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Mechanochemistry-Directed Ligand Design: Development of a High-Performance Phosphine Ligand for Palladium-Catalyzed Mechanochemical Organoboron Cross-Coupling

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ABSTRACT: Mechanochemical synthesis that uses transition-metal catalysts has attracted significant attention due to its numerous advantages, including low solvent waste, short reaction times, and the avoidance of problems associated with the low solubility of starting materials. However, even though the mechanochemical reaction environment is largely different from that of homogeneous solution systems, transition-metal catalysts, which were originally developed for use in solution, have been used directly in mechanochemical reactions without any molecular-level modifications to ensure their suitability for mechanochemistry. Alas, this has limited the development of more efficient mechanochemical cross-coupling processes. Here, we report a conceptually distinct approach, whereby mechanochemistry-directed design is used to develop ligands for mechanochemical Suzuki-Miyaura cross-coupling reactions. The ligand development was guided by the experimental observation of catalyst deactivation via the aggregation of palladium species, a problem that is particularly prominent in solid-state reactions. By embedding the ligand into a polyethylene glycol (PEG) polymer, we found that phosphine-ligated palladium(0) species could be immobilized in the fluid phase created by the PEG chains, preventing physical mixing of the catalyst into the crystalline solid phase and thus undesired catalyst deactivation. This catalytic system showed high catalytic activity in reactions of polyaromatic substrates close to room temperature. These substrates usually require elevated temperatures to be reactive in the presence of catalyst systems with conventional ligands such as SPhos. The present study hence provides important insights for the design of high-performance catalysts for solid-state reactions and has the potential to inspire the development of industrially attractive, almost solvent-free mechanochemical cross-coupling technologies.

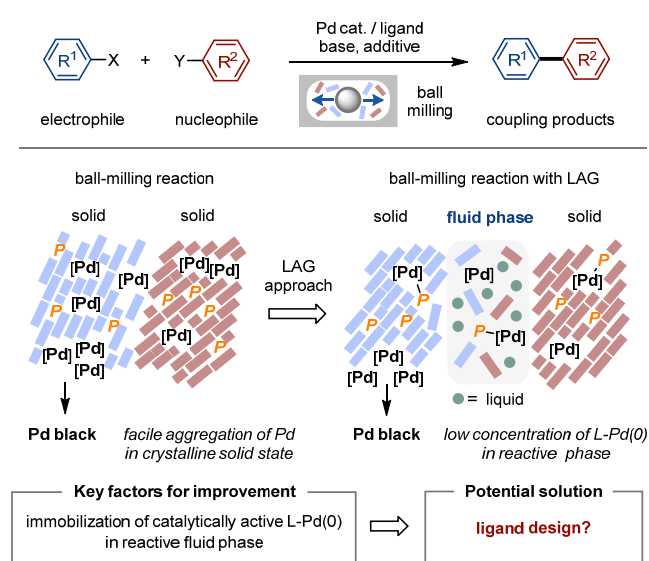
INTRODUCTION

Mechanochemical organic synthesis using ball milling has attracted considerable interest as it represents a powerful alternative to conventional synthetic reactions in solution.^{1–18} The advantages of a synthetic approach that uses ball milling include the minimization of solvent waste in reactions, fast reaction kinetics, and the avoidance of having to use inert gases. These advantages allow the entire procedure to be conducted in air without necessitating any special precautions or synthetic techniques.^{1–18} To date, the benefits of mechanochemistry have been demonstrated in a wide variety of organic reactions.^{1–18} In particular, mechanochemical palladium-catalyzed cross-coupling reactions have emerged as practical tools for the preparation of functional organic materials, bioactive molecules, and pharmaceuticals. This reaction type offers both environmental and economic advantages.^{19–49} So far, mechanochemical Suzuki-Miyaura,^{19–32} Buchwald-Hartwig,^{33–37} Mizoroki-Heck,^{38–40} Negishi,⁴¹ Sonogashira,^{42–45} as well as a C–S bond-forming coupling⁴⁶ and a C–H arylation^{47–49} reactions have been developed (Figure 1a).

Despite the increasing importance of mechanochemical cross-coupling processes in organic synthesis, there are no systematic design guidelines for the development of efficient high-performance palladium-based catalysts for mechanochemical reactions. Although it is clear that the reaction environment of a mechanochemical reaction is largely different from that of a homogeneous system in solution, mechanochemical cross-coupling reactions still use currently palladium-based catalysts that were originally designed for use in solution.^{50–56} Even though the catalyst

performance is acceptable in many cases, the reactions of solid substrates are often inefficient because the requirement profile of these catalysts is – at least partially – inconsistent with mechanochemical conditions, where these shortcomings are often amplified (Figure 1a).^{30,32,57–60} Our previous mechanistic studies revealed that, in a solid-state mixture under mechanochemical conditions, off-cycle palladium species without supporting ligands rapidly aggregate into dense nanoparticles, leading to catalyst deactivation via the formation of palladium black.^{28,33} This finding was supported by solid-state (SS) NMR and transmission electron microscopy (TEM) analyses. To improve the efficiency of mechanochemical cross-coupling with solid substrates, liquid-assisted grinding (LAG) has been employed (Figure 1a).^{26,28,30,32} Such liquid additives likely facilitate the formation of a fluid phase in which the reaction occurs primarily, thus enabling solid-state coupling.^{28,30,32} However, this approach is still ineffective for solid polyaromatic substrates, which often require elevated temperatures and are thus associated with high energy consumption.³⁰ The low catalyst efficiency observed when using the LAG approach is caused by the low concentration of the palladium-based catalytic active species in the more reactive fluid phase during the ball-milling mixing process. The palladium species may also be mixed into the less reactive crystalline solid-state domain (Figure 1a).^{30,32} In other words, the undesired aggregation of off-cycle palladium(0) species in the crystalline solid-phase is inevitable, even under LAG conditions.^{28,33} It should also be noted here that the use of single-component ligand-coordinated palladium catalysts did not improve the reaction efficiency (for details, see the Supporting Information).

a. Mechanochemical palladium-catalyzed cross-coupling



b. Mechanochemistry-directed ligand design for cross-coupling (this work)

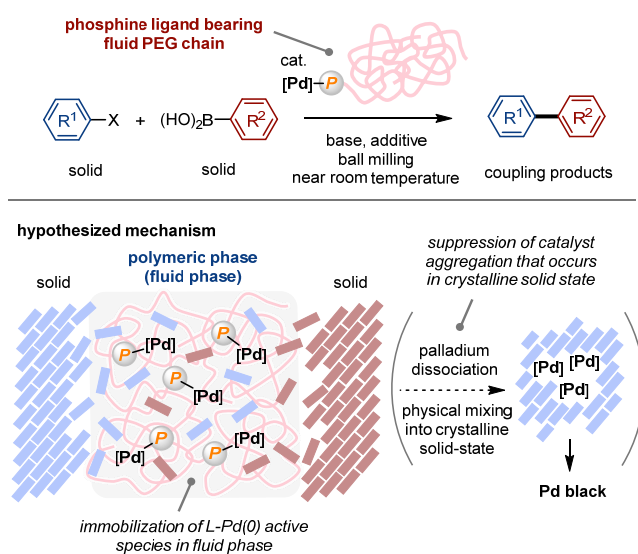


Figure 1. Development of a new phosphine ligand specifically designed for mechanochemical cross-coupling reactions.

