Selective Mechanochemical Monoarylation of Unbiased Dibromoarenes by *In-situ* Crystallization

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Supporting Information Placeholder

ABSTRACT: Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions of liquid, unbiased dibromoarenes under mechanochemical conditions selectively afford the monoarylated products. The lower reactivity of the crystalline monoarylated products relative to the liquid starting materials should be attributed predominantly to the low diffusion efficiency of the former in the reaction mixture, which results in a selective monoarylation. The present study sheds light on a novel approach using *in-situ* phase transitions in solids to design selective organic transformations that are difficult to achieve via conventional solution-based synthesis.

Recently, mechanochemical organic transformations using a ball mill have attracted considerable interest as a green and sustainable synthetic technique.[1] Apart from the environmental benefits, mechanochemical approaches could potentially provide exciting opportunities to access large areas of hitherto unexplored chemical space that exhibit reactivity and selectivity different to that of conventional solution-based reactions.[1] Although some unique reactivity patterns have already been discovered,[1d, 2-16] the development of site- and chemoselective synthetic strategies using mechanochemistry that enable the rapid construction of molecular complexity remains unexplored.[13]

Mono-selective Suzuki-Miyaura cross-coupling reactions of dihaloarenes would represent an ideal method for the synthesis of functionalized aryl halides, which are useful building blocks for the construction of complex polyaromatic structures.[17-22] Conventionally, chemists rely on the use of starting materials that bear different halide groups with a relatively large reactivity difference or the use of an excess of dihaloarenes to achieve high selectivity toward monoarylation.[17] However, many of these approaches are costly and wasteful. Although the monoarylation of unbiased dihaloarenes with certain halide groups through elaborate catalyst design and/or the fine-tuning of reaction parameters such as temperature, solvent, and additives has been reported,[18-22] the exploration of conceptually new and generally applicable strategies to control and improve the monoarylation selectivity remains in high demand.

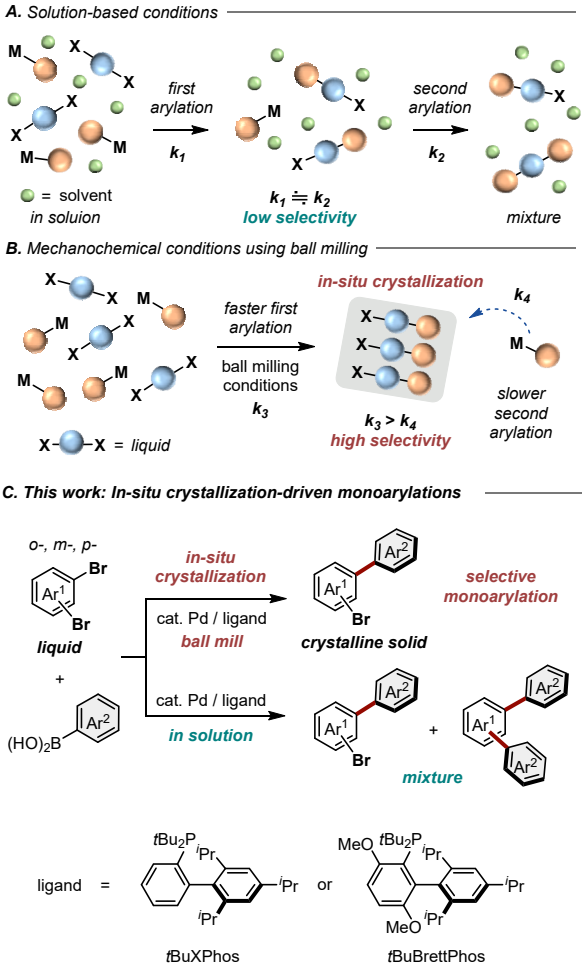


Figure 1. Concept of *in-situ* crystallization-driven selective transformations using mechanochemistry.

