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Mechanochemistry-directed ligand design for enhanced reactivity and enantioselectivity in solventless palladium-catalyzed conjugate arylations

Keisuke Kondo,^a Hina Shoji,^a Koji Kubota ^{*ab} and Hajime Ito ^{*ab}

Mechanochemical organic transformations catalyzed by transition-metal catalysts have emerged as efficient, solvent-minimized, and sustainable approaches for the synthesis of valuable molecules. Notably, these reactions often exhibit enhanced reaction rates that are not achievable in traditional solution-based systems, highlighting the unique benefits of mechanochemistry. Yet, the heterogeneous solid-state reaction environment often poses challenges to achieving high catalytic activity and stereoselectivity when catalytic systems developed for solution are applied under mechanochemical conditions. Herein, we report the development of a bipyridine ligand bearing a poly(ethylene)glycol (PEG) chain to enable highly efficient mechanochemical palladium-catalyzed conjugate addition of arylboronic acids. Traditional bipyridine ligands, originally developed for solution, show poor performance under mechanochemical conditions, highlighting the effectiveness of the PEGylated ligand. Furthermore, we discovered that a chiral pyridine–oxazoline ligand with a PEG chain enables mechanochemical asymmetric conjugate addition to chromone derivatives with superior yield and enantioselectivity compared to conventional chiral ligands optimized for solution. The present study represents the first example of mechanochemistry-directed ligand design for an enantioselective reaction. This approach is expected to accelerate the development of transition-metal-catalyzed reactions that are otherwise difficult to accomplish with ligands developed for solution-based chemistry.

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Introduction

Mechanochemical organic synthesis using ball milling is an exciting research field that has led to solvent-less and sustainable synthetic solutions.^{1–18} In particular, mechanochemical transition-metal-catalyzed transformations have been extensively studied for the synthesis of valuable molecules in an environmentally friendly manner.^{19–21} These reactions typically rely on the use of catalytic systems originally developed for conventional solution-based reactions.^{22–31} However, due to the different reaction environments found in heterogeneous mechanochemical-based and homogeneous solution-based conditions, achieving high catalytic activity with traditional solution-based catalytic systems is often challenging and requires laborious optimization studies.^{22–32} Consequently, certain transition-metal-catalyzed reactions have not yet been successfully realized under mechanochemical conditions. Associated with this challenge, there are still only a few reports on mechanochemical enantioselective reactions using chiral transition-metal catalysts, as it is often difficult to achieve

simultaneously high product yield and high enantioselectivity.^{25,33–36} This difficulty is likely due to strong anisotropic interactions with surrounding molecules in solids, which are more pronounced than in solution, and which can interfere with chiral recognition of the catalysts, often reducing stereoselectivity under mechanochemical conditions. However, no clear catalyst-design principle has been established to address this challenge. Therefore, the exploration of new catalysts based on unique design principles for mechanochemical reaction environments is desirable for the development of highly efficient, stereoselective, and industrially attractive transition-metal-catalyzed mechanochemical reactions.

We have previously reported the first example of the development of a transition-metal-based catalytic system specifically designed for the use under mechanochemical reaction conditions.³⁷ We found that phosphine ligands bearing poly(ethylene)glycol (PEG) chains were capable of promoting highly efficient mechanochemical palladium-catalyzed Suzuki–Miyaura cross-coupling reactions under mild conditions (Scheme 1a). Notably, this mechanochemistry-directed ligand design created a catalytic system with superior activity compared to traditional catalysts, significantly expanding the substrate scope. Mechanistic studies showed that these new ligands facilitate the immobilization of palladium-based active species in the fluid polymeric phase created by the PEG chains,

^aDivision of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, Japan. E-mail: kbt@eng.hokudai.ac.jp; hajito@eng.hokudai.ac.jp