Given that the broad success of solution-based palladium-catalyzed cross-coupling reactions has been aided by the design and discovery of high-performance ligands,^{50–56} we envisaged that the development of a ligand designed specifically for use under mechanochemical conditions could potentially resolve the aforementioned problems regarding catalyst deactivation. In turn, this new design approach could also potentially lead to improvements in efficiency and the scope of solid substrates that can be used under mild mechanochemical cross-coupling conditions. Based on our previous mechanistic studies,^{28,30,32} we recognized that a conceptually distinct, mechanochemistry-directed design is necessary for ligand development in this field. Our ligand design was inspired by recent studies on the development of nanocarbon/polyethylene glycol (PEG) composite materials, which exhibit a phase-separated structure of nanocarbons and PEG chains.^{61,62} This phase-separation behavior led us to consider that a phosphine ligand bearing a flexible PEG chain may potentially serve as a high-performance ligand in mechanochemical coupling reactions of solid substrates by preventing the deactivation of the palladium-based catalyst (Figure 1b). We anticipated that a PEGylated phosphine ligand could allow for efficient immobilization of a phosphine-ligated palladium(0) species in the fluid polymeric domain created by the PEG chain, thus preventing the catalyst being mixed into the crystalline solid phase (Figure 1b). Consequently, catalyst deactivation via the formation of palladium black would be suppressed, enabling efficient cross-coupling reactions under mild mechanochemical conditions (Figure 1b).^{28–30,33} Although Lamaty and co-workers have conducted a pioneering study on mechanochemical Mizoroki-Heck reactions using PEG as a polymer-assisted grinding (POLAG) additive³⁸, there are no reports on the use of PEGylated phosphine ligands in mechanochemical cross-coupling reactions.

Herein, we report that our approach based on mechanochemistry-directed ligand design enables the development of a practically useful palladium-based catalytic system that facilitates organoboron cross coupling under mild mechanochemical conditions near room temperature. We found that the use of phosphine ligands that bear a PEG chain significantly promoted solvent-less mechanochemical coupling reactions involving a variety of solid polyaromatic substrates that could hitherto not be used with catalysts originally designed for use under conventional solution-based conditions. This is the first example of the design and development

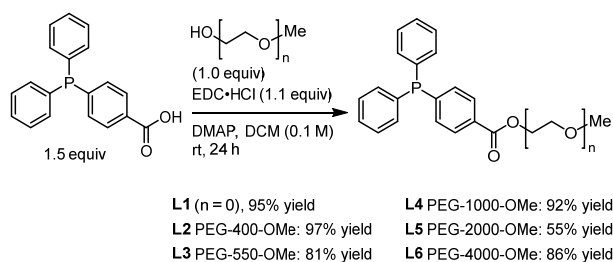
of a transition-metal-based catalytic system specifically for use in a mechanochemical reaction environment. The present study thus constitutes an important milestone toward the rational design of high-performance transition-metal-based catalysts and potentially enables the development of efficient, energy-saving, environmentally friendly, and industrially attractive solvent-free mechanochemical cross-coupling processes.

RESULTS AND DISCUSSION

Ligand Development

Based on our previous mechanistic studies^{28,30,32} and on the mechanochemistry-directed ligand design shown in Figure 1b, we commenced our initial ligand development by synthesizing structurally simple, triphenylphosphine derivatives bearing a PEG chain (Scheme 1). The target phosphine ligands can be easily prepared in one step via a condensation between commercially available 4-(diphenylphosphanyl)benzoic acid and the corresponding alcohol (Scheme 1). We prepared six phosphine ligands that bear PEG chains of different lengths (**L1**: n = 0; **L2**: PEG-400-OMe; **L3**: PEG-550-OMe; **L4**: PEG-1000-OMe; **L5**: PEG-2000-OMe; **L6**: PEG-4000-OMe). These ligands can be isolated in good yield (55–97%) by simple reprecipitation. Although these phosphine ligands are new compounds, structurally similar phosphine ligands bearing PEG chains have already been synthesized and used as recyclable, water-soluble ligands for solution-based cross-coupling reactions.^{63–68}

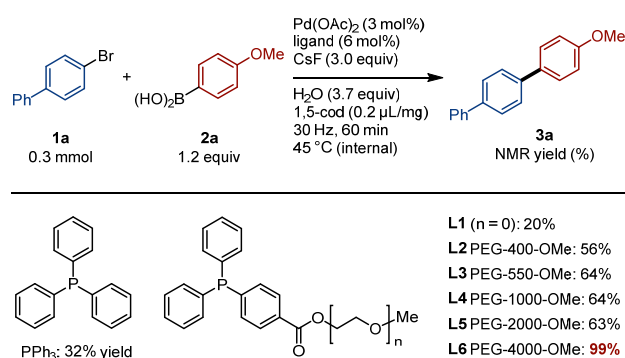
Scheme 1. Synthesis of PEGylated Triphenylphosphine Ligands L1-L6.^a



^aFor details of the reaction conditions, see the Supporting Information.

We then conducted the mechanochemical reaction using the ligands with PEG chains under mild conditions at near room temperature to confirm the feasibility of the above-mentioned ligand concept. All mechanochemical reactions were conducted in a Retsch MM400 mixer mill (stainless-steel milling jar; 30 Hz; stainless-steel balls). Initially, we investigated the mechanochemical cross-coupling reactions of 4-bromo-1,1'-biphenyl (**1a**) with (4-methoxyphenyl)boronic acid (**2a**) in the presence of 3 mol% Pd(OAc)₂, 6 mol% ligand, CsF (3.0 equiv), H₂O (3.7 equiv), and 1,5-cyclooctadiene (1,5-cod; 0.2 μL/mg), which acts as a stabilizer for the active monomeric Pd(0) species,^{28–30,33} at 45 °C for 60 min (Scheme 2). We used a temperature-controllable heat gun to adjust the reaction temperature, which was confirmed using thermography immediately after opening the milling jar (for details, see the Supporting Information). We have previously reported that Buchwald-type ligands are effective for mechanochemical cross-coupling.^{28–30} In fact, the use of a simple phosphine ligand such as PPh₃ provided coupling product **3a** in only 32% yield. In the presence of Pd(OAc)₂/**L1**, **3a** was also obtained in 20%. However, the reaction using **L2**, a ligand with a relatively short PEG chain (PEG-400), provided **3a** in a better yield (56%). While ligands **L3–L5** showed a similar level of catalytic activity (63–64%), the use of **L6**, with a relatively long PEG chain (PEG-4000), dramatically accelerated the cross-coupling reaction and delivered **3a** in quantitative yield (99%).

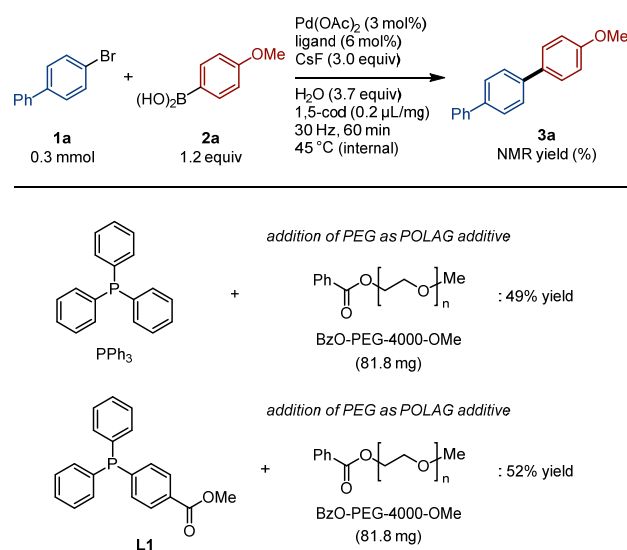
Scheme 2. Mechanochemical Coupling Reactions Using PEG-Chain-Bearing Triphenylphosphine Ligands L1–L6.^a



^aConditions: **1a** (0.30 mmol), **2a** (0.36 mmol), Pd(OAc)₂ (0.009 mmol), ligand (0.018 mmol), CsF (0.9 mmol), H₂O (1.11 mmol), and 1,5-cod (0.20 μL mg⁻¹) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 70 °C to ensure an internal reaction temperature of 45 °C.

