond-forming reactions. These reactions were often used to synthesize the natural products, medicinal compounds, polymer, and organic materials [48–52]. In general, these cross-coupling reactions are carried out in organic solvents. Although

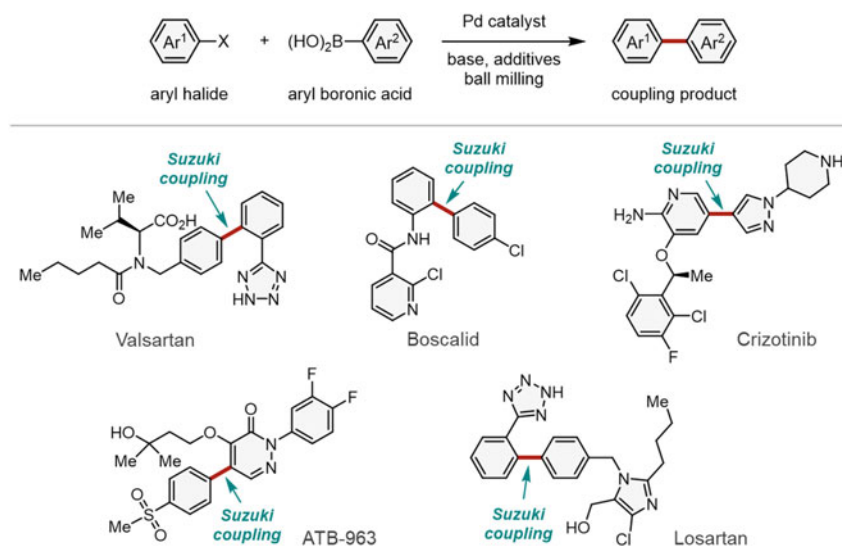


**Fig. 1.3** Typical procedure for setting up mechanochemical organic reactions

the benefits of solution-based reactions are well established, the value of palladium-catalyzed cross-coupling methods becomes more apparent when mechanochemical cross-coupling reactions are considered, in the term of solvent-waste and environmental protection [53, 54]. Additionally, mechanochemical cross-coupling reactions are potentially particularly useful for the preparation of large polyaromatic organic materials, which are prepared from substrates that are poorly soluble substrates due to strong intermolecular interactions [55, 56]. The development of highly efficient palladium-catalyzed solid-state cross-coupling reactions that are not affected by solubility issues would provide useful synthetic solutions for accessing unexplored chemical space for the discovery of new organic materials, which could not be synthesized under solution conditions.

## 1.2 Mechanochemical Suzuki–Miyaura Cross-Coupling Reaction

The Noble-prize-winning palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl halides with organoboron reagents represent the most powerful, versatile, and well-established class of carbon–carbon bond-forming reactions. Therefore, the reaction has found wide applications in both academic and industrial settings (Fig. 1.4) [48–52].



**Fig. 1.4** Representative examples of compounds synthesized by Suzuki–Miyaura cross-coupling reactions

In general, Suzuki–Miyaura cross-coupling reactions are carried out in organic solvents. The solvent-free mechanochemical cross-coupling reactions have many advantages compared with such solution-based approaches. One is the amount of waste derived from organic solvents that could be greatly reduced, especially in large-scale synthesis [53, 54]. Second is the solvent-free mechanochemical reactions that could be particularly useful for the preparation of organic materials that are often prepared from poorly soluble substrates due to the strong intermolecular interactions [55, 56]. Third advantage is the set-up for mechanochemical cross-coupling reactions that is much simpler than that for solution-based reactions. Given these attractive benefits, several mechanochemical approaches for Suzuki–Miyaura cross-coupling reactions have been developed. The chronology of mechanochemical Suzuki–Miyaura cross-coupling reactions is shown in Fig. 1.5.

In 2000, the first examples of a Suzuki–Miyaura cross-coupling reactions using ball milling were reported by Peters, Axelsson, and coworkers [57]. They found that mechanochemical Suzuki–Miyaura coupling reactions proceeded well in the presence of tetrakis(triphenylphosphine)palladium(0) with sodium chloride as grinding auxiliary in a Fritsch Planetary Micro Mill Pulversette. Notably, all the reactions can be carried out in air, which shows the simplicity of the developed procedure. However, the aryl halide scope is generally limited to liquid substrate. Under optimized conditions, the yields of the synthesized biaryls are relatively poor when solid aryl halides are used. In 2003, Leadbeater and coworkers reported the ligand-free protocol for mechanochemical Suzuki–Miyaura cross-coupling reactions [58].

