

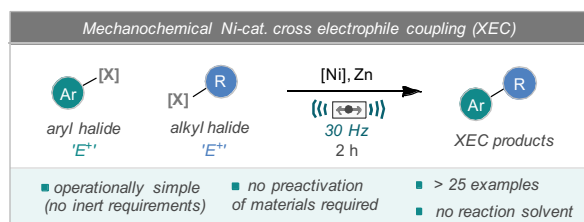
A Ball Milling-Enabled Cross-Electrophile Coupling

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ABSTRACT: The nickel-catalyzed cross-electrophile coupling of aryl halides and alkyl halides enabled by ball-milling is herein described. Under a mechanochemical manifold, the reductive C–C bond formation was achieved in the absence of bulk solvent and air/moisture sensitive set-ups, in reaction times of 2 hours. The mechanical action provided by ball milling permits the use of a range of zinc sources to turnover the nickel catalytic cycle, enabling the synthesis of 28 cross-electrophile coupled products.

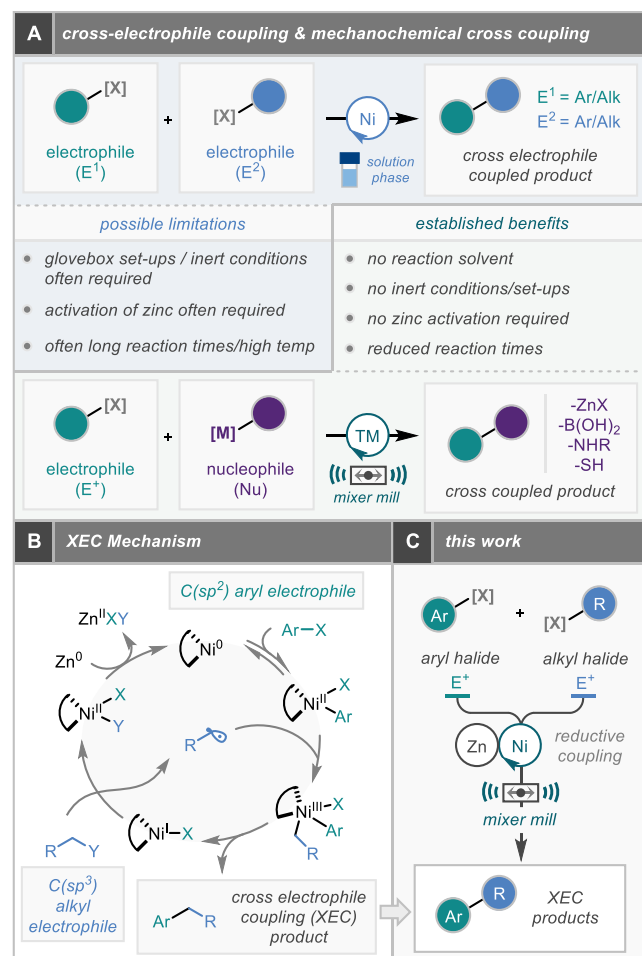
Owing to the ability to rapidly assemble molecules and related analogues, transition-metal-catalyzed cross coupling methodology has become a stalwart approach in both industrial and academic settings.¹ Cross electrophile coupling (XEC), pioneered in contemporary synthesis by Weix and co-workers,^{2,3} represents a particularly promising advancement in this area in terms of broadening the accessible chemical space through cross-coupling chemistry. These recent developments have employed nickel catalysis to enable the coupling of two traditionally “electrophilic” species, for example a C(sp²) aryl electrophile and a C(sp³) alkyl electrophile (Scheme 1A, top). Extensive mechanistic studies on this transformation have elucidated that a unified single electron transfer mechanism is in operation for the activation of alkyl halides to the corresponding alkyl radical species which then engages in subsequent coupling with aryl halides through a reductive elimination pathway (Scheme 1B).⁴ Uncovering this key interplay of redox activation has opened avenues in reaction design in cross-electrophile coupling and has sparked new discoveries in the area.⁵ However, despite the advances to date, a majority of the reductive methodologies developed have relied on the use of highly inert glovebox reaction set-ups.^{2,3,6} These methods can also suffer from capricious activation of zinc (or manganese) metal reductants as well as long reaction times and high reaction temperatures in some instances.