Importantly, when the reaction was carried out in the presence of PPh₃ and a POLAG additive,^{38,69–71} a benzoyl-protected PEG (BzO-PEG-4000-OMe) with a structure that resembles that of **L6**, the yield of **3a** was only moderate (49%) (Scheme 3). We also tested the reaction with **L1** under these POLAG conditions, and while the yield of **3a** improved (52%),^{38,69} it was still significantly lower than when using **L6** (Scheme 3). These results suggest that the introduction of the PEG chain onto the phosphine ligand is essential to achieve the observed dramatic acceleration effect. We also confirmed that the use of phosphine ligands bearing other classes of polymeric chains such as polystyrene, polystyrene-crosslinked with divinylbenzene, and polyamide did not promote the coupling reaction (for details, see the Supporting Information), demonstrating the importance of the PEG chain.⁷² The addition of H₂O and 1,5-cod is required for the high reactivity in the presence of the Pd(OAc)₂/**L6** catalytic system (for details, see the Supporting Information).

Scheme 3 Reactions Under POLAG Conditions.^a

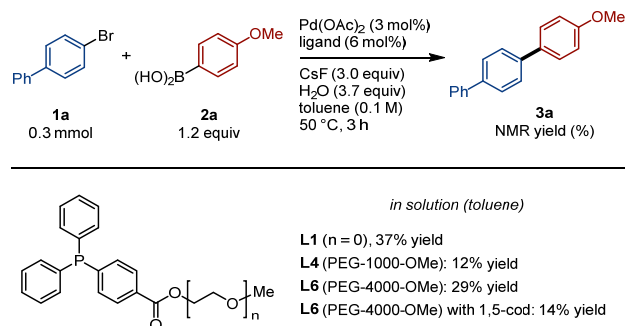


^aConditions: **1a** (0.30 mmol), **2a** (0.36 mmol), Pd(OAc)₂ (0.009 mmol), ligand (0.018 mmol), CsF (0.9 mmol), H₂O (1.11 mmol), 1,5-cod (0.20 μL mg⁻¹), and BzO-PEG-4000-OMe (81.8 mg) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 70 °C to ensure an internal reaction temperature of 45 °C.

Next, we carried out the reaction under solution-based conditions using toluene (0.1 M) at 50 °C to confirm whether the acceleration effect arising from the PEGylated phosphine ligand is only observed under solvent-less mechanochemical conditions (Scheme 4). We found that coupling product **3a** was obtained in 37% yield when **L1** was used, which is similar to the result obtained under mechanochemical conditions. However, the use of PEG-bearing ligands **L4** and **L6** did not improve the efficiency in solution and **3a** was obtained in lower yield (12% and 29%, respectively) relative to the mechanochemical procedure, even after increasing the reaction time (3 h). A reaction in the presence of 1,5-cod also delivered **3a** in merely poor yield (14%). These results suggest that the PEGylated

phosphine ligands only improve the reaction efficiency under mechanochemical conditions.

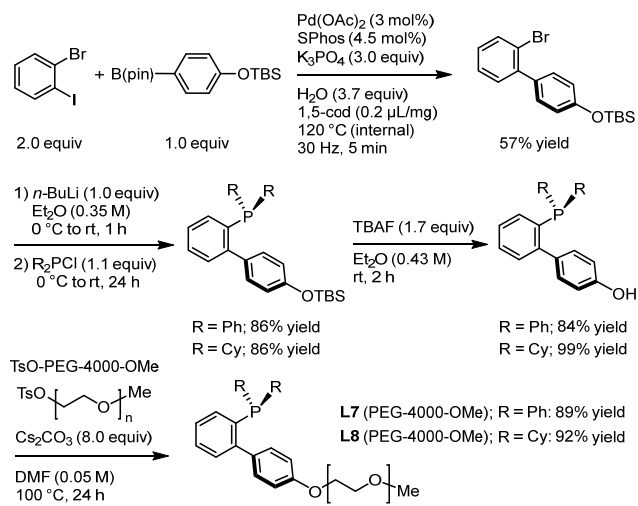
Scheme 4. Reactions in Solution.^a



^aConditions: **1a** (0.30 mmol), **2a** (0.36 mmol), Pd(OAc)₂ (0.009 mmol), ligand (0.018 mmol), CsF (0.9 mmol), and H₂O (1.11 mmol) in toluene (3 mL) at 50 °C for 3 h.

Next, we optimized the structure of the substituents on the phosphine ligand. We focused on a biaryl structure because weak coordination of the aryl ring in the biaryl moiety to a palladium center can be expected to promote the formation of a catalytically active phosphine-ligated palladium(0) species, as has been demonstrated for Buchwald-type ligands.^{50–56} The target biaryl PEGylated phosphine ligands (**L7** and **L8**) were successfully synthesized in four steps (Scheme 5). The first step is a Suzuki-Miyaura cross-coupling of 1-bromo-2-iodobenzene. Due to its high efficiency and operational simplicity, our previously developed mechanochemical catalytic system, Pd(OAc)₂/SPhos/1,5-cod, was used for the coupling reaction,^{30,32} providing the desired monoarylated product in 57% yield. Next, a diphenyl phosphine or dicyclohexyl phosphine moiety was introduced via lithiation of the aryl bromide with *n*-BuLi, followed by desilylation of the *tert*-butyldimethylsilyl (TBS) group with tetra-*n*-butylammonium fluoride (TBAF), giving the corresponding phenol derivatives in good yield (72% and 85% yield over two steps, respectively). Finally, substitution with a PEG-tosylate provided the target biaryl-type PEG (PEG-4000-OMe) bearing phosphine ligands (**L7** and **L8**) in high yield (89% and 92% yield, respectively). It should be noted here that these ligands show high stability toward atmospheric oxygen and moisture. Even after exposure to air for a month significant degradation was not observed via ³¹P NMR analysis.