We have previously reported broadly applicable solid-state cross-coupling reactions using mechanochemistry.[23,24] In these previous studies, we discovered a considerable reactivity gap between liquid and solid aryl halides under the solvent-free cross-coupling reactions that are typical for

mechanochemistry. This is probably due to the relatively poor mixing efficiency of the solid reactants under the mechanochemical conditions, which results in a lower reactivity compared to liquid substrates. Ondruschka and coworkers also reported the similar phenomenon in the mechanochemical Suzuki-Miyaura coupling reactions.[25] Inspired by this unique profile of mechanochemical cross-coupling reactions, we hypothesized that a new and complementary approach to control chemical reactivity and selectivity could be developed through a mechanistically distinct approach. Specifically, we envisioned that *in-situ* crystallization of the arylation products could be used to develop a selective mechanochemical monoarylation of dihaloarenes (Figure 1). Under conventional, solution-based conditions, Suzuki-Miyaura cross-coupling reactions of unbiased dihaloarenes tend to provide a mixture of mono- and diarylated products (Figure 1A and 1C).[17] Under Hu's solution-based conditions, cross-coupling reactions of dihaloarenes selectively provide the diarylated products via a preferential oxidative addition mechanism.[26] However, our working hypothesis is based on the notion that one of the two halide moieties could potentially be selectively arylated under mechanochemical conditions when the liquid starting material is more reactive than the corresponding monoarylated crystalline solid (Figure 1B and 1C).[23,24] This unique approach, based on *in-situ* phase transitions, would provide an efficient route to structurally complex polyaromatic compounds via selective stepwise cross-coupling strategies.

Initially, we conducted preliminary kinetic studies to confirm the reactivity difference between liquid and solid monohalides as test substrates in mechanochemical cross-coupling reactions (Figure 2). Reactions were conducted in a Retch MM400 ball mill in a stainless-steel milling jar (1.5 mL) at 25 Hz using one stainless-steel ball (diameter: 3 mm). As periodic sampling of the mechanochemical reaction runs would require stopping the mill and opening the jar, each data point was obtained from an individual reaction. In the presence of a catalytic amount of $Pd(OAc)_2$/*t*BuXPhos[27,28] and 1,5-cyclooctadiene (1.5-cod) as a liquid grinding additive,[1,23,24] the mechanochemical cross-coupling of liquid bromobenzene (**1a**) with phenylboronic acid (**2a**) proceeded readily to afford the coupling product (**3a**) in good yield after an induction period of 40 min (Figure 2a). Low conversion rates were observed when solid aryl halides (**1b** and **1c**) were employed (Figure 2a). This result suggests a considerable reactivity gap between liquid and solid aryl halides in such mechanochemical cross-coupling reactions. This is probably due to the relatively poor mixing efficiency of the crystalline solid reactants under the applied mechanochemical conditions, where organic molecules are arranged tightly and regularly.[29] In contrast, the reactivity of liquid and solid aryl halides (**1a**–**1c**) was almost similar to that under conventional solution conditions (Figure 2b).

Based on this preliminary investigation, we proceeded to investigate the *in-situ* crystallization-driven monoarylation of liquid 1,2-dibromobenzene (**1d**) with 4-(dimethylamino)phenylboronic acid (**2b**) under mechanochemical conditions (Scheme 1), which furnished monoarylated **3d** in good yield with high selectivity (78% yield; **3d**/**4d** = 90:10). In contrast, under solution conditions, the diarylated product was obtained as the major product (**3d**/**4d** = 30:70). We confirmed that the starting material **1d** still remained after the mechanochemical reaction (22% recovery of **1d**). Unfortunately, prolonging the reaction time or increasing catalyst loading did not lead to a higher conversion of **1d** (See the SI for details).