^bInstitute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido, Japan



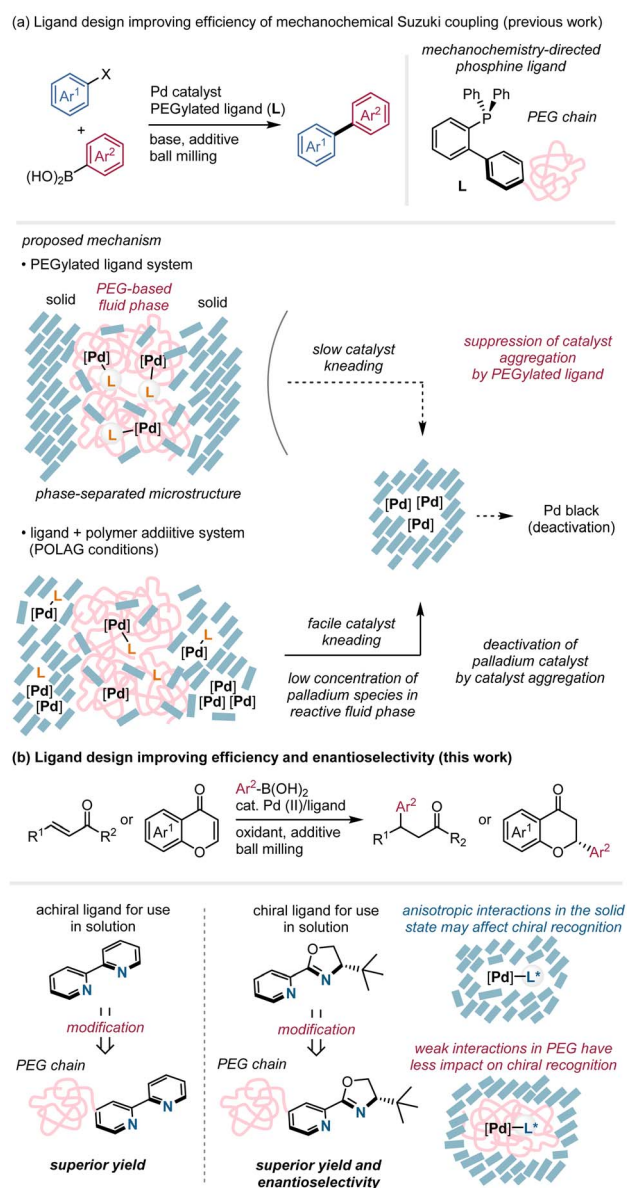
which results in prevention of the aggregation-induced deactivation of the catalyst in the crystalline solid phase (Scheme 1a). In contrast, reactions employing transitional catalysts under the polymer-assisted grinding (POLAG) conditions fail to sufficiently inhibit catalyst deactivation, owing to the low concentration of palladium-based active species in the reactive fluid phase (Scheme 1a).^{37–39}

Motivated by this success, we explored whether this mechanochemistry-directed ligand design could facilitate the development of highly efficient, new transition-metal-catalyzed mechanochemical reactions that are challenging to achieve with traditional catalysts originally designed for the use in solution. In the present study, we succeeded in developing the first mechanochemical protocol for palladium-catalyzed conjugate arylation reactions enabled by a mechanochemistry-directed PEGylated bipyridine ligand (Scheme 1b).^{40–45} Since

the first report by Miyaura and co-workers,⁴⁰ the palladium-catalyzed conjugate addition of arylboronic acids has been widely used in organic synthesis to construct β -functionalized carbonyl compounds. However, a mechanochemical protocol for the palladium-catalyzed conjugate addition of arylboronic acids has not yet been explored. Our initial studies revealed that traditional bipyridine ligands, which are used in the solution-based conjugate addition, show poor catalytic activity under mechanochemical conditions.^{42–45} In contrast, a newly developed PEGylated bipyridine ligand facilitates the mechanochemical conjugate addition to give the desired arylated products in excellent yield. While the previously reported solution-based methods typically require long reaction times (*ca.* 12–72 hours),^{40–45} our mechanochemical reaction proceeds rapidly (\sim 60 min). Furthermore, we envisioned that the fluid PEG domain, where weak interactions between the palladium catalyst and substrate molecules exist, could offer a reaction environment suitable for the chiral recognition of chiral catalysts in the solid state, and thus high enantioselectivity could be achieved under mechanochemical conditions (Scheme 1b). Based on this concept, we developed a chiral pyridine-oxazoline ligand bearing a PEG chain and tested its catalytic activity in a mechanochemical palladium-catalyzed enantioselective conjugate addition.^{46–51} Fortunately, this new chiral catalytic system affords the targeted products in higher yield and enantioselectivity than traditional catalysts that use *t*-BuNicox or *t*-BuPyOx under mechanochemical conditions. Notably, this is the first example of an enantioselective mechanochemical metal-catalyzed 1,4-addition reaction. Our results suggest that mechanochemistry-directed ligand design can significantly accelerate the development of highly efficient mechanochemical transition-metal-catalyzed reactions, which are otherwise challenging to achieve using conventional ligands.