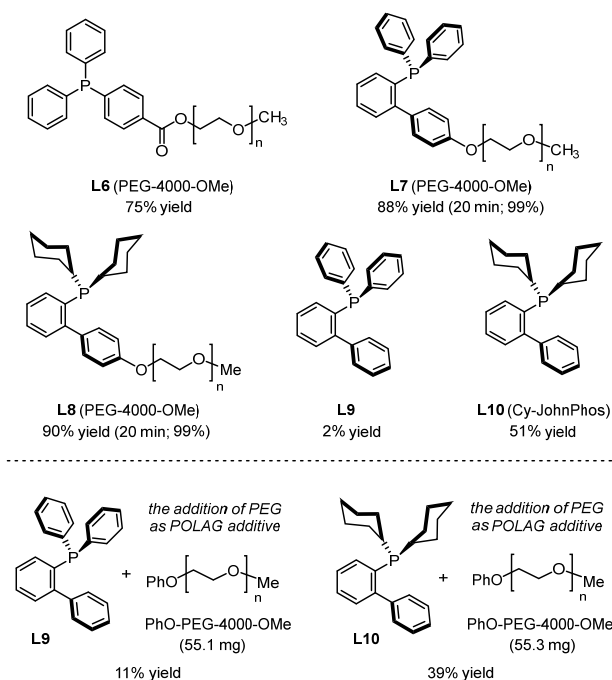
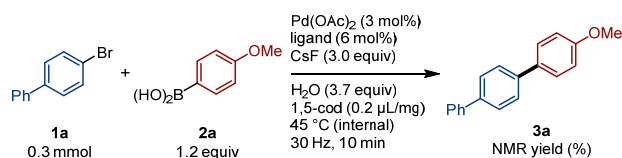
Scheme 5. Synthesis of Biaryl PEGylated Phosphine Ligands **L7** and **L8**.^a



^aFor details of the reaction conditions, see the Supporting Information.

We then investigated the performance of the biaryl PEGylated phosphine ligands **L7** and **L8** in the mechanochemical Suzuki-Miyaura cross-coupling reactions (Scheme 6). When **L7** or **L8** were used as ligands, the reactions showed faster kinetics than when triphenyl phosphine-type PEG ligand **L6** was used, and coupling product **3a** was obtained in excellent yield (88% and 90% yield, respectively). A reaction time of 20 min afforded **3a** in quantitative yield using either **L7** or **L8**. We confirmed that when the corresponding biaryl phosphine ligands that do not contain the PEG chain, i.e., **L9** or **L10** (Cy-JohnPhos), were used, the yield of **3a** decreased significantly (2% and 51%, respectively) under the present mild conditions. Furthermore, the reactions with **L9** or **L10** in the presence of a phenoxy-protected PEG (PEG-4000-OMe) POLAG additive, provided much lower yields of **3a** than the reactions using **L7** or **L8** (11% and 39%, respectively). These results indicate that the introduction of a PEG chain onto the ligands is likely a dominant factor for the observed acceleration, albeit that further fine-tuning of the ligand structure also led to further improvements in the performance of the catalysts.^{50–56}

Scheme 6. Application of Biaryl PEG-Bearing Phosphine Ligands in the Mechanochemical Cross-Coupling Reactions.^a



^aConditions: **1a** (0.30 mmol), **2a** (0.36 mmol), Pd(OAc)₂ (0.009 mmol), ligand (0.018 mmol), CsF (0.9 mmol), H₂O (1.11 mmol), and 1,5-cod (0.20 μL mg⁻¹) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 70 °C to ensure an internal reaction temperature of 45 °C.

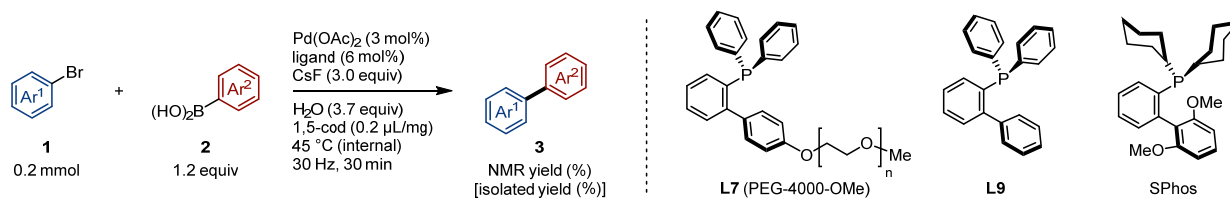
In our previously reported mechanochemical cross-couplings, we found that SPhos gave the highest catalytic activity in mechanochemical Suzuki-Miyaura cross-coupling reactions.^{30,32} Accordingly, we speculated that a PEGylated SPhos

ligand could potentially significantly improve the catalytic activity. We therefore synthesized the PEGylated SPhos-type ligand **L11** to compare its catalytic performance with that of **L7** and **L8** (for details, see the Supporting Information). When SPhos was used as a ligand under the present mild conditions for short reaction time (10 min), **3a** was obtained in 22% yield (Scheme S5). Unfortunately, we also found that the yield of **3a** was not improved when **L11** was used for the cross-coupling (12% yield; Scheme S5), suggesting that **L7** and **L8** are so far the best ligands for this mechanochemical protocol.