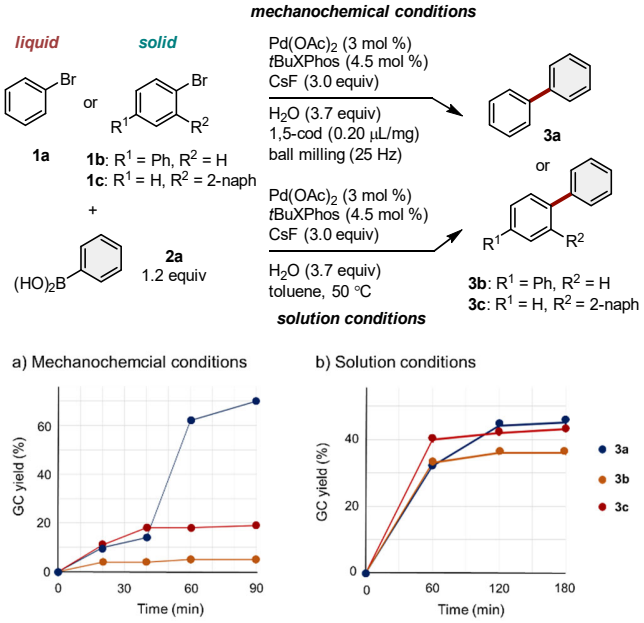
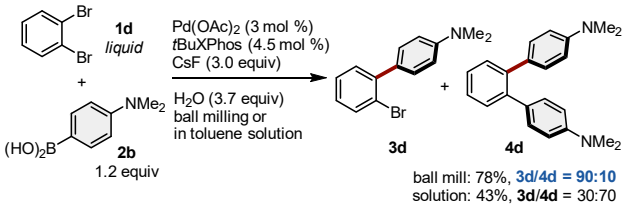


Figure 2. Kinetic studies under mechanochemical and solution-based conditions.

Scheme 1. Monoarylation of Unbiased 1,2-Dibromobenzene (1d) under Mechanochemical Conditions[a,b]

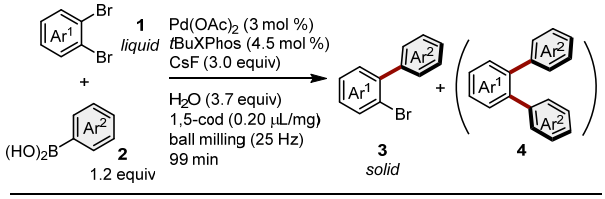


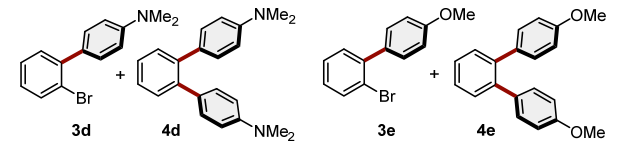
[a]Mechanochemical conditions: **1d** (0.30 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (0.009 mmol), *t*BuXPhos (0.0135 mmol), CsF (0.9 mmol), H_2O (20 μL), and 1,5-cod (0.20 μL/mg) in a stainless-steel ball-milling jar (1.5 mL) with a stainless-steel ball (diameter: 3 mm). Solution conditions: **1d** (0.30 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (0.009 mmol), *t*BuXPhos (0.0135 mmol), CsF (0.9 mmol), H_2O (20 μL), and toluene (0.1 M), 50 °C, 24 h. [b]NMR yields are shown.

Next, we examined mechanochemical mono-selective cross-coupling reactions of 1,2-dibromobenzenes with different arylboronic acids (Table 1).[29] Under the applied mechanochemical conditions, the reactions of liquid 1,2-dibromobenzene (**1d**) and 1,2-dibromo-4,5-difluorobenzene (**1e**) with *p*-methoxyboronic acid (**2c**) provided the corresponding monoarylated products (**3e** and **3f**) with excellent monoarylation selectivity (**3e**/**4e** = 92:8; **3f**/**4f** = 92:8). On the other hand, under solution conditions, product mixtures were obtained (**3e**/**4e** = 60:40; **3f**/**4f** = 65:35). 2-Naphthaleneboronic acid derivatives (**2d** and **2e**) were cleanly coupled with **1d** to provide the corresponding monoarylated products (**3g** and **3h**) in good yield with high selectivity. 1-Naphythaleneboronic acid derivatives (**2f** and **2g**) also provided the corresponding monoarylation products (**3i**, **3j** and **3k**) with excellent selectivity under mechanochemical

conditions. We found that the cross-coupling of **1d** with 3-(trifluoromethyl)phenylboronic acid (**2h**) provided a mixture of mono- and diarylated products (**3l**/**4l** = 65:35) under mechanochemical conditions, which could probably be rationalized in terms of **3l** being a liquid. This result is consistent with our proposed mechanism.