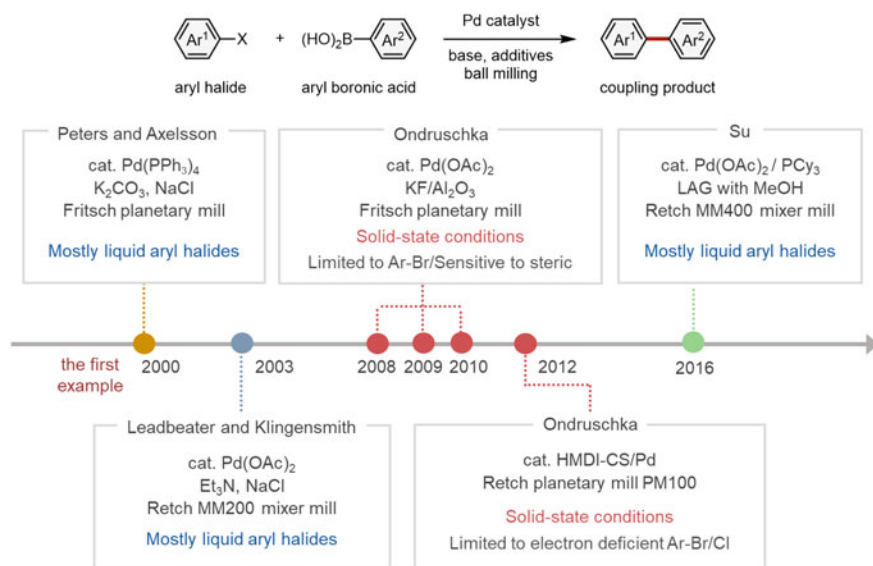


Fig. 1.5 Mechanochemical Suzuki–Miyaura cross-coupling reactions

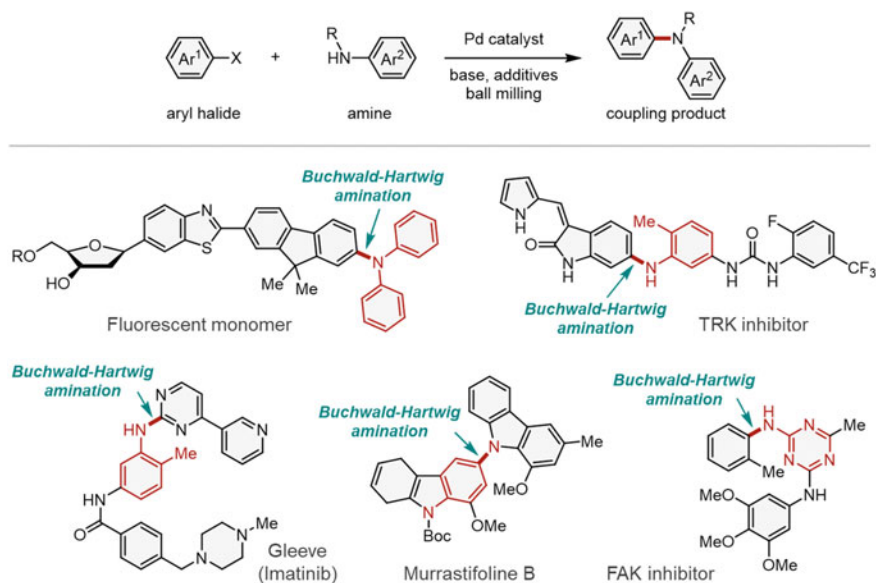


They used a Retsch MM200 mixer mill and sodium chloride as a grinding auxiliary. Optimization of reaction conditions showed that Pd(OAc)<sub>2</sub> was more reactive than PdCl<sub>2</sub> or Pd<sub>2</sub>(dba)<sub>3</sub> in the ligand-free catalytic system, and triethylamine was the best base for this reactions. This method is general and various aryl halides react in air to give the desired coupling products in good yields. However, for solid-state reactants, only electron-deficient aryl halides such as methyl 4-bromobenzoate and 4-bromobenzaldehyde are applicable to this reaction. In addition, when aryl chlorides were used, the products were obtained in low yield. Ondruschka, Stolle, and coworkers used a Fritsch Planetary Micro Mill Pulverisette to investigate the mechanochemical Suzuki–Miyaura cross-coupling reactions [59–62]. A solid-supported base such as KF/Al<sub>2</sub>O<sub>3</sub> was crucial for effective solid-state reactions. The reactions proceed well, and the desired coupling products were obtained in good yields. In this paper, the effect of the mechanochemical parameters on the efficiency of solid-state cross-coupling reactions was also investigated [60]. This was the first solid-state approach for mechanochemical palladium-catalyzed Suzuki–Miyaura cross-coupling reaction using ball milling. However, the substrate scope is relatively limited to and sensitive to steric effects and substituents at the *meta* positions of aryl boronic acids greatly decreased yields. In 2012, Ondruschka and coworkers reported another variant of palladium-catalyzed Suzuki–Miyaura cross-coupling reactions in a planetary ball mill. In this reaction, a crosslinked chitosan/Pd(II) catalyst was used [63]. Notably, the reactions can be applicable to solid aryl iodides, bromides, and chlorides, and coupling products were obtained in good yields. However, for aryl chlorides, an electron-withdrawing groups such as a nitro group is needed for sufficient conversion.