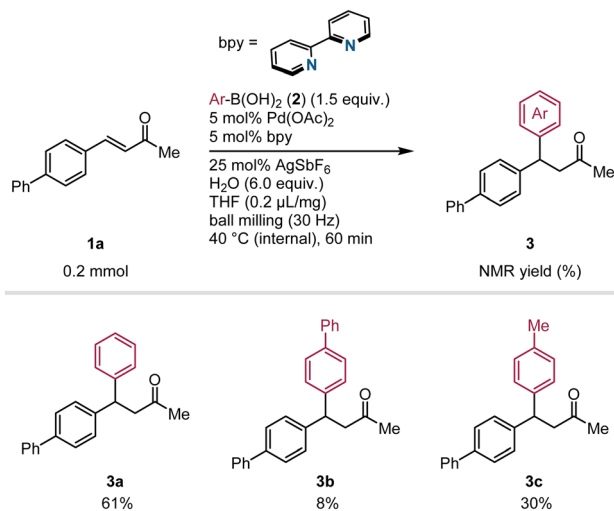
Results and discussion

We commenced this study by optimizing the reaction conditions for the palladium-catalyzed 1,4-addition using 2,2'-bipyridine (bpy) as the ligand, which is the ligand traditionally used under the solution-based conditions reported by Lu and co-workers (for details, see page S20 in the SI).⁴² All mechanochemical reactions were carried out in a RetschMM400 mixer mill (stainless-steel milling jar: 1.5 mL; stainless-steel ball: 7 mm diameter). 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 SI).⁵² After extensive optimization, we found that the conjugate arylation of phenylboronic acid (2a) to (*E*)-4-[(1,1'-biphenyl)-4-yl]but-3-en-2-one (1a) gave the desired product (3a) in moderate yield (61%) in the presence of 5 mol% Pd(OAc)₂, 5 mol% bpy, 25 mol% AgSbF₆, H₂O (6.0 equiv.) and THF (0.2 μ L mg⁻¹) at 40 °C (Scheme 2). The silver salt was added to generate the catalytically active cationic palladium species.⁵³ It also plays a role in regenerating the active palladium(II) species from catalytically inactive palladium(0), which can form *via* homocoupling of arylboronic acids.⁵³ Attempts to improve the reaction yield were unsuccessful. Under the optimized conditions,



Scheme 1 The development of mechanochemistry-directed ligands.

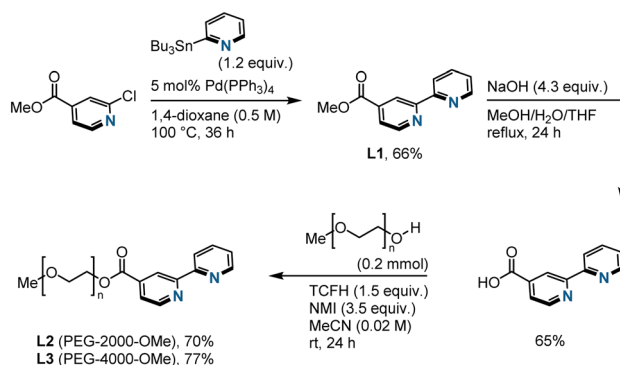




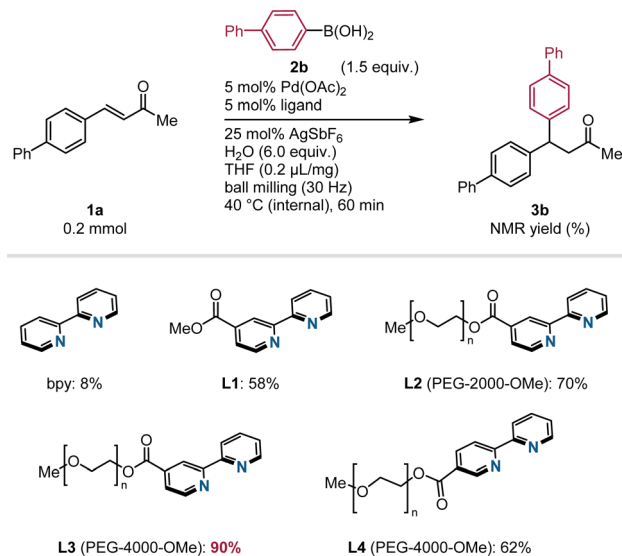
Scheme 2 Initial attempts at palladium-catalyzed mechanochemical conjugate additions using bpy as the ligand.