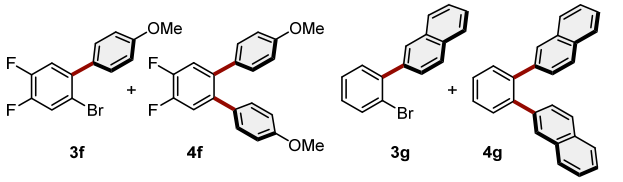
Table 1. *In-situ* Crystallization-driven Monoarylation of 1,2-Dibromobenzenes[a]





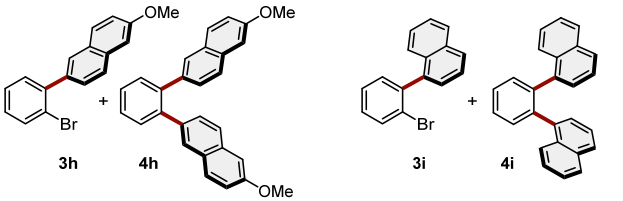
ball mill: 78% (**3d** + **4d**, **3d/4d = 90:10**)[b]
isolated yield of **3d**: 68%
solution: 43% (**3d** + **4d**, **3d/4d** = 30:70)[b]

ball mill: 89% (**3e** + **4e**, **3e/4e = 92:8**)[b]
isolated yield of **3e**: 72%
solution: 41% (**3e** + **4e**, **3e/4e** = 60:40)[b]



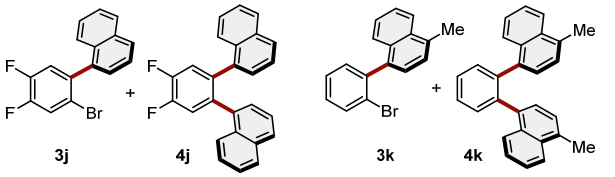
ball mill: 78% (**3f** + **4f**, **3f/4f = 92:8**)[b]
isolated yield of **3f**: 68%
solution: 29% (**3d** + **4d**, **3f/4f** = 65:35)[b]

ball mill: 77% (**3g** + **4g**, **3g/4g = 91:9**)[c]
isolated yield of **3g:** 66%
solution: 36% (**3g** + **4g**, **3g/4g** = 61:39)[c]



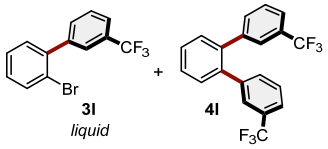
ball mill: 80% (**3h** + **4h**, **3h/4h = 89:11**)[c]
isolated yield of **3h**: 65%
solution: 28% (**3h** + **4h**, **3h/4h** = 59:41)[c]

ball mill: 64% (**3i** + **4i**, **3i/4i = 97:3**)[c]
isolated yield of **3i**: 54%
solution: 30% (**3i** + **4i**, **3i/4i** = 70:30)[c]



ball mill: 71% (**3j** + **4j**, **3j/4j = 96:4**)[b]
isolated yield of **3j**: 50%
solution: 30% (**3j** + **4j**, **3j/4j** = 71:29)[b]

ball mill: 69% (**3k** + **4k**, **3k/4k = 98:2**)[c]
isolated yield of **3k**: 58%
solution: 25%, (**3k** + **4k**, **3k/4k** = 80:20)[c]

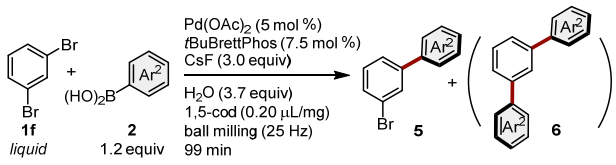


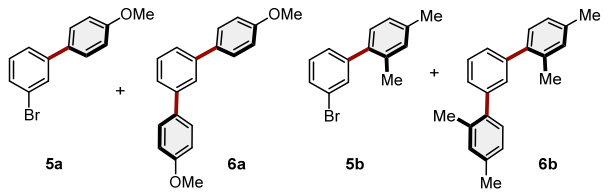
ball mill: 81% (**3l** + **4l**, **3l/4l = 65:35**)[c]
isolated yield of **3l**: 52%
solution: 57% (**3l** + **4l**, **3l/4l** = 24:76)[c]

[a]For experimental details, see the SI. [b]^{1}H or ^{19}F NMR yields are shown. [c]GC yields are shown.