Previous studies of mechanochemical Suzuki–Miyaura cross-coupling reactions mainly focused on the advantages of performing the reactions under solvent-free conditions in terms of green chemistry. In 2016, Su and coworkers discovered that introducing a small amount of liquid during grinding significantly accelerated the mechanochemical Suzuki–Miyaura cross-coupling reactions of aryl chlorides [64]. When alcohols were used as LAG additives, they observed unexpected improvements in the product yields in mechanochemical coupling of aryl chlorides. They proposed that alkoxides formed in situ from K<sub>2</sub>CO<sub>3</sub> under ball milling conditions and alcohol additives promote oxidative addition. In Pd(OAc)<sub>2</sub>/PCy<sub>3</sub>/MeOH system, various aryl chlorides reacted with aryl boronic acids to form the desired coupling products in high yield. However, this reaction was not applicable to solid aryl chlorides.

### 1.3 Mechanochemical Buchwald–Hartwig Amination Reactions

The carbon–nitrogen bond is widely found in functional materials, pharmaceutical drugs, fragrances, and organic dyes. The palladium-catalyzed cross-coupling reactions of amines and aryl halides (i.e., the Buchwald–Hartwig amination) are widely



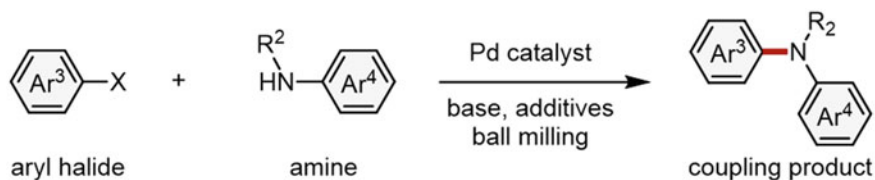
**Fig. 1.6** Representative examples of compounds synthesized by Buchwald–Hartwig amination reactions

used for the preparation of aniline derivatives in both academic and industrial settings (Fig. 1.6) [65]

This solution-based method has been applied to a wide range of substrates combinations and its synthetic utility has been well established [65]. On the other hand, mechanochemical variants have recently been developed (Fig. 1.7). In 2018, Su and coworkers reported the first solvent-free Buchwald–Hartwig amination by using a Pd(OAc)<sub>2</sub>/XPhos catalytic system under mechanochemical conditions [66]. The desired amination products were obtained in good to high yield. The use of Na<sub>2</sub>SO<sub>3</sub> as a solid grinding additive is essential for this reaction. In 2019, Browne and coworkers developed a mechanochemical Buchwald–Hartwig amination with alkylamine as nucleophiles in the presence of Pd-PEPSI catalyst [67]. Although the efficiency and robustness of these reactions are remarkable, the substrate scope is mostly limited to liquid substrates.

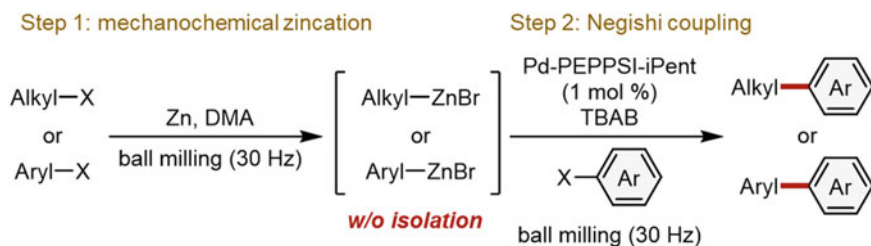
## 1.4 Mechanochemical Negishi Cross-Couplings

In 2018, Browne and coworkers reported the first mechanochemical preparation of organozinc reagents and their use in Negishi cross-coupling reactions (Fig. 1.8) [68]. Various organozinc can be prepared via the mechanochemical reactions between alkyl halides and commercially available zinc metal. Addition of a coupling partner



