

# A Robust Pd-Catalyzed C-S Cross-Coupling Process Enabled by Ball-Milling

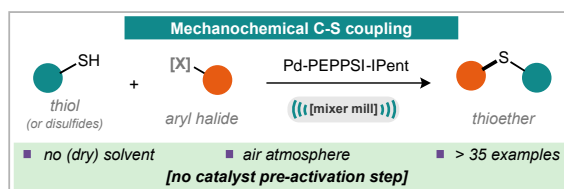
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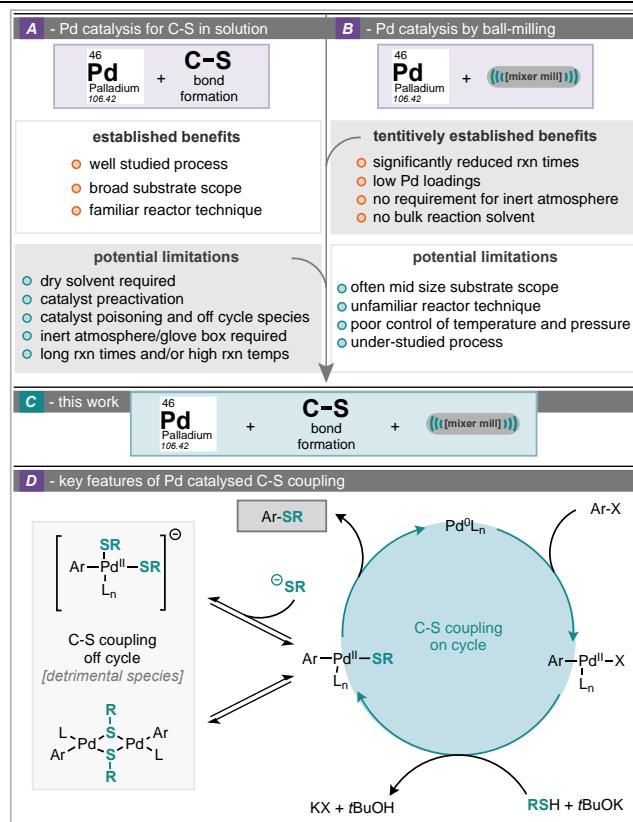
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## Supporting Information

**ABSTRACT:** An operationally simple mechanochemical C-S coupling of aryl halides with thiols has been developed. The reaction process operates under bench-top conditions without the requirement for (dry) solvent, inert atmosphere, or catalyst pre-activation. The reaction is finished within three hours. The reaction is demonstrated across a broad range of substrates; the inclusion of zinc metal has been found to be critical in some instances, especially for coupling of alkyl thiols.



The synthesis of C-S bonds plays a crucial role in the discovery and production of biologically active compounds including pharmaceuticals, natural products and agrochemicals. Metal-based procedures remain a popular method for forming C-S bonds due to synthetic simplicity and modularity.<sup>1a-e</sup> The first Pd-catalysed variant was presented by Migita and co-workers<sup>2</sup> and since this pioneering work many different Pd-catalysed protocols have been developed (Scheme 1, A).<sup>3a-h</sup> The focus of these reports has been on expanding the range of amenable substrates through development of privileged pre-catalysts and ligands as well as developing lower reaction temperatures or shorter reaction times. Despite each step of the proposed catalytic cycle being well understood, high temperatures and long reaction times are often required for C-S coupling. This is typically associated with the ability of palladium catalysts to form detrimental off-cycle resting states (Scheme 1, D).<sup>4a,4b</sup> A number of reports have targeted ligand / pre-catalyst design to minimise these deactivating pathways and promote reductive elimination. In particular, it has been shown that bidentate phosphine ligands such as BINAP,<sup>5a</sup> Josiphos-SL009-1,<sup>5b</sup> and XantPhos<sup>5c</sup> can be employed to minimise deactivation by nucleophilic thiolate ligands. More recently, monophosphine ligands have exhibited some success for C-S coupling at lower temperatures with soluble bases.<sup>5d</sup> However, the use of phosphine ligands carries the potential issue of dissociation from the metal centre, particularly for those ligands with larger cone angles.<sup>6</sup> An elegant solution to this has been the design of Pd-NHC complexes<sup>7a-g</sup> such as the Pd-PEPPSI pre-catalysts developed by Organ and co-workers.<sup>7d</sup>