Next, we investigated the monoarylation of 1,3-dibromobenzene (**1f**) (Table 2).[30] We found that the use of *t*BuBrettPhos instead of *t*BuXPhos generally afforded higher yields of the monoarylation product **5** (see the SI for details). The mechanochemical cross-coupling reactions with aryl boronic acids (**2c**, **2d**, **2i**, and **2f**) afforded the corresponding monoarylation products (**5a**–**5d**) with good to high selectivity. In sharp contrast, under solution conditions, the diarylated products were obtained as major products.

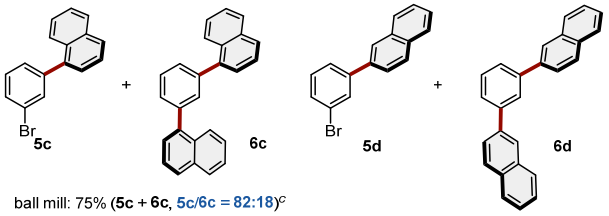
Table 2. *In-situ* Crystallization-driven Monoarylation of 1,3-Dibromobenzene (1f)[a]





ball mill: 72% (**5a** + **6a**, **5a/6a = 88:12**)[b]
isolated yield of **5a**: 63%
solution: 39% (**5a** + **6a**, **5a/6a** = 38:62)[b]

ball mill: 68% (**5b** + **6b**, **5b/6b = 95:5**)[c,d]
isolated yield of **5b**: 56%
solution: 42% (**5b** + **6b**, **5b/6b** = 49:51)[c]



ball mill: 75% (**5c** + **6c**, **5c/6c = 82:18**)[c]
isolated yield of **5c**: 55%
solution: 29% (**5c** + **6c**, **5c/6c** = 59:41)[c]

ball mill: 56% (**5d** + **6d**, **5d/6d = 85:15**)[c,e]
isolated yield of **5d**: 41%
solution: 66% (**5d** + **6d**, **5d/6d** = 32:68)[b]

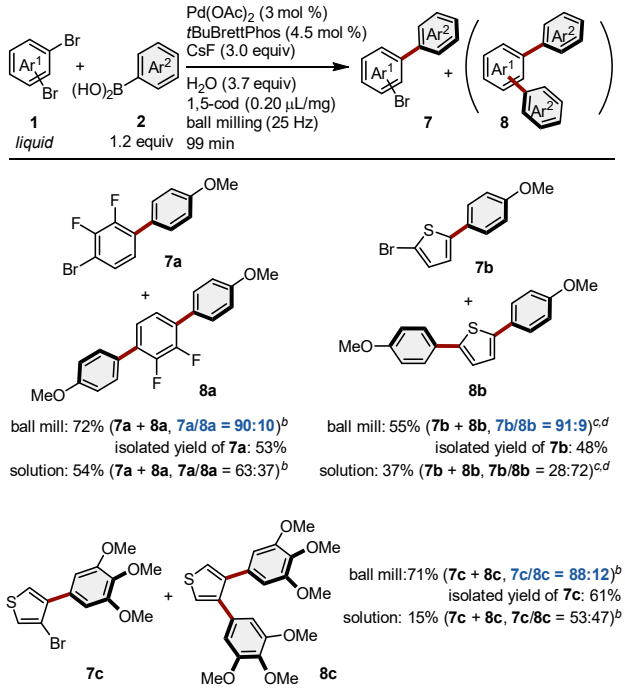
[a]For experimental details see the SI. [b]^{1}H NMR yields are shown. [c]GC yields are shown. [d]1,5-cod (0.10 μL/mg) was used. [e]1,5-cod (0.80 μL/mg) and *t*BuXPhos were used; reaction time: 3 h.

To explore the scope of the *in-situ* crystallization strategy further, other classes of dibromoarenes were tested (Table 3).[30] The reaction of a liquid 1,4-dibromobenzene derivative with fluorine atoms (**1g**) using *t*BuBrettPhos also smoothly furnished the corresponding monoarylated product (**7a**) with high selectivity under the mechanochemical conditions (**7a**/**8a** = 90:10). This method could also be successfully applied to dibromothiophenes (**1h** and **1i**), providing the desired monoarylation products (**7b** and **7c**) with high selectivity (**7b**/**8b** = 91:9; **7c**/**8c** = 88:12). Notably, the reactions of these substrates in solution using the same catalytic system afforded a mixture of mono- and diarylated products.