the reaction using 4-biphenylboronic acid (**2b**) and 4-methylphenylboronic acid (**2c**) gave poor results (8% and 30% yield, respectively). These results as well as our previous study on the development of mechanochemistry-directed phosphine ligands motivated us to explore 2,2'-bipyridine ligands bearing a PEG chain to realize highly efficient mechanochemical palladium-based 1,4-arylation reactions.

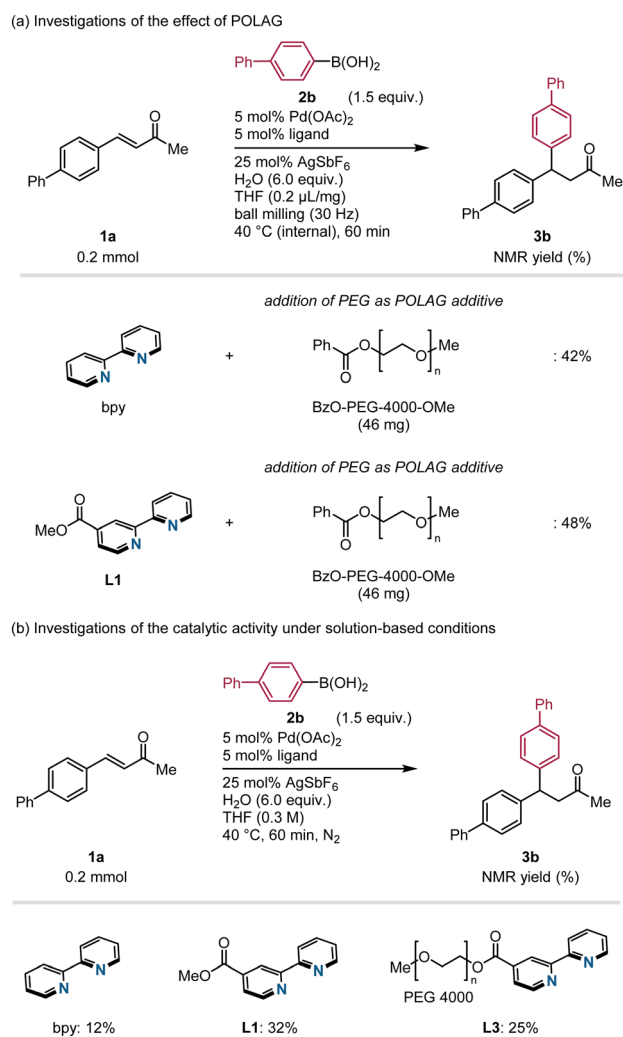
Based on our previous report,³⁷ we designed two PEG-bound bipyridine ligands (**L2** and **L3**) (Scheme 3). The target ligands were successfully synthesized from commercially available methyl 2-chloroisonicotinate in three steps (Scheme 3). The first step is a Stille cross-coupling with 2-(tributylstannyl)pyridine, which readily afforded the desired mono-methyl-ester-substituted bipyridine (**L1**) in 66% yield. Next, hydrolysis of the ester group provided the corresponding carboxylic acid in 65% yield. Finally, a condensation with the corresponding poly(ethylene)glycol mono-methyl ether afforded **L2** (PEG-2000-OMe) and **L3** (PEG-4000-OMe) in 70% and 77% yield, respectively.³⁴ Although these bipyridine ligands are new compounds and their application in catalysis has not been explored before, structurally similar PEGylated bipyridines have been



Scheme 3 Synthesis of PEGylated bipyridine ligands **L2** and **L3**.



Scheme 4 Testing the catalytic activity of PEGylated bipyridine ligands **L1**–**L4**.

