



Solvent-free mechanochemical Buchwald–Hartwig amination of aryl chlorides without inert gas protection

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ABSTRACT

A solvent-free Buchwald–Hartwig amination had been developed under high-speed ball-milling conditions, which afforded the desired products with moderate to high yields. The addition of sodium sulfate was found to be crucial for improving both the performance and the reproducibility. Comparative solvent-free stirring experiments implicated the importance of mechanical interaction for the transformation, and the inert gas was proved to be unnecessary for this amination.

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Introduction

High-speed ball milling (HSBM) has been emerged as a mechanochemical technique for green synthesis by inputting mechanical force to the reaction system. During the past decade, HSBM promoted mechanical reactions have been widely studied and its feature had been summarized continuously,¹ including high efficiency, special selectivity, and ignorance of substance solubility. Hitherto, a panel of organic reactions have been investigated under HSBM conditions successfully,² among which high-efficiency solvent-free cross-couplings have been achieved.³ Despite these achievements, the aryl bromide still dominates the substrate of mechanical cross-couplings. The more economic attracting aryl chlorides failed in the most cases, which may be due to its reluctance toward oxidative addition.⁴ Although the elevation of temperature could be chosen to promote these transformations as the conventional solvent-based reactions, the mechanical reactions are expected to excite higher activity by mechanical interaction directly, which makes the mechanical cross-coupling of aryl chlorides especially challenging.

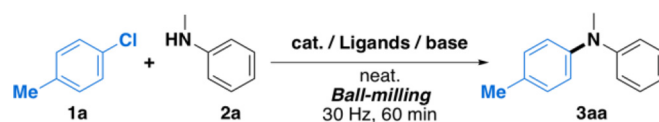
During our continuous exploration of mechanochemistry,⁵ a mechanical Suzuki–Miyaura reaction of aryl chlorides had been developed by our group recently,⁶ where the oxidative addition was accounted by a drop of methanol hypothetically. Inspired by this exciting result, we started to investigate the cross-coupling

of aryl chlorides under HSBM conditions, and the Buchwald–Hartwig amination, as one of the most powerful tools for C–N bond construction,⁷ was chosen to evaluate the impacts from amines which may influence the catalytic system by ligation. Previously, this amination had been studied in solvent-free manner successfully, providing excellent results.⁸ Interestingly, a HSBM-like process had been reported by Beletskaya et al. using a vibrator.^{8c} However, this transformation of aryl bromides at 100 °C was suspected as a heat-promoted process, and the mechanical Buchwald–Hartwig amination of aryl chlorides remain unexplored. Herein, we wish to unveil our preliminary result on mechanical Buchwald–Hartwig amination of aryl chlorides, which could be performed without deliberate inert gas protection. The grinding auxiliaries were considered to be crucial for the transformation, where sodium sulfate was the optimal choice.

At the commencement, the coupling between *p*-chlorotoluene **1a** and *N*-methylaniline **2a** was chosen as the model reaction for investigation. Unfortunately, the initial attempts using our previous established liquid-assisted grinding (LAG) condition⁶ failed to furnish the catalytic cycle, which gave approximately 5% yield after 60 min' grinding. A fast survey of liquids indicated the monophosphine/LAG system may be not suitable for the reaction (see [Supporting Information for more details](#)). Subsequently, chemical conditions were tested and optimized for this transformation under the HSBM conditions, and the selected results were presented in [Table 1](#)⁹. Monophosphines failed again to maintain the catalytic cycle ([Table 1](#), entry 1), while bidentate bis(diphenylphosphine) ligands examined didn't give any trace of

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Table 1
Optimization of reaction conditions^a.

Entry	Cat	Ligand	Base	% yield ^b
1	Pd(OAc) ₂	Monophosphines ^c	NaO ^t Bu	<5
2	Pd(OAc) ₂	Bis(diphenylphosphines) ^d	NaO ^t Bu	n.d.
3	Pd(OAc) ₂	Davephos	NaO ^t Bu	38
4	Pd(OAc)₂	XPhos	NaO^tBu	42 (75)^e
5	Pd(OAc) ₂	SPhos	NaO ^t Bu	17
6	Pd(OAc) ₂	JohnPhos	NaO ^t Bu	12
7	PdCl ₂	XPhos	NaO ^t Bu	37
8	Pd ₂ (dba) ₃	XPhos	NaO ^t Bu	25
9	Pd(TFA) ₂	XPhos	NaO ^t Bu	40
10	Pd(OAc) ₂	XPhos	NaOMe	23 (60) ^e
11	Pd(OAc) ₂	XPhos	KO ^t Bu	23
12	Pd(OAc) ₂	XPhos	NaOH	21
13	Pd(OAc) ₂	XPhos	K ₃ PO ₄	15
14 ^f	Pd(OAc) ₂	XPhos	NaO ^t Bu	45
15 ^g	Pd(OAc) ₂	XPhos	NaO ^t Bu	36

^a Reaction conditions unless noted otherwise: 0.5 mmol *N*-methylaniline, 0.6 mmol *p*-chlorotoluene, 4 mol% cat., 8 mol% Ligand, 2.0 equiv. base were added to the 25 mL stainless-steel vessel with two stainless-steel balls ($\phi = 1.4$ cm), which was then ground at 30 Hz for 60 min.