Su (2018)	Browne (2019)
cat. Pd(OAc) <sub>2</sub> /Xphos Na(O-t-Bu), Na <sub>2</sub> SO <sub>4</sub> Retch MM400 mixer mill <b>Mostly liquid aryl halides</b>	cat. Pd-PEPPSI- <i>i</i> Pent K(O-t-Bu), sand Retch MM400 mixer mill <b>Mostly liquid aryl halides</b>

**Fig. 1.7** Mechanochemical Buchwald–Hartwig amination reactions



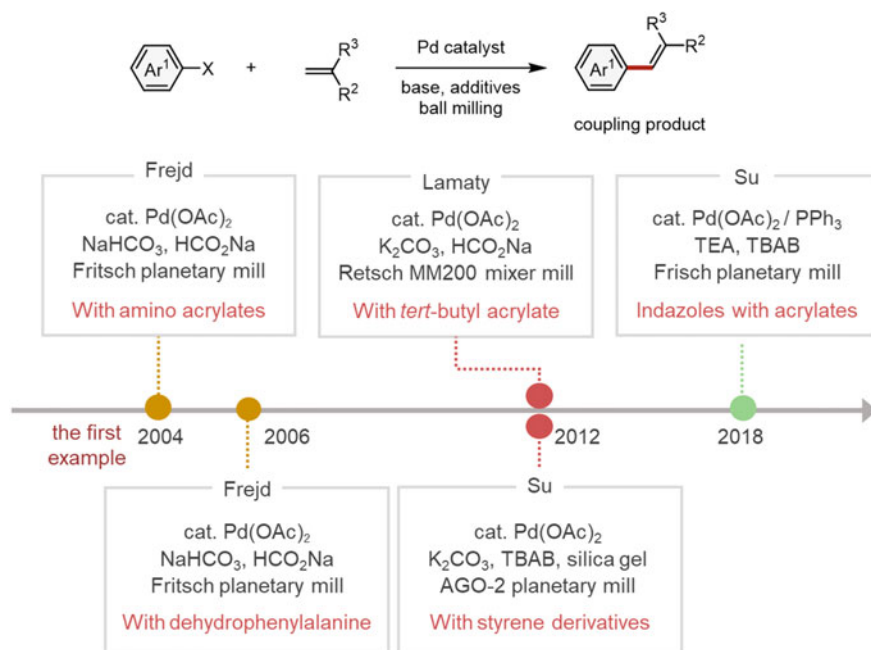
**Fig. 1.8** Mechanochemical Negishi cross-coupling reactions

to the reaction crude mixture along with a palladium catalyst and tetrabutylammonium bromide (TBAB) enables a mechanochemical Negishi coupling reaction to be performed in a one-pot, two-step process. This method is a simple operation and is carried out in air without the use of inert gases. This study shows that mechanochemistry offers exciting opportunities for the preparation of air-sensitive organometallic reagents in air and their concomitant use in cross-coupling reactions in a one-pot procedure.

## 1.5 Mechanochemical Mizoroki–Heck Cross-Coupling

Mizoroki–Heck reactions are useful for the stereoselective synthesis of multi-substituted alkenes. In 2004, Frejd and coworkers reported the first examples of mechanochemical Mizoroki–Heck reactions [69]. The reactions of aryl halides with

protected amino acrylates in the presence of  $\text{Pd}(\text{OAc})_2$  under mechanochemical conditions in a Fritsch Planetary Micro Mill Pulverisette give the coupling products with high stereoselectivity. They also reported that similar mechanochemical conditions can be used with dehydrophenylalanines to afford the corresponding coupling products in high yields [70]. An efficient mechanochemical method for stereoselective synthesis of (*E*)-stilbenes was reported by Su and coworkers in 2012 [71]. In this paper, they proposed that the metal colloids formed in situ were stabilized by the TBAB grinding additives, and this facilitates the mechanochemical reaction. In the same year, Lamaty and coworkers reported the mechanochemical Mizoroki–Heck reactions of aryl halides with *tert*-butyl acrylate. The reaction proceeded well when poly(ethylene glycol) (PEG) was added as a grinding additive [72]. The PEG additive melts during the reaction because of the slight frictional heating caused by ball milling. Therefore, the reaction proceeds smoothly in the polymer medium. Additionally, they proposed that oxygen atoms in PEG can coordinate with the palladium catalyst to enhance the reactivity. Although this approach using polymer-based additives is notable, the scope is limited, other acrylates and styrene have poor yields of the coupling products. In addition, the reaction did not proceed when aryl chlorides and bromides were used under the developed conditions. In 2018, Su and coworkers reported a similar mechanochemical Mizoroki–Heck reactions of 3-bromoindazoles. The reaction provides a highly efficient route to the tyrosine kinase inhibitor axitinib [73] (see Fig. 1.9).