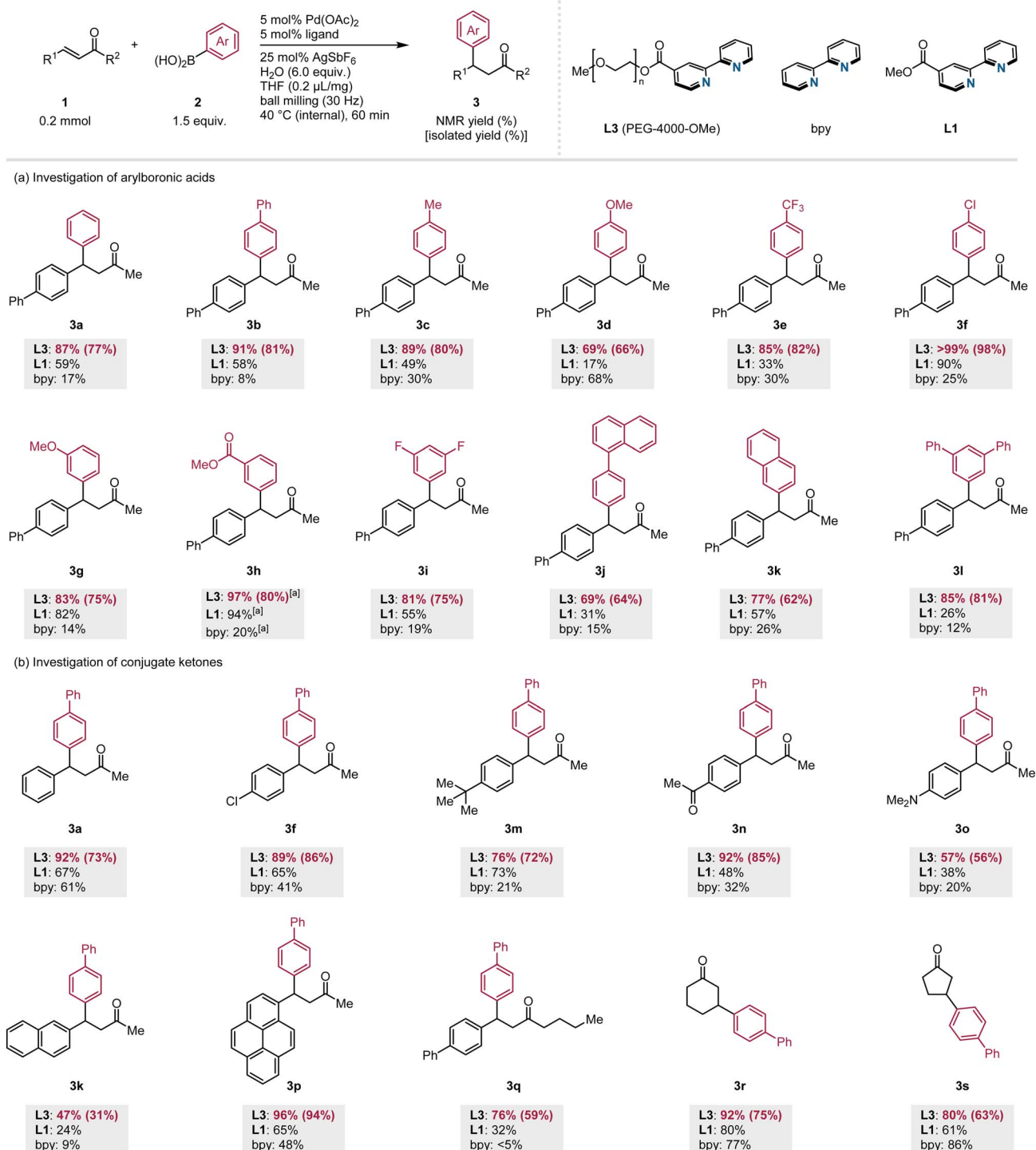


Scheme 5 Control experiments.



synthesized and used to generate water-soluble metal complexes for applications in chemical biology⁵⁵ and oxidize alcohols under aerobic conditions.⁵⁶

Next, we applied the ligands **L1**–**L3** in the palladium-catalyzed mechanochemical 1,4-addition between **1a** and **2b** (Scheme 4). The reaction using the mono-methyl-ester-substituted bipyridine **L1** improved the reactivity, albeit that