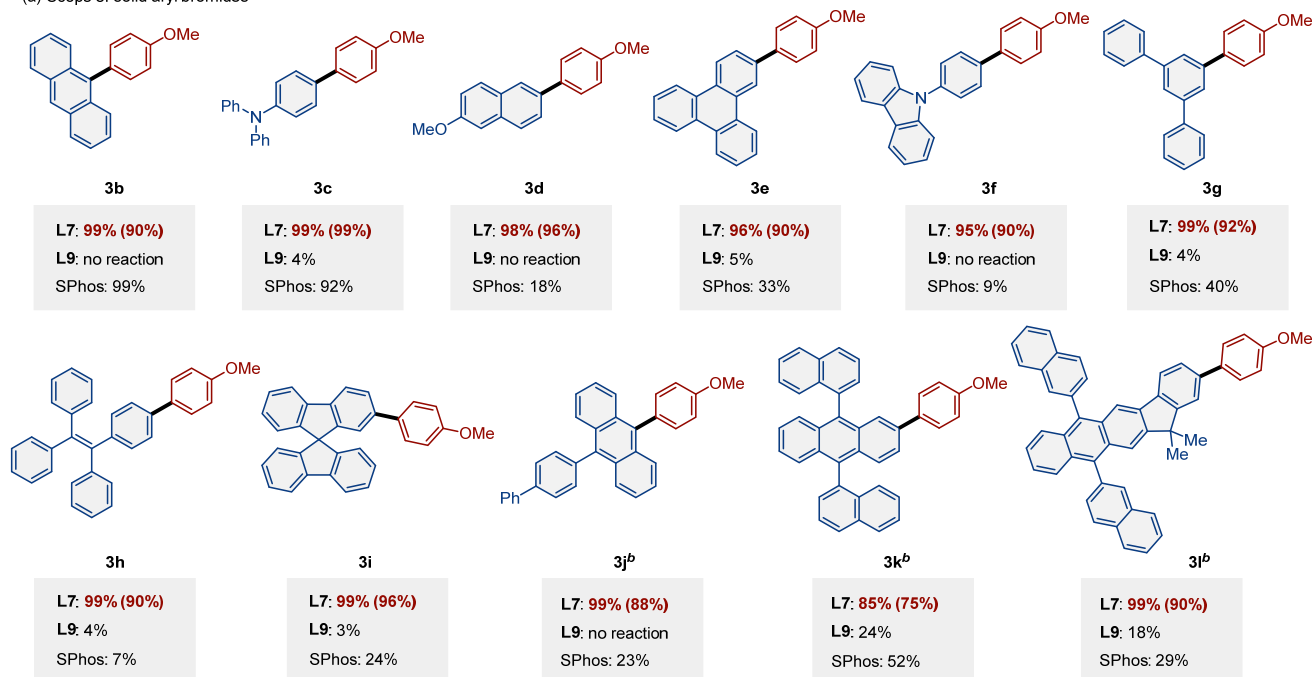
Substrate Scope

To evaluate the performance of the newly developed Pd(OAc)₂/**L7**/1,5-cod catalytic system, mechanochemical cross-coupling reactions with a variety of solid aryl bromides were tested (Table 1a). We selected eleven aryl bromides bearing relatively large polyaromatic structures as coupling partners because these solid substrates often show low reactivity and require high reaction temperatures for efficient cross-coupling.^{30,32} In fact, although 9-bromoanthracene (**1b**) and 4-bromo-*N,N*-diphenylaniline (**1c**) efficiently reacted in the presence of the Pd(OAc)₂/SPhos/1,5-cod catalytic system under near-room-temperature conditions, the reactions of aryl halides bearing larger conjugated systems such as 2-bromotriphenylene (**1e**) and 9-(4-bromophenyl)-9*H*-carbazole (**1f**) afforded poor results (Table 1a). However, we found that substrates **1b–1f** react smoothly with **2a** in the presence of the Pd(OAc)₂/**L7** to give the desired coupling products (**3b–3f**) in high to quantitative yield (90–99%). Importantly, the reactions using **L9**, which is a ligand that does not contain a PEG chain but otherwise resembles **L7**, did not proceed or provided only a small amount of product, suggesting the importance of having a PEG chain on the ligand. Mechanochemical cross coupling of other polyaromatic halides (**1g–1i**) showed a similar reactivity profile in which **L7** afforded the products in significantly higher yield than SPhos or **L9** (Table 1a). We have previously reported that these polyaromatic halides react efficiently in the presence of the Pd(OAc)₂/SPhos/1,5-cod catalytic system at much higher temperature (120 °C). The fact that the reactions with **L7** proceed at near room temperature (45 °C) suggests that **L7** is substantially advantageous in terms of energy savings.^{30,32}

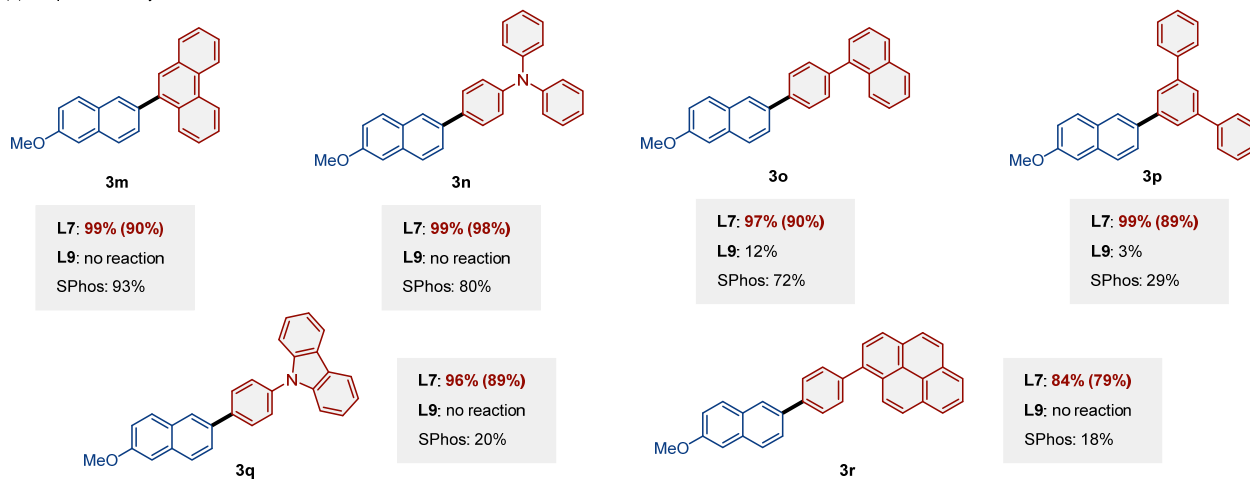
Table 1. Evaluation of the Performance of the Newly Developed Phosphine Ligand L7.^a



(a) Scope of solid aryl bromides



(b) Scope of solid arylboronic acids



^aUnless otherwise noted, the following reaction conditions were used for the solid-state cross-coupling reactions: **1** (0.20 mmol), **2** (0.24 mmol), Pd(OAc)₂ (0.006 mmol), ligand (0.012 mmol), CsF (0.6 mmol), H₂O (0.74 mmol), and 1,5-cod (0.20 μL mg⁻¹) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 70 °C to ensure an internal reaction temperature of 45 °C. ^bReaction time: 90 min.

Subsequently, we turned our attention to the scope of arylboronic acids tolerated under the applied reaction conditions (Table 1b). Arylboronic acids derived from phenanthrene and triphenylamine (**2b** and **2c**) afforded the corresponding coupling products (**3m** and **3n**) in good yield in the presence of the

Pd(OAc)₂/SPhos/1,5-cod system (93% and 80%, respectively). However, as observed with the aryl bromides, arylboronic acids bearing large polyaromatic systems (**2d–2g**) showed poor results when SPhos was used as a ligand. In contrast, when using the PEGylated ligand **L7**, these polyaromatic boronic acids

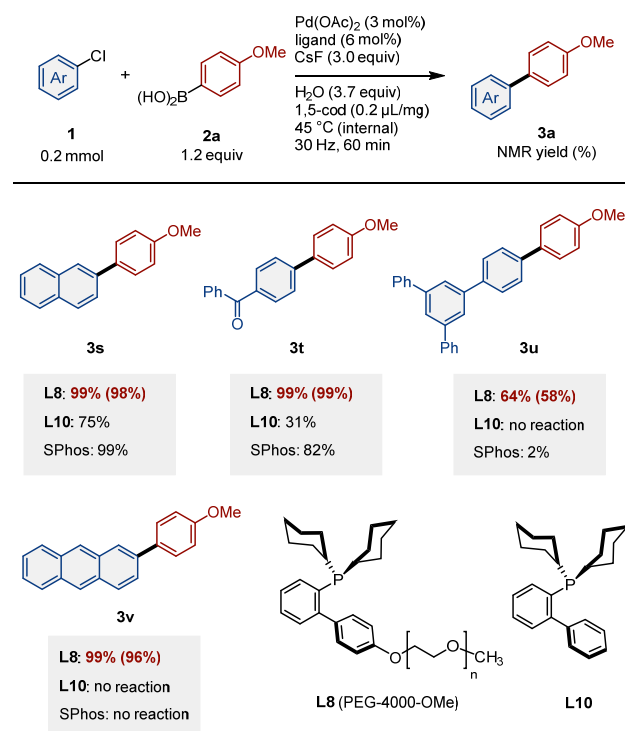
(**2d–2g**) reacted smoothly to afford the desired products (**3o–3r**) in excellent yield (84–99%). Conversely, **L9** did not show such high catalytic activity.

The cross-coupling of solid aryl chlorides is quite challenging due to the intrinsic inertness of carbon–chlorine bonds and the poor mixing efficiency of solid substrates.^{20,26} We found that a more electron-donating ligand (**L8**) showed remarkable catalytic activity in the mechanochemical coupling of solid aryl chlorides under mild reaction conditions (Table 2).⁷³ For example, the reactions of 2-chloronaphthalene (**1m**) and (4-chlorophenyl)(phenyl)methanone (**1n**) with (4-methoxyphenyl)boronic acid (**2a**) proceeded to give the desired coupling products (**3s** and **3t**) in quantitative yield (99% yield in both cases). Furthermore, polycyclic 4-chloro-5'-phenyl-1,1':3',1''-terphenyl (**1o**) and 2-chloroanthracene (**1p**) reacted smoothly to furnish the corresponding products (**3u** and **3v**) in good to excellent yield (64% and 99%, respectively). While the reactions of **1m** or **1n** using SPhos proceeded well, the same catalytic system showed poor activity in the presence of **1o** and **1p**. Moreover, the use of **L10** gave poor results, confirming the requirement of a PEG chain on ligand **L8**.