**Scheme 1. Catalytic cycle for C-S coupling**

These catalysts have been reported for carbon-heteroatom coupling,<sup>7e</sup> including the synthesis of thioethers from aryl halides and thiols.<sup>7a,7f</sup> In the most part, previous examples of C-S coupling protocols in solution require an inert atmosphere, (dry) solvent and/or catalyst preactivation.

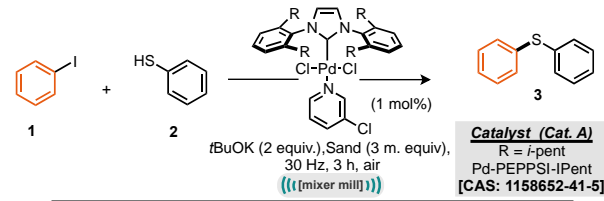
Recent progress in mechanochemical synthesis and ball-milling has led to the investigation of several organic reactions using this unique reactor environment. Very recently a few general trends have started to emerge about the potential benefits that ball-milling might offer, such as, new reactivity, decreased reaction times or alternative selectivity.<sup>8a-k</sup> In the context of Pd-catalyzed cross-coupling reactions by ball-milling we and others have found a seemingly decreased sensitivity to air and moisture for both Buchwald-Hartwig and Negishi cross-coupling processes (Scheme 1, B).<sup>8k, 9a-f</sup> We hypothesised that the use of mechanochemistry could allow us to overcome several of the limitations encountered by solution-based Pd-catalyzed, C-S approaches, whilst simultaneously allowing us to further explore and understand the method of ball-milling (Scheme 1, C). Our results are reported herein.

Studies commenced by employing our recent reaction conditions used for a Buchwald-Hartwig amination reaction under milling conditions.<sup>9a</sup> Iodobenzene (**1**) and thiophenol (**2**) could be coupled successfully using Pd-PEPPSI-IPent (1 mol %) as catalyst, potassium tert-butoxide (2 equiv.) as base and sand (3 mass equiv.) as grinding auxiliary. Grinding auxiliaries are often used when there are one or more liquid reagents and provide a solid surface to host the liquid materials and permit more efficient energy transfer from the balls to the reactants.<sup>8</sup> Mass equivalents of grinding auxiliaries are measured as a mass of all reagents combined multiplied by the corresponding number of equivalents. Notably, the materials were added to the milling jar under an air atmosphere, i.e. no precaution was taken for the exclusion of air or moisture from the reaction mixture. The jars were milled for 3 hours at 30 Hz. Under these conditions, the reaction afforded the arylated thiol product (**3**) in 76% yield as determined by <sup>1</sup>H NMR (Table 1, entry 1). The reaction parameters were then refined to further optimise the reaction. Screening commenced by evaluating the grinding agent used where it was found that 2 mass equivalents of sand provided an improvement, giving the desired cross-coupled product in 90% isolated yield (Table 1, entry 3). After screening a small range of six NHC-Pd catalysts (SI Table 1) it was found that the Pd-PEPPSI-IPent catalyst was optimal and the loading of this catalyst could be lowered to 0.5 mol % (Table 1, entry 8). Notably, omission of the palladium catalyst resulted in no reaction (Table 1, entry 6), which is a key observation given that trace metals (such as iron and cobalt) from the stainless steel balls and jar have previously been implicated as non-innocent in some ball-milled processes.<sup>8l</sup> The reaction time could also be lowered to 90 minutes was sufficient for the coupling of these parent substrates giving an isolated yield of 92% for the cross-coupled product **3**. No improvements were observed by changing the base used or by altering the number of equivalents of base used (Table 1, entries 10-14).