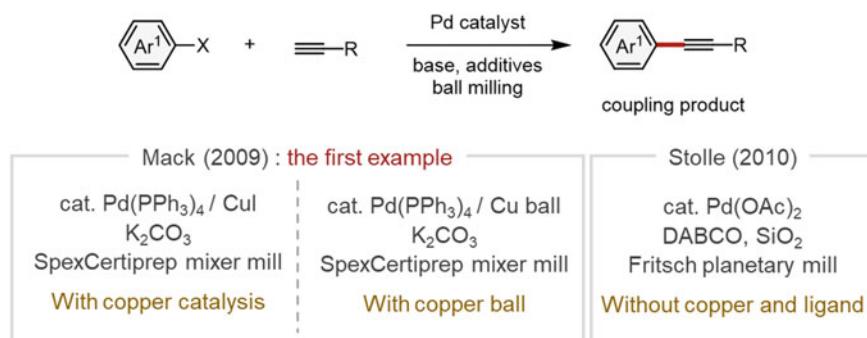
**Fig. 1.9** Mechanochemical Mizoroki–Heck reactions

## 1.6 Mechanochemical Sonogashira Coupling

In 2009, Mack and coworkers reported the first examples of solvent-free Sonogashira coupling reactions using ball mill (Fig. 1.10) [74]. The reactions of aryl halides with terminal alkynes in the presence of both palladium and copper catalysts provided the coupling products in good to high yields. They also developed that the reaction using copper milling balls without a copper catalyst proceeded well to provide the desired internal alkynes in good yield [74]. In 2010, Stolle and coworkers reported the mechanochemical palladium-catalyzed Sonogashira reaction could be performed without the use of copper catalysis in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) as a base [75].

Despite the significant progress described above, palladium-catalyzed cross-coupling reactions using mechanochemistry have remained underdeveloped and the scope of applicable substrates needs significant improvement. The previous methods mostly focused on liquid substrates that serve as not only coupling partners but also reaction solvents. In fact, only a limited number of solid-state cross-coupling reactions under mechanochemical conditions have been reported. Moreover, the scope of these reactions is significantly restricted and low conversion rate are common. Thus, the author decided to focus on re-designing cross-coupling system for the development of a broadly applicable mechanochemical solid-state cross-coupling protocol, which may potentially unlock versatile applications for synthesis and enable us to investigate unexplored chemical space that cannot be accessed by conventional solution-based approaches.

Chapter 2 describes the first example of general solid-state C–N cross-coupling reactions using mechanochemistry. The key finding of this study is that olefin additives can act as efficient molecular dispersants for the palladium-based catalyst in solid-state media to facilitate the challenging solid-state cross-coupling reactions. Beyond the immediate utility of this protocol, this strategy could inspire the development of industrially attractive solvent-free palladium-catalyzed cross-coupling processes for other valuable synthetic targets.



**Fig. 1.10** Mechanochemical Sonogashira reactions

Chapter 3 describes the first broadly applicable mechanochemical solid-state palladium-catalyzed Suzuki–Miyaura cross-coupling reactions using ball mill. The author discovered that the addition of small amounts of olefins dramatically improves the progress. The developed system shows a substantially broadened substrate scope and the first solid-state organoboron cross-coupling reaction of unactivated aryl chlorides. In addition, experimental mechanistic studies to elucidate the role for the olefin additives in these solid-state cross-coupling reactions are also described.

Chapter 4 describes the solid-state Suzuki–Miyaura cross-coupling of insoluble aryl halides under high-temperature ball milling conditions. This method enables the highly efficient cross-couplings of insoluble aryl halides with large polyaromatic structures that are barely reactive under conventional solution-based conditions. This study, thus, provides a practical method for accessing unexplored areas of chemical space through molecular transformations of insoluble organic compounds that cannot be carried out by any other approach.

Chapter 5 describes polymer-assisted grinding (POLAG), a ball milling technique based on the use of polymer additives, which was applied to mechanochemical solid-state Suzuki–Miyaura cross-coupling reactions of insoluble aryl halides. When the addition of polytetrafluoroethylene (PTFE) as a POLAG under high-temperature ball-milling conditions, the efficiency of this challenging solid-state cross-coupling was successfully improved.