Scheme 6 Substrate scope of the mechanochemical palladium-catalyzed conjugate addition to α,β -conjugated ketones. Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv.), Pd(OAc)₂ (5 mol%), ligand (5 mol%), AgSbF₆ (25 mol%), H₂O (6.0 equiv.) and THF (0.2 μL/mg⁻¹) in a stainless-steel milling jar (1.5 mL) using a stainless-steel ball (diameter: 7 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 40 °C. Yields were determined via ¹H NMR analysis. Isolated yields are shown in parentheses. ^aA preset temperature of 120 °C to ensure an internal reaction temperature of 60 °C.



the yield was still moderate (58%). Fortunately, **L2** showed better catalytic activity (70%), and **L3**, which bears an even longer PEG chain, improved the reaction efficiency further (90%). Testing a bipyridine ligand bearing a PEG chain (PEG-4000-OMe) at a different position (**L4**) furnished **3b** in moderate yield (62%). Although further investigation is warranted, we propose that **L3**, being less electron-donating than **L4**, exhibits superior catalytic performance because a higher Lewis acidity at the palladium center is crucial for this reaction.

To clarify the effectiveness of the PEGylated ligands, we carried out the reactions under polymer-assisted grinding (POLAG) conditions (Scheme 5a).^{38,39} When the reactions using bpy or **L1** in the presence of a POLAG additive, *i.e.*, a benzoyl-protected PEG (BzO-PEG-4000-OMe) with a structure that resembles that of **L3**, were conducted, **3b** was obtained in only moderate yield (bpy: 42%; **L1**: 48%), *i.e.*, a significantly lower yield than when using PEGylated ligand **L3**. These results highlight the importance of a PEG chain that is covalently connected to the ligand framework for achieving efficient 1,4-addition under mechanochemical conditions. We propose that covalent attachment of the PEG chain to the ligand promotes effective immobilization of palladium-based active species within the fluid polymeric phase generated by the PEG chains, thereby enhancing catalytic performance in the 1,4-addition.³⁷

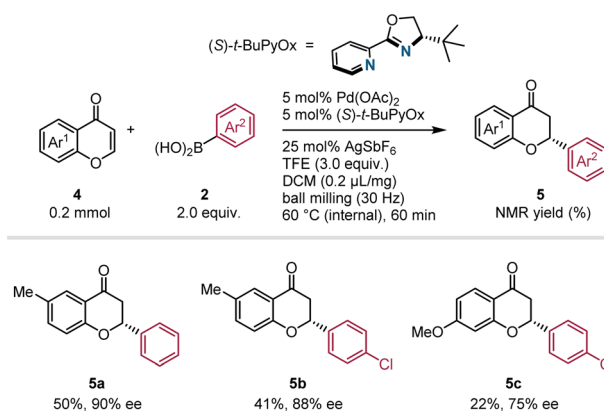
To confirm whether the acceleration effect arising from the use of the PEGylated bipyridine ligands is only observed under mechanochemical conditions, we carried out solution-based reactions using THF (0.3 M) at 40 °C (Scheme 5b). The conjugate addition using bpy or **L1** afforded **3b** in 12% or 32% yield, respectively, which is comparable to the results obtained under mechanochemical conditions. In contrast, the reaction using **L3** yielded **3b** in only 25% yield, which is significantly lower than when using **L3** under mechanochemical conditions (90%). These results suggest that the PEGylated bipyridine ligands only improve the reaction efficiency under mechanochemical conditions.

Next, we investigated the substrate scope of the mechanochemical palladium-catalyzed conjugate addition of arylboronic acids to α,β -conjugated carbonyl compounds facilitated using the newly developed ligand **L3** (Scheme 6). Overall, **L3** showed a significantly higher catalytic activity in reactions with a variety of arylboronic acids than conventional bipyridine ligands (**3a–3l**) (Scheme 6a). The conjugate addition of phenyl boronic acids bearing electron-donating groups at the para position proceeded smoothly to give the desired products in high yield (**3c**: 80%; **3d**: 66%). Furthermore, the reactions using boronic acids with electron-deficient groups at the para position, such as trifluoromethyl and chlorine groups, also afforded excellent results (**3e**: 82%; **3f**: 98%). Meta-substituted arylboronic acids readily reacted and the desired products (**3g–3i**) were obtained in good to high yield (**3g**: 75%; **3h**: 80%; **3i**: 75%). In particular, **L3** showed excellent catalytic activity in reactions with π -conjugated boronic acids (**2j–2l**) when compared to **L1** and bpy (**3j**: 64%; **3k**: 62%; **3l**: 81%).