Finally, we proceeded to investigate the mechanochemical cross-coupling reactions of poorly soluble aryl halides to see whether our developed ligands are effective for the reactions of this class of compounds (Scheme 7). We examined the reaction of Vat Orange 3 (**1q**), a pigment with very low solubility in common organic solvents such as toluene ($<3 \times 10^{-5}$ M). The use of such poorly soluble aryl halides often significantly decreases the efficiency of conventional solution-based cross-coupling reactions.^{30,74,75} Although we have previously demonstrated that our mechanochemical protocol using Pd(Oac)₂/SPhos/1,5-cod facilitates the efficient Suzuki–Miyaura cross-coupling of poorly soluble aryl halides, elevated reaction temperatures (120 °C) are still required.³⁰ However, we found that the use of our newly developed ligands (**L7** and **L8**) facilitates the cross-coupling of **1q** at a lower reaction temperature (80 °C), and affords the coupling product (**3w**) in high yield (88% and 87%, respectively). The use of SPhos resulted in a lower yield of **3w** (69%), suggesting that the PEGylated ligands are also effective for the coupling reactions of poorly soluble aryl halides and that these reactions can be conducted under milder conditions than is possible using previously reported catalysts. Next, we tested the reaction of 3,6,11,14-tetrabromodibenzo[g,p]chrysene (**1r**),^{76–78} which is also poorly soluble in toluene ($<4 \times 10^{-5}$ M). Although the use of **L7** furnished

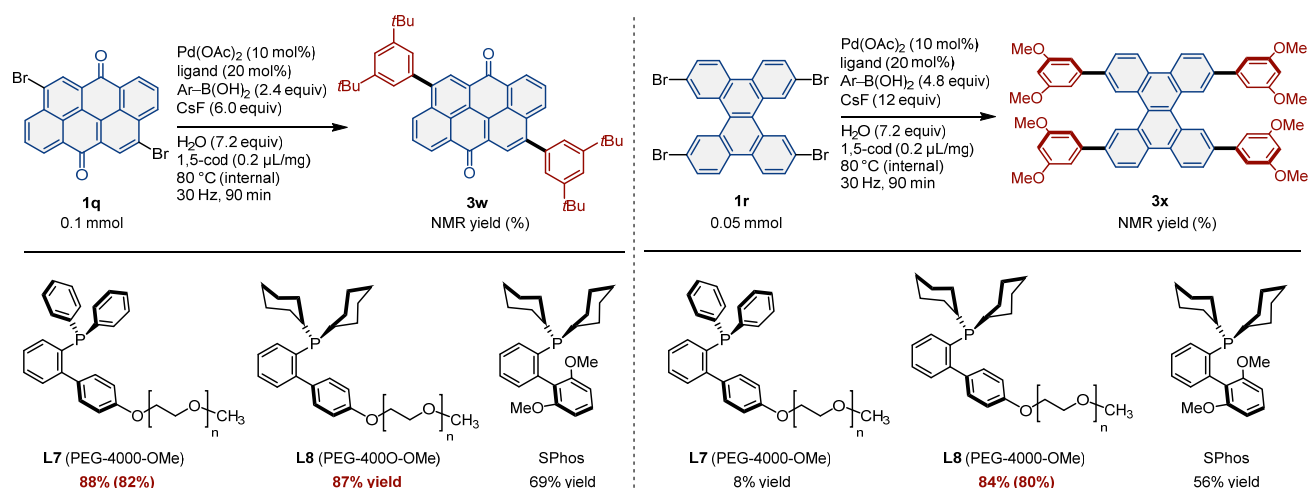
coupling product **3x** in poor yield (8%), a high yield (84%) of **3x** was obtained when **L8** was used. In contrast, the use of SPhos provided **3x** in merely moderate yield (56%), highlighting the high activity of **L8**.

Table 2. Application of PEGylated Ligand L8 to the Mechanochemical Cross Coupling of Solid Aryl Chlorides.^a



^aConditions: **1** (0.20 mmol), **2** (0.24 mmol), Pd(OAc)₂ (0.006 mmol), ligand (0.012 mmol), CsF (0.6 mmol), H₂O (0.72 mmol), and 1,5-cod (0.20 μL mg⁻¹) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 70 °C to ensure an internal reaction temperature of 45 °C.

Scheme 7. Application of the PEGylated Phosphine Ligands to the Mechanochemical Cross Coupling of Poorly Soluble Aryl Halides.^{a,b}



^aThe following reaction conditions were used for the cross-coupling of **1q**: **1q** (0.10 mmol), **2** (0.24 mmol), Pd(OAc)₂ (0.01 mmol), ligand (0.02 mmol), CsF (0.6 mmol), H₂O (0.72 mmol), and 1,5-cod (0.20 μL mg⁻¹) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 150 °C to ensure an internal reaction temperature of 80 °C. ^bThe following reaction conditions were used for the cross-coupling of **1r**: **1r** (0.05 mmol), **2** (0.24 mmol), Pd(OAc)₂ (0.005 mmol), ligand (0.01 mmol), CsF (0.6 mmol), H₂O (0.72 mmol), and 1,5-cod (0.20 μL mg⁻¹) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (5 mm). Ball milling (30 Hz) was carried out while using a heat gun with a preset temperature of 150 °C to ensure an internal reaction temperature of 80 °C.

Mechanistic Studies

To gain mechanistic insight into the observed acceleration effect caused by the PEGylated phosphine ligands, we used powder X-ray diffraction (PXRD) analysis to characterize the solid-state structure of the ball-milled mixtures in the presence of PEGylated ligands (Figure 2). All samples were obtained by ball milling (30 Hz) while using a heat gun with a preset temperature of 70 °C to ensure an internal reaction temperature of 45 °C. A room-temperature PXRD analysis of ball-milled aryl bromide **1a**, ball-milled arylboronic acid **2a**, ball-milled PEGylated ligand **L6**, as well as a ball-milled mixture of **1a**, **2a**, and **L6** (Figure 2) showed that the diffraction pattern of the ball-milled mixture of **1a**, **2a** and **L6** is the sum of the diffraction patterns of each ball-milled component (**1a**, **2a**, and **L6**) and that a new crystalline phase was not observed. This result suggests that the crystallites of **1a** and **2a** still exist in the mixture and that the complete formation of an amorphous phase of solid substrates in the presence of **L6** does not occur under the applied conditions. Therefore, the fluid PEG chain of the ligand and the crystalline solid substrates should form a fluid/crystalline phase-separated structure under mechanochemical conditions.^{61,62}

Subsequently, we carried out a differential scanning calorimetry (DSC) analysis (Figure 3). The DSC analysis was carried out on a ball-milled (30 Hz; 45 °C; 30 min) mixture of aryl bromide **1g** and **L6**. The results showed two melting events for **L6** and **1g** at 55.5 °C and 104.7 °C, respectively, which suggests that a considerable amount of crystallites of **1g** remain intact under the mechanochemical conditions in the presence of **L6**, which is consistent with the PXRD results. We also noted that the melting point of a ball-milled sample of **1g**, in the absence of **L6**, changed from 104.7 °C in the mixture with **L6** to 111.9 °C, and that the peak broadened significantly. This slight lowering of the melting point of **1g** also suggests that the PEG

chain interacts with **1g**, whereby it partially forms a fluid phase with **1g** at the interface of the two species in the phase-separated structure.^{30,32} The DSC analysis of other solid substrates also showed a lowering of their melting points when mixed with a PEGylated phosphine ligand (for details, see the Supporting Information).