Chapter 6 describes the development of a high-performance phosphine ligand for palladium-catalyzed Suzuki–Miyaura cross-coupling reactions. Notably, the newly developed the phosphine ligand-bearing PEG chain showed much greater efficiency than previous catalysts originally developed for conventional solution-based conditions. Based on PXRD, DSC, SS  $^{31}\text{P}$  NMR, and TEM analysis, the author proposes that the PEGylated ligands allow the phosphine-ligated palladium(0) species to be efficiently immobilized in the fluid amorphous phase created by the PEG chain, suppressing the catalyst deactivation via undesired palladium aggregation that occurs in the crystalline solid phase.

Chapter 7 describes selective mechanochemical monoarylation of unbiased dibromoarenes by in-situ crystallization. Suzuki–Miyaura cross-coupling reactions of unbiased dibromoarenes in solution tend to provide a mixture of mono- and diarylated products. In this reaction, the author discovered that mechanochemical conditions promote cross-coupling reactions that are selective toward the monoarylation of a wide range of substrates. Based on a mechanistic study, this selectivity results from the conversion of liquid starting materials into less reactive crystalline monoarylated products under the applied mechanochemical conditions.

Chapter 8 describes the first application of piezoelectricity to modulation of metal oxidation states in an organometallic catalytic cycle, enabling ligand-free nickel-catalyzed C–N cross-coupling reactions under solid-state ball-milling conditions. Piezoelectric oxidation of a Ni(II) aryl amido intermediate is proposed to facilitate the challenging C–N reductive elimination. This novel dual nickel/mechanoredox catalytic system was characterized by broad substrate scope, inexpensive catalysts, no requirement of bulk solvents, short reaction time (60 min), multi-gram scale synthesis, and all synthetic operation can be carried out under air without complicated reaction setups.

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# Chapter 2

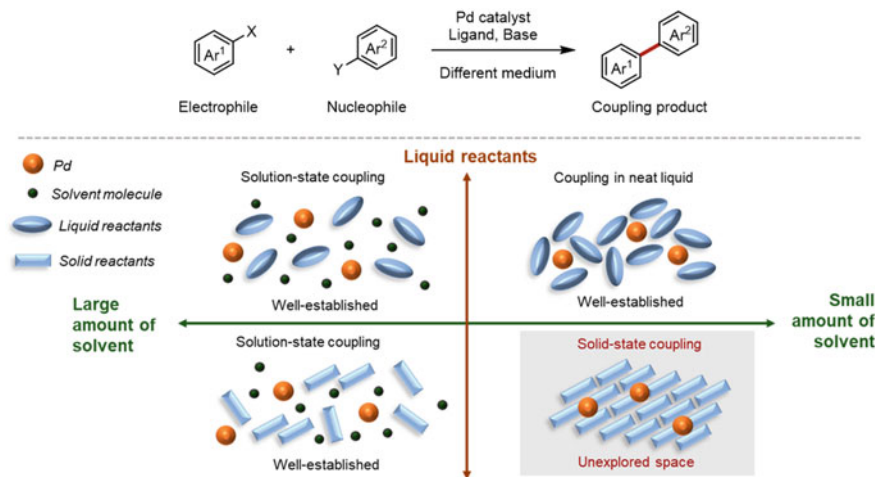
## Olefin-Accelerated Solid-State C–N Cross-Coupling Using Mechanochemistry



### 2.1 Introduction

Historically, most organic transformations have been carried out in solution. Such solution-based organic syntheses generally require liquid organic solvents to dissolve reactants or catalysts in a reaction flask. Accordingly, the pharmaceutical industry and the fine chemicals industry strongly depend on solvent-based organic synthesis, which has led to serious problems with regard to solvent waste, as organic solvents usually account for approximately 80–90% of the total mass used in any organic reaction [1–3]. Although solvent recycling is a very effective way to reduce solvent waste, organic chemists should focus on (re)designing organic syntheses to use less or no solvent. In this context, solid-state organic transformations have attracted considerable attention as cleaner and sustainable synthetic alternatives [4–7]. In addition, these methods would be exciting opportunities to access large areas of hitherto unexplored chemical space that exhibit different reactivity and selectivity compared to conventional solution-based reactions [8–20].