With optimal conditions identified (Table 1, entry 8), application to a range of aryl halides was explored (Scheme 2). It was quickly discovered that many examples required longer than 90 mins, the reactions were therefore run for 3 hours as the standard procedure. In all cases reactions were run under an air atmosphere and afforded the desired products in a moderate to excellent yield (43% to 92% isolated yields, Scheme 2). Initial testing found that the reaction was tolerant for aryl bromides and the more electronically challenging aryl chlo-

rides in addition to aryl iodides. The reaction is tolerant for the sterically demanding mesityl functionality (Scheme 2, compound **8**) as well as other ortho-substituted substrates (Scheme 2, compounds **6** and **7**). 1-bromo naphthalene was also successfully coupled in 76% yield demonstrating the steric tolerance of this reaction. These conditions were also applicable to a range of electron rich and electron deficient aryl halides.

**Table 1. Optimization of mechanochemical C-S coupling**



Entry	variation from 'standard conditions'	Yield of <b>3</b> [%] <sup>[a]</sup>
1	none	76
2	no grinding agent	0
3	grinding agent: Sand (2 mass equiv.)	94 (90)
entries below this line contain sand (2 mass equiv.)		
4	2 hours reaction time	95
5	1.5 hour reaction time	96 (92)
entries below this line run for 1.5 hours		
6	No Catalyst	0
7	Cat A [2 mol%]	96
8	Cat A [0.5 mol%]	95 (92)
9	Cat A [0.25 mol%]	31
entries below this line contain [0.5 mol%] Cat A		
10	tBuOK (1 equiv.)	32
11	tBuOK (3 equiv.)	5
12	tBuOK (1.5 equiv.)	49
13	tBuONa (2 equiv.)	13
14	Cs <sub>2</sub> CO <sub>3</sub> (2 equiv.)	6

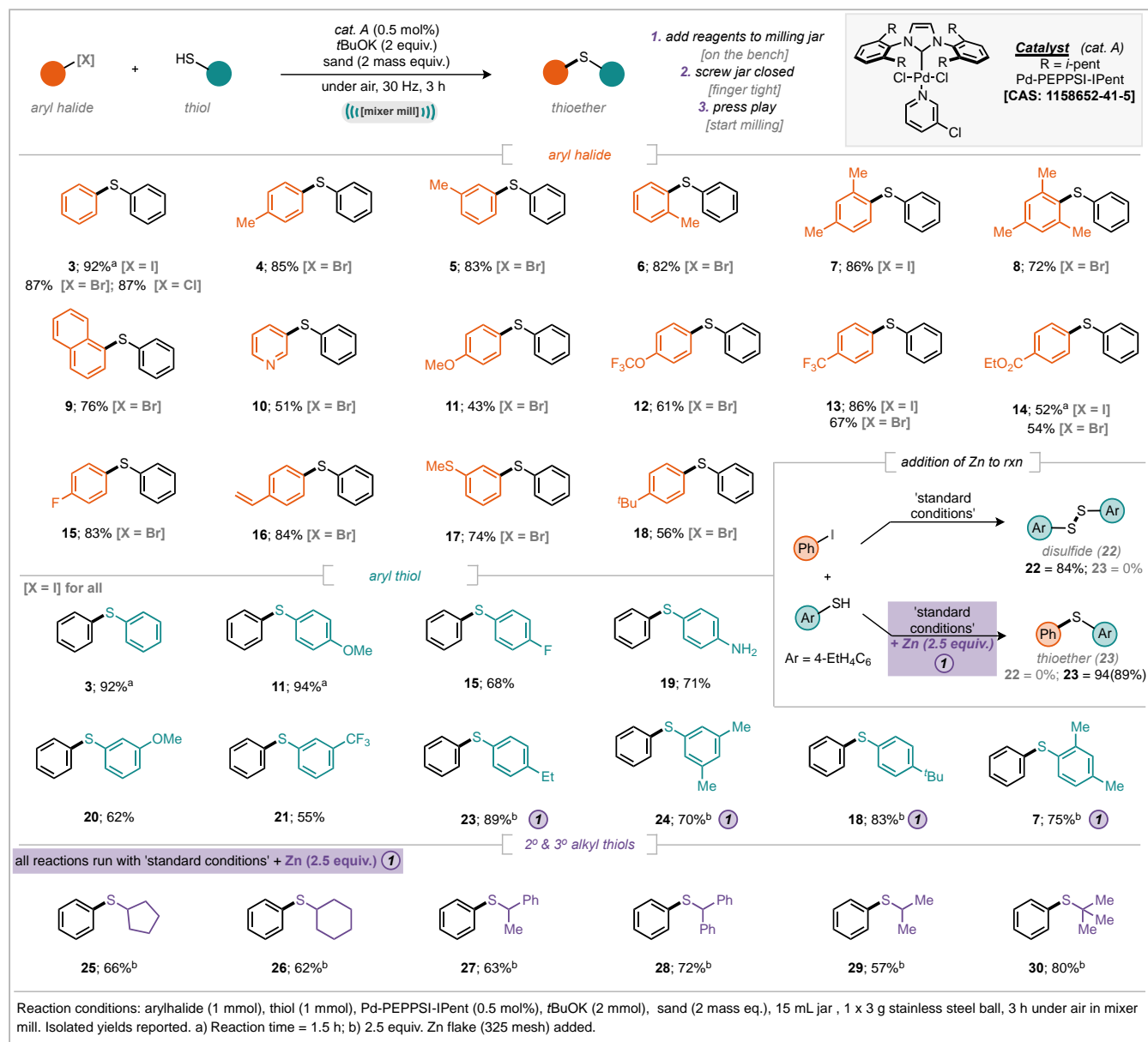
[a] Yield determined by <sup>1</sup>H NMR using mesitylene as internal standard, numbers in parentheses represent isolated yields.