Moreover, **L3** facilitates the reactions of various types of α,β -conjugated carbonyl compounds with significantly better results compared to conventional ligands (**3a–3s**) (Scheme 6b).

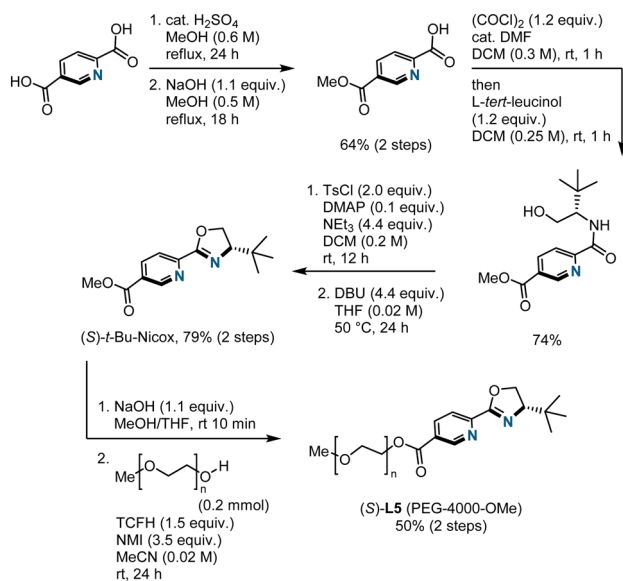
Ketones bearing various functional groups such as chloro (**1c**), *tert*-butyl (**1d**), acetyl (**1e**), and amino (**1f**) groups reacted smoothly to yield the corresponding products (**3f–3o**) in good to excellent yield (**3f**: 86%; **3m**: 72%; **3n**: 85%; **3o**: 56%). The conjugate addition of **2b** to ketones with π -extended arene moieties (**1g** and **1h**) also proceeded efficiently (**3k**: 31%; **3p**: 94%). The reaction using an *n*-propyl-substituted ketone (**1i**) proceeded with slightly decreased yield, but **L3** still showed significantly higher catalytic activity than **L1** and bpy (**3q**: 59%). Furthermore, cyclic ketones (**1j** and **1k**) were also compatible with this reaction and **3r** and **3s** were formed in 75% and 63% yield, respectively.

Next, we investigated the applicability of this mechanochemistry-directed ligand design to the development of a new enantioselective catalytic system for another mechanochemical reaction. Based on the previous solution-based conditions for the palladium-catalyzed enantioselective conjugate addition reported by Stoltz and co-workers,⁵⁷ we conducted initial optimization studies for a mechanochemical palladium-catalyzed enantioselective conjugate addition to chromone derivatives using (*S*)-*t*-Bu-PyOx, which is the optimal chiral ligand under Stoltz's conditions. We obtained arylated product **5a** in moderate yield with high enantioselectivity (50%, 90% ee) following the reaction between 6-methylchromone (**4a**) and phenylboronic acid (**2a**) in the presence of 5 mol% Pd(OAc)₂, 5 mol% (*S*)-*t*-Bu-PyOx, 25 mol% AgSbF₆, 2,2,2-trifluoroethanol (TFE) (3.0 equiv.), and DCM (0.2 μ L mg⁻¹) (Scheme 7). The obtained enantioselectivity (90% ee) is comparable to that of the solution-based protocol, albeit that the yield of the mechanochemical reaction was not sufficient (50%). The reaction of 4-chlorophenylboronic acid (**2f**) also delivered high enantioselectivity, albeit only a low yield (41%, 88% ee). Unfortunately, the mechanochemical reaction of 7-methoxychromone (**4b**) in the presence of (*S*)-*t*-Bu-PyOx provided the product in merely low yield and enantioselectivity (22%, 75% ee). These unsatisfactory results with (*S*)-*t*-Bu-PyOx under mechanochemical conditions motivated us to develop mechanochemistry-directed chiral pyridine-oxazoline ligands.



Scheme 7 Initial attempts at mechanochemical asymmetric conjugate addition using the (*S*)-*t*-BuPyOx ligand.