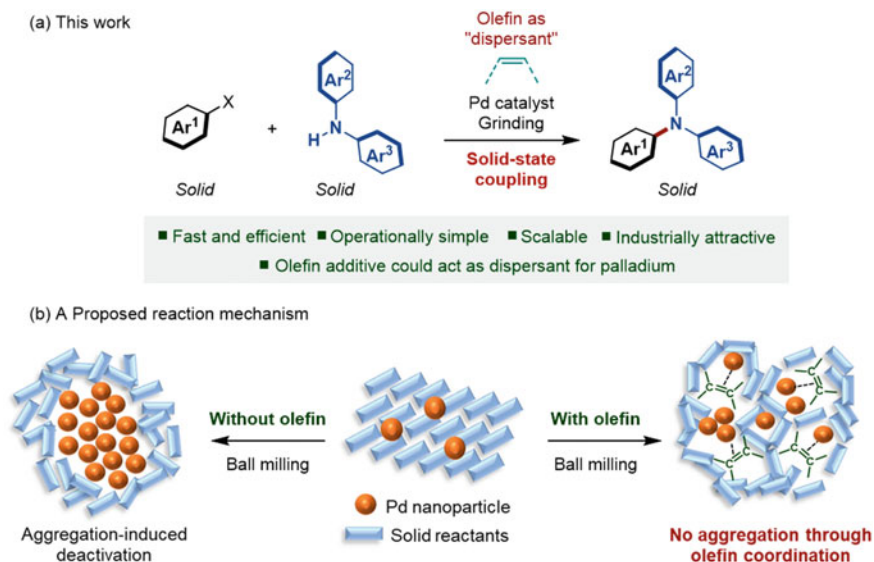
Palladium-catalyzed cross-coupling reactions have long been used as arguably the most powerful, versatile, and well-established organic transformations with broad applications ranging from natural product synthesis and medicinal chemistry to polymer and materials science [21–24]. Despite recent significant progress, the exploration of new strategies, reaction media, and concepts for the improvement of the sustainability of cross-coupling reactions still remains an important and challenging research subject. Conventionally, palladium-catalyzed cross-coupling reactions of liquid and solid substrates are conducted in organic solvents (Fig. 2.1) [21, 22]. When using liquid substrates, the cross-coupling reactions can in some cases be carried out under neat conditions, where liquid substrates serve as reactants and reaction solvent (Fig. 2.1) [25–32]. Whereas the benefits of these solution-based reactions are well established, the value of palladium-catalyzed cross-coupling processes becomes even more apparent when solid-state cross-coupling reactions are considered, especially in the context of solvent-waste prevention and environmental



**Fig. 2.1** Current application range of palladium-catalyzed cross-coupling reactions

protection [4–7]. In addition, solid-state coupling reactions should be particularly useful for poorly soluble substrate classes such as large polycyclic aromatics due to strong intermolecular interactions (e.g.,  $\pi$ – $\pi$  interactions). Nevertheless, the solid state has remained extremely limited as a reaction medium for palladium-catalyzed cross-coupling processes (Fig. 2.1) [21, 22]. Thus, the author sought to re-design palladium-based catalyst systems for the solid state, which could potentially unlock versatile applications for solid-state synthesis.

Mechanochemical solvent-free reactions using ball milling or milling with a catalytic amount of liquid, the so-called liquid-assisted grinding (LAG), have emerged as powerful alternatives to synthesis in solution [33–40], and mechanochemical palladium-catalyzed cross-coupling reactions have already been reported [41–53]. However, these methods focus mostly on neat liquids [41–46, 48–53]. For solid-state substrates, the scope is significantly more restricted, and low conversion rates are common [42, 47, 49]. Here, the author reports the development of the first potentially general and scalable solvent-free method for solid-state palladium-catalyzed C–N cross-coupling reactions using mechanochemistry (Fig. 2.2a) [54]. The key finding in this study is that the addition of a small amount of olefin dramatically accelerates these challenging solid-state cross-coupling reactions. Based on a transmission electron microscopy (TEM) analysis, the author discovered that some such olefin additives can act as efficient molecular dispersants for palladium catalysts in solid-state media to inhibit undesired aggregation of the catalyst that may lead to catalyst deactivation (Fig. 2.2b). The newly developed protocol should be particularly useful for the rapid access to structurally complex triaryl amines, which can be found in a wide range of organic materials including solar cells and light-emitting diodes (Fig. 2.2a) [55–57]. In fact, the author will demonstrate (*vide infra*)



**Fig. 2.2** Olefin accelerated solid-state cross-coupling reactions using mechanochemistry

that when using the solid-state cross-coupling reaction presented herein, arylamine-based hole-transporting materials can be prepared faster and in better yield relative to conventional methods [57]. Thus, the author anticipates that the present solvent-free solid-state palladium-catalyzed cross-coupling reactions may potentially find broad applications in industrially relevant syntheses.