It is worth noting that for electron poor examples **13** and **14**, the reaction was also performed in the absence of catalyst whereby no desired product was observed demonstrating that the reaction does not proceed by an S<sub>N</sub>Ar mechanism under these conditions. Notably, 3-bromopyridine was tolerated affording the product **10** in a moderate 51% yield. Substrates containing acidic sites (carboxylic acid, phenol) were unsuccessful in the coupling reaction.

The reaction scope with respect to the thiol component was first explored for aryl thiols using iodobenzene as the coupling partner. A range of aryl thiols were coupled successfully under the standard conditions. It was shown that for 4-aminothiophenol, C-S coupling was favoured over C-N coupling of the aniline functionality leading to thioether **19** in 71% yield. However, it was found that some examples (Scheme 2, compounds **23**, **24**, **18** and **7**) did not afford the desired thioether products but instead gave the corresponding disulfide of the thiol starting material. This was investigated further using 4-ethylthiophenol (Scheme 2) as model substrate. Under the standard reaction conditions, milling 4-ethylthiophenol with iodobenzene afforded none of the thioether product and 84% of the disulfide (**22**) (Scheme 2). We hypothesised that inclusion of a reductant might enable the desired thioether formation.<sup>10</sup> To our delight, addition of Zn metal as a reductant led to the observation of no disulfide and 72% of the desired arylated thiol product (**23**) (SI Table 4, entry 2). After a short optimisation, it was found that 2.5

equiv. of zinc metal was optimal, affording the cross-coupled

product **23** in 89% isolated yield (Scheme 2).