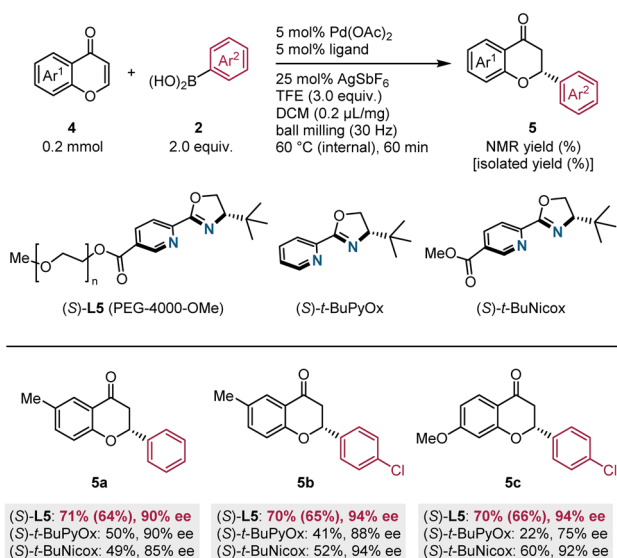




Scheme 8 Synthesis of PEGylated chiral pyridine-oxazoline ligand (*S*)-L5.

A chiral pyridine-oxazoline ligand bearing a PEG chain [(*S*)-L5] was successfully synthesized in seven steps (Scheme 8). (*S*)-*t*-BuNicox was synthesized from commercially available isochinomeronic acid *via* condensation, selective hydrolysis, amidation, and intramolecular cyclization according to a literature report by Oestreich and co-workers.⁵⁸ Next, the ester group was saponified and a reaction with PEG-4000-OMe was conducted to afford (*S*)-L5 in 50% yield over two steps.

Subsequently, we evaluated the catalytic activity of (*S*)-L5 in the palladium-catalyzed enantioselective conjugate addition under mechanochemical conditions (Scheme 9). We found that



Scheme 9 Highly efficient mechanochemical enantioselective conjugate addition enabled by mechanochemistry-directed ligand design.

the reactions using (*S*)-L5 as a chiral ligand provided the desired products in higher yield and enantioselectivity than the reactions using (*S*)-*t*-BuPyOx (**5a**: 64%, 90% ee; **5b**: 65%, 94% ee; **5c**: 66%, 94% ee) under mechanochemical conditions. The use of a non-PEGylated analogue, (*S*)-*t*-Bu-Nicox, improved the efficiency slightly, albeit that the results did not reach the outcomes achieved using (*S*)-L5, demonstrating the importance of the PEG moiety for improving the catalytic activity and enantioselectivity under mechanochemical conditions. Furthermore, while Stoltz's conditions require 12 hours,⁵⁷ this mechanochemical enantioselective conjugate addition proceeds rapidly, reaching completion within 60 minutes.

Conclusions

In summary, we have developed the first mechanochemical protocol for a solvent-less palladium-catalyzed conjugate arylation, which was enabled by designing new mechanochemistry-directed bipyridine and chiral pyridine-oxazoline ligands. Traditional bipyridine ligands optimized for solution-based reactions usually show poor activity under mechanochemical conditions. In contrast, the newly developed PEGylated bipyridine ligand demonstrated significantly improved efficiency in the solvent-less mechanochemical environment. Whereas solution-based methods typically require up to 72 hours to reach completion, the mechanochemical conditions developed here enable much faster reaction kinetics, completing the reactions for most substrates in only 60 minutes. Furthermore, we discovered that the introduction of a PEG chain onto a chiral pyridine-oxazoline framework not only enhanced the catalytic activity but also resulted in higher enantioselectivity for the conjugate arylation of chromone derivatives. For example, a representative case showed 94% ee, compared to 75% ee when the conventional solution-based ligands were used. The present study thus showcases that the development of mechanochemistry-directed ligands has significant potential to accelerate the development of highly efficient, stereoselective, and sustainable mechanochemical transition-metal-catalyzed transformations under solvent-minimized conditions.

Author contributions

Koji Kubota and Hajime Ito conceived and designed the study. All authors co-wrote the paper. Keisuke Kondo and Hina Shoji performed the chemical experiments and analyzed the data. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d6mr00032k>.



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