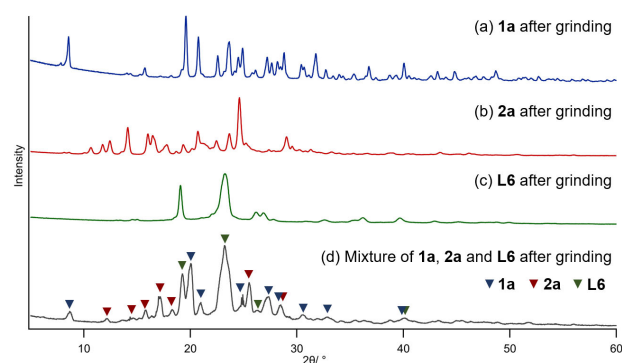


Figure 2. PXRD analysis of a ball-milled mixture of **1a**, **2a**, and **L6** and of the individual components. The PXRD measurements were conducted at room temperature. The samples were obtained by ball milling (30 Hz) for 30 min while using a heat gun with a preset temperature of 70 °C to ensure an internal temperature of 45 °C.

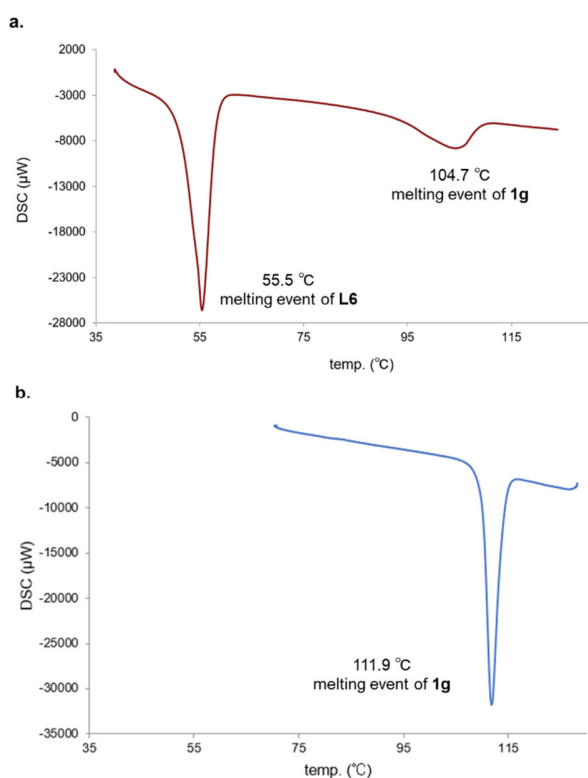


Figure 3. DSC analysis of ball-milled samples of (a) a mixture of **1g** and **L6** and (b) **1g**. The samples were obtained by ball milling (30 Hz) for 30 min while using a heat gun with a preset temperature of 70 °C to ensure an internal temperature of 45 °C.

Next, solid-state (SS) ^{31}P NMR measurements of the crude reaction mixtures were conducted in order to obtain information on the phosphine-ligated palladium species (Figure 4). Crude mixtures obtained from reactions of **1a** with **2a** under the optimized conditions for 30 min were used for the SS ^{31}P NMR analysis. The SS ^{31}P NMR spectrum of the ball-milled mixture of **1a** and **2a** in the presence of the $\text{Pd}(\text{OAc})_2$ (3 mol%)/**L6** (6 mol%) showed that the signals derived from **L6** (-5.45 ppm) had completely disappeared, and only one broad signal (25.3 ppm) was observed. Given that two equivalents of **L6** were used relative to the quantity of palladium, the signal is likely derived from a palladium species ligated by two phosphine ligands. This result suggests that the **L6**-ligated palladium species are generated quantitatively, even under the mild ball-milling conditions (Figure 4a).^{78–82} Notably, the SS ^{31}P NMR spectrum of the reaction mixture of **1a** and **2a** in the presence of the $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%) and the benzoyl-protected PEG (BzO-PEG-4000-OMe) POLAG additive, showed a mixture of signals derived from PPh_3 and the PPh_3 -ligated palladium species (Figure 4b). Following a reaction that only uses PPh_3 , the major signal observed was that of free PPh_3 (Figure 4c). Given that the coordination ability of **L6** and PPh_3 should be comparable in solution, the differences observed here between **L6** and PPh_3 under solvent-less mechanochemical conditions are most likely caused by the PEG chain on **L6**. At present, we assume that the stabilizing effect of **L6** is caused by the immobilization of the palladium-phosphine species in the fluid polymeric phase created by the PEG chains. The palladium- PPh_3 complex is likely to be mixed into the crystalline solid

phase, leading to catalyst deactivation via the formation of palladium black following ligand dissociation.

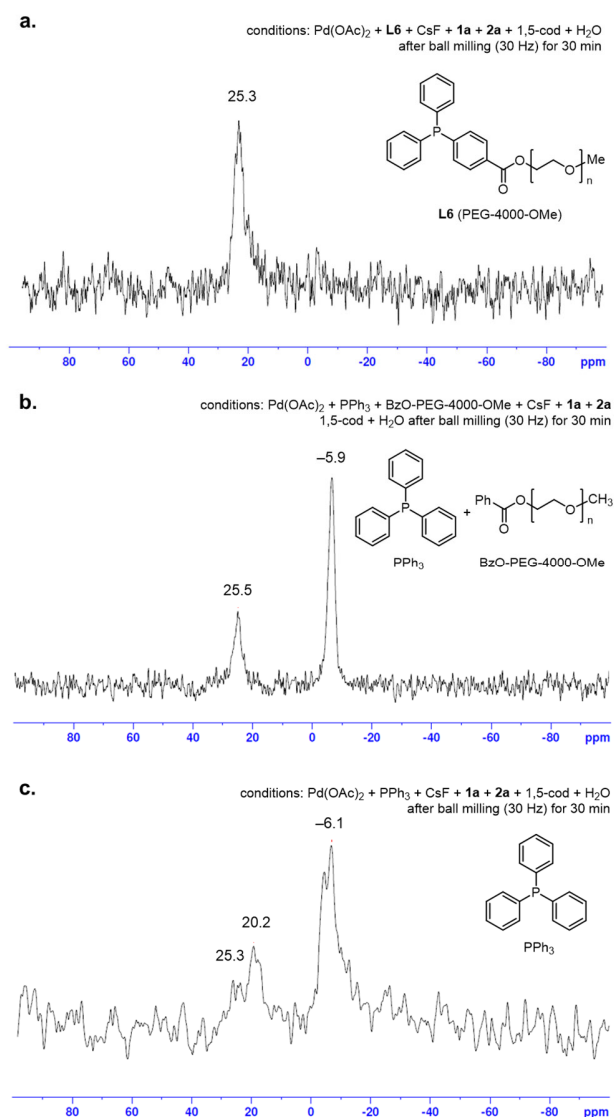


Figure 4. Solid-state (SS) ^{31}P NMR analysis of palladium species in the crude reaction mixtures following solid-state cross-coupling reactions. SS ^{31}P NMR spectra after ball milling of (a) a mixture of **1a** and **2a** in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol%)/**L6** (6 mol%), (b) reaction mixture of **1a** and **2a** in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%) and a benzoyl-protected PEG POLAG additive, and (c) reaction mixture of **1a** and **2a** in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%).