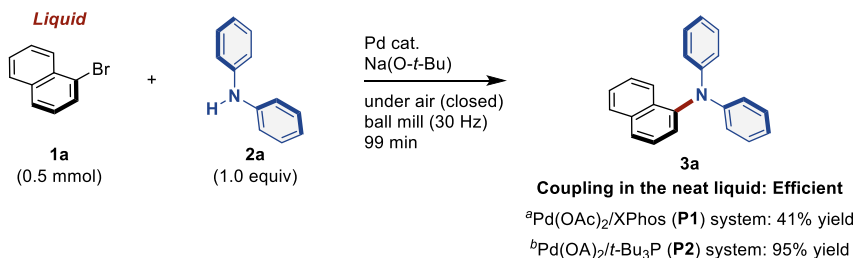
## 2.2 Results and Discussion

**Solid-State Palladium-Catalyzed C–N Cross-Coupling Reactions Using a Molecular Dispersant.** All reactions were conducted in a Retsch MM400 mill (stainless-steel milling jar; 30 Hz; stainless-steel balls). Initially, the author compared the reactivity of liquid 1-bromonaphthalene (**1a**) and solid 1-bromopyrene (**1b**) in the palladium-catalyzed C–N cross-coupling reaction with diphenylamine **2a** under solvent-free mechanochemical conditions (Scheme 2.1). Very recently, Su and coworkers have reported the mechanochemical palladium-catalyzed C–N cross-coupling of aryl chloride using NaCl as a mechanochemical auxiliary [51]. Even though this development is indisputably remarkable, the substrate scope mostly focused on liquid substrates. Thus, the author anticipated that the reaction of liquid substrate **1a** should proceed readily using the Pd(OAc)<sub>2</sub>/XPhos (**P1**) catalyst system developed by Su [51]. Indeed, the corresponding coupling product (**3a**) was obtained in moderate yield (41% yield; Scheme 2.1a). When the author used the Pd(OAc)<sub>2</sub>/*t*-Bu<sub>3</sub>P (**P2**) catalyst system, which is a high-performance catalyst for C–N coupling

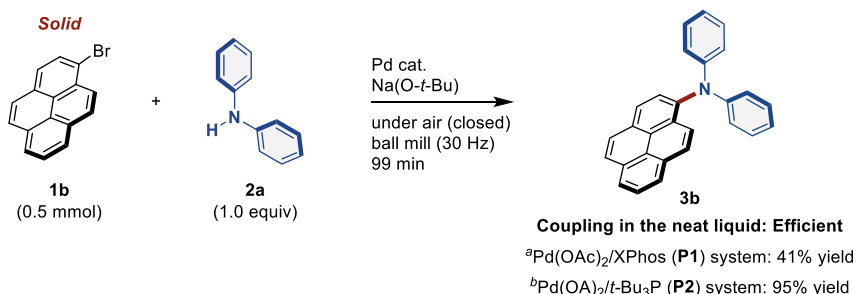
that has been reported by Hartwig and coworkers [58]. **3a** was obtained quantitatively (95% yield; Scheme 2.1a). Other liquid aryl bromides could also be coupled with diphenylamine **2a** in the presence of Pd(OAc)<sub>2</sub>/*t*-Bu<sub>3</sub>P (**P2**) in high yield (see the Supporting Information for details). Then, the author proceeded to investigate the C–N cross-coupling behavior of solid 1-bromopyrene (**1b**). The author found that the solid-state cross-coupling reactions involving **1b** were sluggish using either the Pd(OAc)<sub>2</sub>/XPhos (**P1**) or the Pd(OAc)<sub>2</sub>/*t*-Bu<sub>3</sub>P (**P2**) catalyst systems (3% and 28% yield, respectively; Scheme 2.1b). These results suggest the presence of a considerable reactivity gap between liquid and solid substrates, even under mechanochemical conditions.

The author, therefore, decided to focus on commonly used phosphine ligands in solvent-based systems in order to potentially facilitate the solid-state C–N cross-coupling under mechanochemical conditions (entries 1–10, Fig. 2.3) [54]. Experiments involving catalyst systems consisting of 5 mol% Pd(OAc)<sub>2</sub> and 5 mol% phosphine ligand revealed that the use of bulky and highly electron-donating monophosphines such as Ad<sub>3</sub>P (**P3**) provides the desired coupling product in low yield (18% yield; entry 1). In contrast, the use of Cy<sub>3</sub>P (**P4**) did not afford the targeted coupling product (entry 2). The reaction did not proceed when commonly used Buchwald-type ligands such as **P5–P9** were employed (entries 3–7) [54]. While **P5** is a highly effective ligand for C–N cross-coupling reactions in solvents at room temperature, the

(a) Liquid substrate (**1a**) was used.



(b) Solid substrate (**1b**) was used.



**Scheme 2.1** Comparison of the reactivity of liquid and solid aryl bromides in solvent-free mechanochemical C–N cross-coupling reactions