**Scheme 2. Scope of the mechanochemical palladium catalyzed thioether formation**

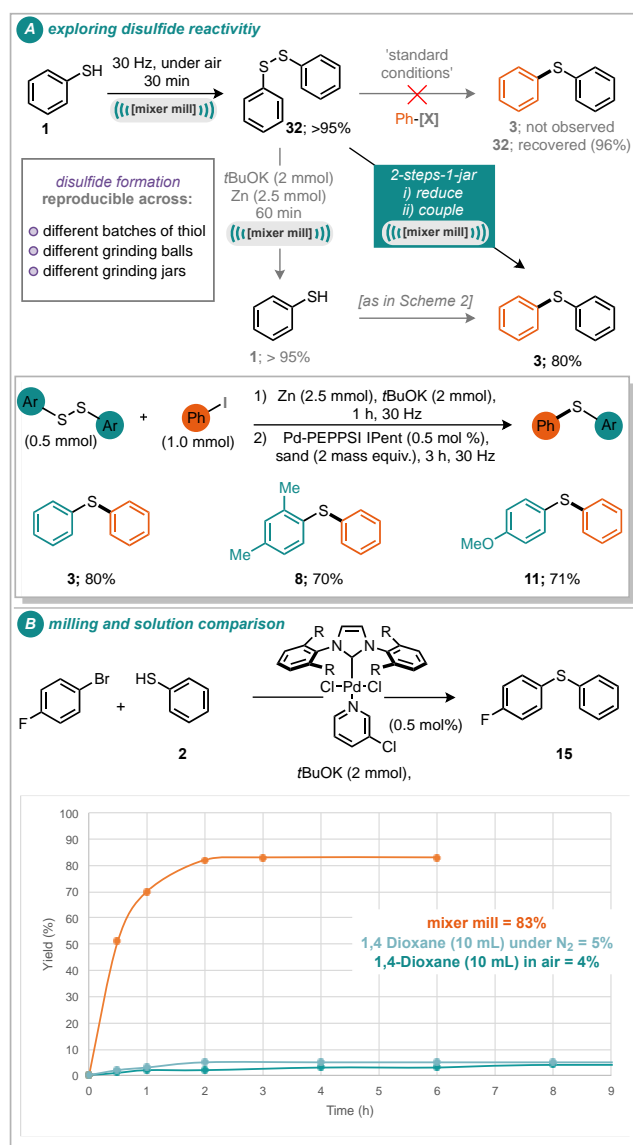
It should be noted that no pre-activation or pre-treatment of the zinc is required.<sup>8k,9c,9f</sup> This solution was applicable to all of the substrates in the aryl thiol scope that were previously unsuccessful and afforded disulfides, delivering the resulting thioether products **23**, **24**, **18** and **7**, in 89%, 70%, 83% and 75% isolated yield respectively (Scheme 2). The addition of zinc did not provide any improvement to substrates that coupled under standard conditions. The coupling of alkyl thiols is known to be more challenging than thiols at sp<sup>2</sup> carbon centres; alkyl thiols differ from aryl thiols in both nucleophilicity and acidity.<sup>7a,11</sup> Under zinc-free conditions, the formation of disulfide products was the dominant pathway in all cases. However, it was found that the addition of 2.5 equivalents of zinc allowed for a range of 2° and 3° alkyl thiols to be coupled efficiently in good to excellent yields (Scheme 2). The reaction was tolerant for both cyclic and acyclic alkyl thiols. De-

sired coupled products were observed for secondary alkyl thiols (Scheme 2, compounds **25-29**) and tertiary thiol (Scheme 2, compound **31**). However, little to no coupled product was observed for primary alkyl thiols. In this case, either no reactivity was seen or a small amount of disulfide was formed (up to 26% for decanethiol). An increased loading of zinc (5 equiv.) reduced the disulfide formed in the reaction to 0%, nevertheless, no coupled product was detected.