Next, to examine if palladium aggregation occurs under our mechanochemical conditions, we used TEM imaging to characterize the *in-situ*-generated palladium nanoparticles in the crude reaction mixture of **1a** and **2a** (Figure 5). The image in Figure 5a clearly shows that, in the presence of the $\text{Pd}(\text{OAc})_2$ (3 mol%)/**L6** (6 mol%), relatively small palladium nanoparticles (approximate size: 2–3 nm) are formed in the reaction mixture. Notably, high levels of aggregation of the palladium particles were not observed, and the particle size was smaller than those previously obtained from reactions that use the

$\text{Pd}(\text{OAc})_2/\text{DavePhos}/1,5\text{-cod}$ catalyst system, which suggests that the PEGylated ligand may reduce the amount of *in-situ*-formed palladium black.²⁸ Conversely, the image obtained of the palladium species formed in the presence of the $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%) catalyst and a benzoyl-protected PEG (BzO-PEG-4000-OMe) POLAG additive, showed much larger palladium particles (approximate size: 2–10 nm) than those observed following the reaction with **L6** (Figure 5b). This result is consistent with Lamaty's report, in which relatively large palladium nanoparticles were formed after ball milling a mixture of a palladium catalyst and PEG under POLAG conditions.³⁸ The palladium species generated following the reaction that used the $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%) catalyst without a PEG additive aggregated into dense particles (Figure 5c). These results demonstrate that PEGylated phosphine ligands can suppress the aggregation of palladium catalysts under mechanochemical conditions.

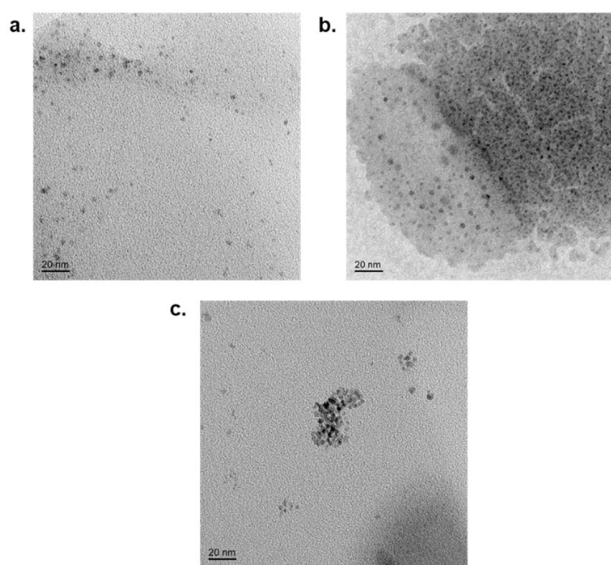
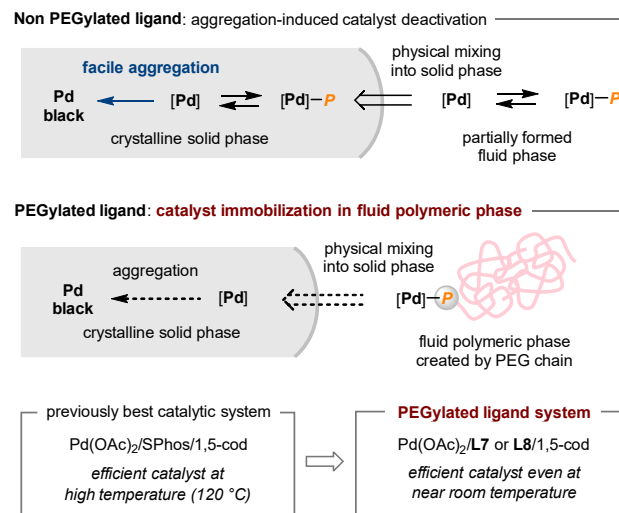


Figure 5. TEM images of the palladium nanoparticles observed in the ball-milled crude reaction mixtures of: (a) a mixture of **1a** and **2a** in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol%)/**L6** (6 mol%), (b) a mixture of **1a** and **2a** in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%) with a benzoyl-protected PEG (BzO-PEG-4000-OMe) POLAG additive, and (c) a mixture of **1a** and **2a** in the presence of $\text{Pd}(\text{OAc})_2$ (3 mol%)/ PPh_3 (6 mol%). Scale bar in the TEM images (bottom left): 20 nm.

The results of these mechanistic studies are summarized in Scheme 8, and the role of the PEGylated ligands is proposed. Based on the PXRD and DSC analysis, we confirmed that a substantial amount of crystallites of the solid substrates remain intact under the mechanochemical conditions in the presence of the PEGylated ligand, suggesting that the ligand and crystalline solid substrates most likely form a fluid/crystalline phase-separated structure (Scheme 8).^{61,62} Based on the SS ³¹P NMR and TEM analysis, we infer that the palladium species formed in the presence of non-PEGylated phosphine ligands are likely to be mixed into the crystalline solid phase and aggregate there into dense nanoparticles, thus leading to catalyst deactivation via the formation of palladium black (Scheme 8). In contrast, in the presence of the PEGylated ligands, this deactivation pathway can be suppressed by efficient immobilization of the phosphine-ligated palladium(0) species in the fluid polymeric phase created by the PEG chain (Scheme 8). These

experimental observations are in good agreement with the approach we propose for mechanochemistry-directed ligand design in Figure 1b. Based on the results of substrate scope, it was found that the newly developed $\text{Pd}(\text{OAc})_2/\mathbf{L7}/1,5\text{-cod}$ and $\text{Pd}(\text{OAc})_2/\mathbf{L8}/1,5\text{-cod}$ systems gave much higher yields of the coupling products than the previous $\text{Pd}(\text{OAc})_2/\text{SPhos}/1,5\text{-cod}$ system in a short reaction time at near room temperature.

Scheme 8. Proposed Mechanistic Role of the Newly Developed PEGylated Ligands.



CONCLUSIONS

Guided by a combination of mechanistic analysis and mechanochemistry-directed ligand design, we have developed new phosphine ligands that are capable of promoting highly efficient mild mechanochemical Suzuki-Miyaura cross-coupling reactions that involve a wide variety of solid coupling partners. This is the first report on the development of a high-performance ligand specifically designed for a mechanochemical reaction environment. Notably, the newly developed ligands, which bear a PEG chain, showed much higher efficiency than previously reported catalysts that were originally developed for conventional solution-based reactions. Based on powder X-ray diffraction, differential scanning calorimetry, solid-state ³¹P NMR, and transmission electron microscopy analyses, we infer that the PEGylated ligands allow phosphine-ligated palladium(0) species to be efficiently immobilized in a fluid phase created by the PEG chains. Deactivation of the catalyst in the crystalline solid phase occurs via aggregation of the palladium to form palladium black, which is suppressed by the immobilization of the palladium in the fluid phase. This study suggests that mechanochemistry-directed ligand design has the potential to inspire the development of powerful transition-metal-catalyzed cross-coupling strategies for the synthesis of valuable molecules in a way that is cost- and energy-efficient as well as environmentally friendly and thus attractive for industrial applications.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>. Experimental procedures, compound characterization data, NMR spectra (PDF).

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Notes

Any additional relevant notes should be placed here.

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