^b Isolated yield based on 5 runs with valid data.

^c Monophosphines tested: PCy₃, P^tBu₃, PPh₃, and P(*o*-Tolyl)₃.

^d Bis(diphenylphosphines) tested: dppe, dppp, dppb, dppf, and Xantphos.

^e Irreproducible data.

^f Pd(OAc)₂ = 10 mol%, XPhos = 20 mol%.

^g Pd(OAc)₂ = 2 mol%, XPhos = 4 mol%. n.d. = not detected.

product (Table 1, entry 2). Fortunately, ligands of biphenylphosphine family¹⁰ could promote the model reaction (Table 1, entries 3–6), where XPhos afforded the best result of 42%. Switching to other palladium source like PdCl₂, Pd₂(dba)₃, and Pd(TFA)₂ didn't give any improvement (Table 1, entries 7–9), while alternating base to NaOMe, KO^tBu, NaOH, and K₃PO₄ led to much worse outcomes (Table 1, entries 10–13), and the reaction didn't work at all with K₂CO₃, NaOAc, DBU, NEt₃, DMAP (not listed). Further attempt increasing the usage of catalyst failed to provide significant improvement, while decreasing the loading resulted in an erosion of yield (Table 1, entries 14–15).

During the reaction optimization, the annoying problem of irreproducibility was found, and was proposed as the insufficient mixing of the slurry-like matter. Increasing the flowability of the mixture had been proved useful,^{5c,11} by screening grinding auxiliaries (G. A.) (Table 2). In this work silica gel suppressed the cross-coupling as reported previously,⁶ while γ -Al₂O₃ still gave a declined result (Table 2, entries 1–2). Commonly used NaCl inhibited the reaction (Table 2, entry 3), meanwhile, KBr or NaBr didn't give any improvement (Table 2, entries 4–5). Fortunately, a yield of 92% was achieved when sodium sulfate was used (Table 2, entry 6), which gave a powder-like mixture. Potassium sulfate also gave a fairly well outcome, however, magnesium or calcium sulfate failed to give any trace of the product (Table 2, entries 7–9). Interestingly, the conventional bases used in the cross-couplings failed to work as grinding auxiliaries (Table 2, entries 10–13). The amount of Na₂SO₄ was also examined, where 2.0 g was the optimal choice for the current system (Table 2, entries 14–16). Subsequently, mixing Na₂SO₄ with the aforementioned salts was surveyed to evaluate the influence from anions (Table 2, entry 17–21). Interestingly, significant suppression was found in all cases, where no reaction occurred with the presence of acetate and phosphate anion. Noticeably, although the bromide and carbonate either suppressed the reaction, an improvement in yield could be found compared with the data above (Table 2, entries 17 vs 4, and 19 vs 8). These results implicated these anions may have an influence on the

Table 2
Optimization of grinding auxiliary.^a

Entry	G.A.	m/g	%yield ^b
1	Silica gel	0.3	n.d.
2	γ -Al ₂ O ₃	0.5	21
3	NaCl	2.0	n.d.
4	KBr	2.0	16
5	KCl	2.0	n.d.
6	Na ₂ SO ₄	2.0	92
7	K ₂ SO ₄	2.0	75
8	MgSO ₄	2.0	n.d.
9	CaSO ₄	2.0	n.d.
10	K ₃ PO ₄	2.0	n.d.
11	K ₂ CO ₃	2.0	n.d.
12	Na ₂ CO ₃	2.0	n.d.
13	NaOAc	2.0	n.d.
14	Na ₂ SO ₄	1.5	72
15	Na ₂ SO ₄	1.0	57
16	Na ₂ SO ₄	2.5	85
17	Na ₂ SO ₄ + KBr	1.5 + 0.5	21
18	Na ₂ SO ₄ + KBr	1.0 + 1.0	n.d.
19	Na ₂ SO ₄ + K ₂ CO ₃	1.5 + 0.5	16
20	Na ₂ SO ₄ + NaOAc	1.5 + 0.5	n.d.
21	Na ₂ SO ₄ + K ₃ PO ₄	1.5 + 0.5	n.d.
22^c	Na₂SO₄	2.0	91
23 ^d	Na ₂ SO ₄	2.0	79

^a Reaction conditions unless noted otherwise: 0.5 mmol *N*-methylaniline, 0.6 mmol *p*-chlorotoluene, 4 mol% Pd(OAc)₂, 8 mol% XPhos, 2.0 equiv. NaO^tBu, and the grinding auxiliary were added to the 25 mL stainless-steel vessel with two stainless-steel balls ($\phi = 1.4$ cm), which was then ground at 30 Hz for 60 min.

^b Isolated yield based on 2 runs.

^c Pd(OAc)₂ = 2 mol%, XPhos = 4 mol%.

^d Pd(OAc)₂ = 1 mol%, XPhos = 2 mol%. n.d. = not detected.

reactions, where the sulfate anion may improve the performance of this reaction. To verify the hypothesis, another comparative experiment had been carried out to add Na₂SO₄ to the conventional solvent-heating reaction. No acceleration or improvement of the reaction was observed, which may be due to the poor solubility

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