The formation of disulfides under the reaction conditions was investigated further by milling thiophenol under air with a 3 g milling ball at 30 Hz (Scheme 3, A). It was found that thiophenol could be cleanly converted to diphenyl disulfide in quantitative yield after just 30 minutes of milling. This result has found to be reproducible across different batches of thiol starting material, different grinding balls and even different

grinding jars (of the same material, size and manufacturing supplier). Aerobic oxidative disulfide formation is well known, but this method in particular appears to be very simple and rapid considering that no other components are added to the reaction vessel. We cannot rule out that metals in the hardened stainless steel of the milling ball and jar are behaving as catalysts in this process – indeed it appears as just about any metal can catalyse this reaction! Notably the disulfide, **32**, does not participate in C-S coupling under the standard reaction conditions, nor those coupling conditions with added zinc. The disulfide can, however, be reduced to the corresponding thiolate in the presence of zinc and potassium *tert*-butoxide, quenching of this mixture delivers the thiol in near quantitative yield. These results, taken together, suggest that the addition of zinc to this reaction process is not merely serving to reduce the disulfide, if it were, one would expect the disulfide to be a competent reactant with standard conditions + zinc, which is not the case.

### Scheme 3. Exploring disulphide reactivity and comparison to solution reaction.



It appears that the zinc inhibits the formation of disulfide; there are potentially several ways that this could occur, including: inhibiting entry to the catalytic off-cycle, lowering the effective concentration of free thiol(ate) or passivating a catalytically active metal found in the stainless steel (those which catalyse aerobic disulfide formation). We do not yet have evidence to further refine this discussion. Nonetheless, disulfides are competent coupling partners if the reaction is run as a two-step-one-jar process whereby the disulfide is initially reduced with zinc and base before opening the jar and adding the aryl halide coupling partner, catalyst and sand to the thiolate mixture. This two-step approach has been demonstrated effective for three examples in good yields (Scheme 3, A). For comparison we have also explored the reaction conditions under solvent approaches (Scheme 3, B). Using the same conditions with 4-fluoro bromobenzene and thiophenol as the starting material, the reaction was run in 1,4-dioxane; the most common solvent used for the coupling of aryl halides and thiols in solution, but in the absence of sand. In the instance that the comparison reaction was run under air no precaution was taken to remove air or moisture and the solvent was simply taken from a non-dried stock bottle, whereas, for the comparison run under nitrogen atmosphere the solvent was taken from a sure-seal bottle. The maximum yield observed after 24 hours was 4% and 5% under air and N<sub>2</sub> respectively as determined by <sup>19</sup>F NMR. The reaction under mechanochemical conditions reached a maximum of 83% after 3 hours. These comparisons certainly point towards unique characteristics offered by ball-milling which are not attainable by solution processing.<sup>13</sup> It is unclear from where the stark contrast derives but this observation is certainly emerging as a theme in reactions of this type.<sup>8</sup> Several solution based protocols for Pd-catalyzed C-S coupling require strong bases or catalyst pre-activation, it may well be the case that the absence of solvent enables bases to exhibit enhanced basicity or nucleophilicity and thus *t*BuOK is effective under milling conditions as base or catalyst activation agent but not in solution. There is also the potential that milling conditions improve the stability of the catalyst by increasing the turnover frequency, regenerating catalytically active species from catalytically inactive species and/or enabling the generation of an anaerobic environment inside the jar. With regards to scale, whilst all of the examples reported here have been conducted at 1 mmol, several previous studies have shown the ability to scale-up ball-milled reactions, attention should be paid to match the volume ratios (volume of free space : volume of balls : volume of sample).<sup>8k, 9d</sup>

In conclusion, a reliable, operationally simple Pd-PEPPSI catalyzed C-S coupling has been developed with relatively short reaction times and without the need for exclusion of air/moisture. This method has been applied to 36 substrates and successfully adapted to a 2 step, 1 pot procedure for disulfide starting materials via the *in-situ* generation of non-malodorous thiolate salts. Compared to a solution approach the reactor environment of ball-milling appears to offer a more robust approach which requires less rigorously dry and oxygen-free conditions.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXX. Optimization data,

experimental procedures, characterization of new compounds and spectral data (PDF)

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### Notes

The authors declare no competing financial interest.

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(13) ICP-MS data was obtained for two samples that had been purified following our standard protocol (described in the SI). Limit of detection for  $^{105}\text{Pd}$  = 0.01698 ppb and  $^{66}\text{Zn}$  = 0.516 ppb.