In order to obtain mechanistic insights, we used powder x-ray diffraction (PXRD) analyses to determine whether crystalline solids of monoarylated products are formed during the reactions (Figure 3). For that purpose, the crude mixture of the cross-coupling reaction between **1d** and **2e** under the mechanochemical conditions was analyzed by PXRD (Figure 3).[31] The diffraction peaks that correspond to crystalline **3h** were observed, suggesting that "*in-situ crystallization*" of **3h** occurred during the reaction. This result supports our proposed mechanism for the selectivity

toward monoarylation under mechanochemical conditions.

Table 3. *In-situ* Crystallization-driven Monoarylation of Other Classes of Substrates[a]



[a]For experimental details, see the SI. [b]^{1}H or ^{19}F NMR yields are shown. [c]GC yields are shown. [d]*t*BuXPhos was used instead of *t*BuBrettPhos.

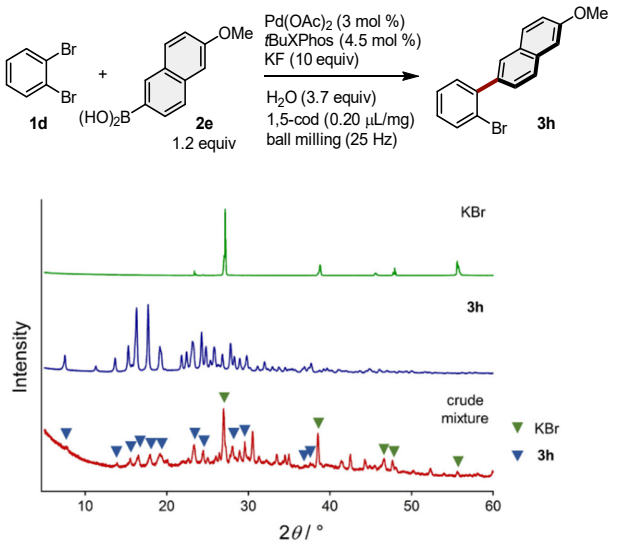
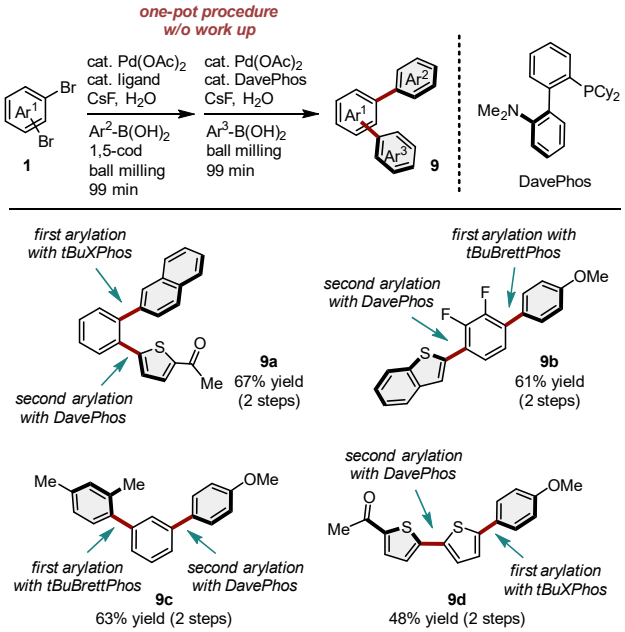


Figure 3. Powder X-ray diffraction analysis of the crude reaction mixture of **3h**.

To demonstrate the practical utility of this method, we investigated a direct one-pot sequential arylation protocol using mechanochemistry (Table 4). For that purpose, the crude mixture of **3** was directly subjected to a one-pot solid-state cross-coupling using different aryl boronic acids and the Pd(OAc)$_2$/DavePhos/1,5-cod catalyst system, which is more active in the solid state than Pd(OAc)$_2$/*t*BuXPhos or Pd(OAc)$_2$/*t*BuBrettPhos.[24] We found that the desired unsymmetrically diarylated products (**9a–9d**) were obtained in good to moderate yield over 2 steps.[32,33] These results suggest that the one-pot mechanochemical coupling strategy enables the rapid and modular construction of complex polyaromatic structures under simple operational conditions in air from readily available starting materials.

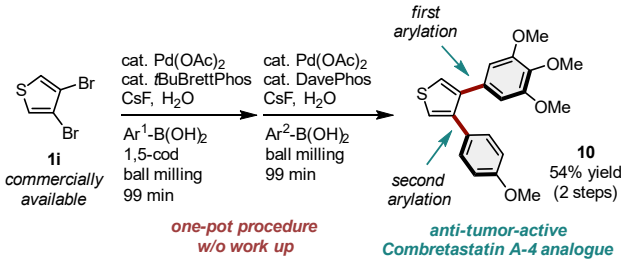
Table 4. One-pot Sequential Arylations of Unbiased Dibromoarenes[a,b]



[a]For experimental details, see the SI. [b]Isolated yields are shown.

To demonstrate the applicability of this newly developed methodology to the synthesis of bioactive molecules, we completed the synthesis of an anti-tumor-active Combretastatin A-4 analogue (**10**) using mechanochemistry (Scheme 2).[34] We confirmed that sequential mechanochemical arylations allowed the rapid one-pot synthesis of **10** in good yield (54% over 2 steps) from commercially available 3,4-dibromothiophene (**1i**). The reported solution conditions require an excess of **1i**, and if reduced to one equivalent, only a very low selectivity toward monoarylation is observed (**7c**/**8c** = 25:75; see the SI for details).[34] It can be feasibly expected that crystallization-driven mechanochemical cross-couplings will find further applications in the selective synthesis of bioactive compounds.

Scheme 2. Rapid Synthesis of Anti-tumor-active Combretastatin A-4 Analogue (10) via One-pot Sequential Mechanochemical Cross-coupling Reaction[a,b]



[a]For experimental details, see the SI. [b]Isolated yield is shown.

In summary, we have developed selective monoarylation reactions for dibromoarenes based on *in-situ*

crystallization under mechanochemical conditions. Suzuki–Miyaura cross-coupling reactions of unbiased dibromoarenes in solution tend to provide a mixture of mono- and diarylated products. However, we 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, we propose that this selectivity results in all likelihood from the conversion of liquid starting materials into less reactive crystalline monoarylated products under the applied mechanochemical conditions. We furthermore demonstrated a rapid, one-pot mechanochemical sequential coupling procedure that represents an efficient and step-economic route to valuable synthetic targets from readily available starting materials.

ASSOCIATED CONTENT

Supporting Information

Methods and Materials, supplementary graphics, characterization data, and references.

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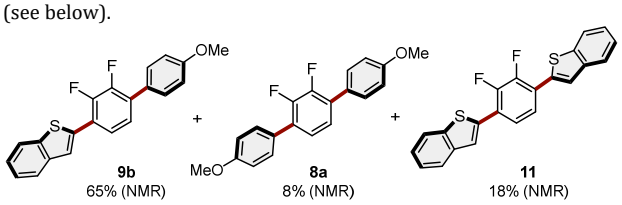
(30) We confirmed that in all cases starting materials still remained after the reactions.

(31) When CsF was used as a base, the diffraction peaks that correspond to **3h** could not be clearly confirmed because the diffraction intensity of CsBr contained in the crude mixture was very strong. Therefore, KF was used instead of CsF for the experiment.

(32) The symmetrically diarylated products are major byproducts of the mechanochemical one-pot sequential cross-coupling reactions. For example, the reaction of **1e** afforded **9b** (65%), **8a** (8%), and **11** (18%) (see below).



9b 65% (NMR) **8a** 8% (NMR) **11** 18% (NMR)

(33) The reaction of **1g** with a mixture of 4-methoxyphenylboronic acid (**2c**, 1.2 equiv) and benzo[*b*]thiophene-2-boronic acid (**2l**, 1.2 equiv) in the presence of $Pd(OAc)_2$/*t*BuXPhos under mechanochemical conditions afforded **9b** (10%), **8a** (2%), and **11** (22%). When the same reaction was performed in toluene at 50 °C, **9b** (34%), **8a** (38%), and **11** (27%) were obtained. These results demonstrate the utility of the stepwise mechanochemical coupling strategy for the selective synthesis of unsymmetrically diarylated products.

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