Whilst mechanochemistry has held a key role in crystal engineering and formulation science for decades,⁷ in recent years rapid and wide-ranging developments have estab-

lished mechanochemistry as a powerful enabling technology in sustainable synthetic method development.⁸ This is primarily due to the unique ability to run organic reactions without the need for bulk reaction solvent, often coupled with drastically reduced reaction times vs. solution-phase counterparts.⁹ Furthermore, mechanochemical ball-milling offers new opportunities in carrying out reaction systems classically requiring air/moisture sensitive set-ups under an air atmosphere.¹⁰ For these reasons mechanochemical synthesis – and especially mechanochemical catalysis – has been highlighted for its compatibility with the 12 principles of green chemistry,¹¹ and highly pertinent to sustainability metrics such as atom economy and process mass intensity¹², which are of increasing importance in industrial route design and development. Advances in mechanochemical cross coupling¹³ have established the fusion of electrophilic aryl halides and a variety of nucleophilic species including organozinc reagents,¹⁴ boronic acids,¹⁵ amines,¹⁶ alkenes/alkynes,¹⁷ and thiols¹⁸ (Scheme 1A, bottom). Despite this, these techniques remain in their infancy and further exploration is needed to fully uncover the opportunities that mechanochemistry can offer, in turn increasing adoption of this enabling technology. Accordingly, a mechanochemical approach to cross-electrophile coupling (XEC), negating the need for pre-functionalised reagents, forging C–C bonds using a base-metal catalyst, under an air atmosphere, and all in the absence of bulk reaction solvent, would be of interest to synthetic communities and facilitate further im-

plementation of this synthetic transformation in both industrial and academic settings, and herein we wish to report our findings (Scheme 1C).

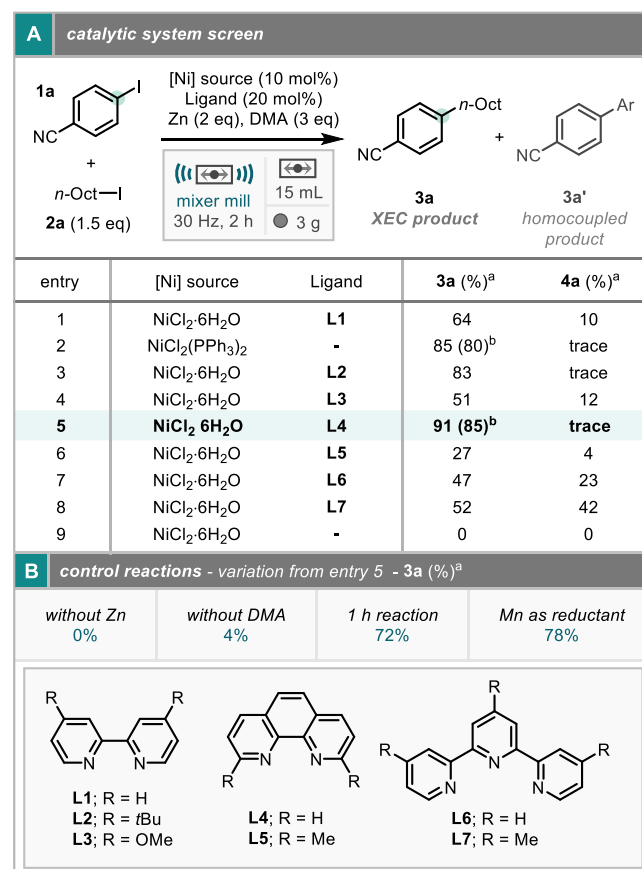
Scheme 1. Mechanochemistry in transition-metal catalyzed cross-coupling



Our investigations into mechanochemical cross-electrophile coupling began *via* assessing the reaction of 4-iodobenzonitrile (**1a**, Scheme 2A) and 1-iodooctane (**2a**) with a variety of nickel-based catalyst systems using zinc metal as the reductant. Preliminary optimisation studies (see supporting information for further details) revealed that cross electrophile coupled product (XEC product, **3a**) could be achieved in good yield in a mechanochemical environment in just 2 hours (compared to 12h+ routinely used in XEC coupling methodology)² by employing 1.5 equivalents of alkyl halide, 2 equivalents of zinc metal as a reductant, and 3 equivalents of DMA as a liquid-assisted grinding (LAG) agent (64%, Scheme 2A, entry 1).¹⁹ Further screening of pre-catalysts and ligand systems uncovered that – whilst NiCl₂(PPh₃)₂ provided increased yields (85%, entry 2) – inexpensive, readily available salt NiCl₂·6H₂O provided further improved yields, when coupled with bi-pyridyl-based ligand sets, with 1,10-phenanthroline (**L4**) proving optimal (91%, entry 5). Interestingly the use of tri-dentate ligand systems substantially increased the observation of homo-coupled bi-aryl product **3a'** (entries 7-8). Notably, in the absence of ligand, no cross-electrophile product was observed,

and the reaction returned both halide starting materials untouched (entry 9). To probe the reaction further, several control reactions were performed (Scheme 2B). It was shown that in the absence of the zinc reductant, no reaction occurs, and without the DMA additive, the reaction performs very poorly returning <5% product (**3a**).²⁰ Furthermore, an alternative reductant frequently used in cross-electrophile coupling, manganese metal, was shown – in the place of zinc – to maintain excellent reactivity affording the XEC product **3a** in 78% yield.^{2,3}

Scheme 2. Optimization of the mechanochemical cross-electrophile coupling of aryl iodides and alkyl iodides

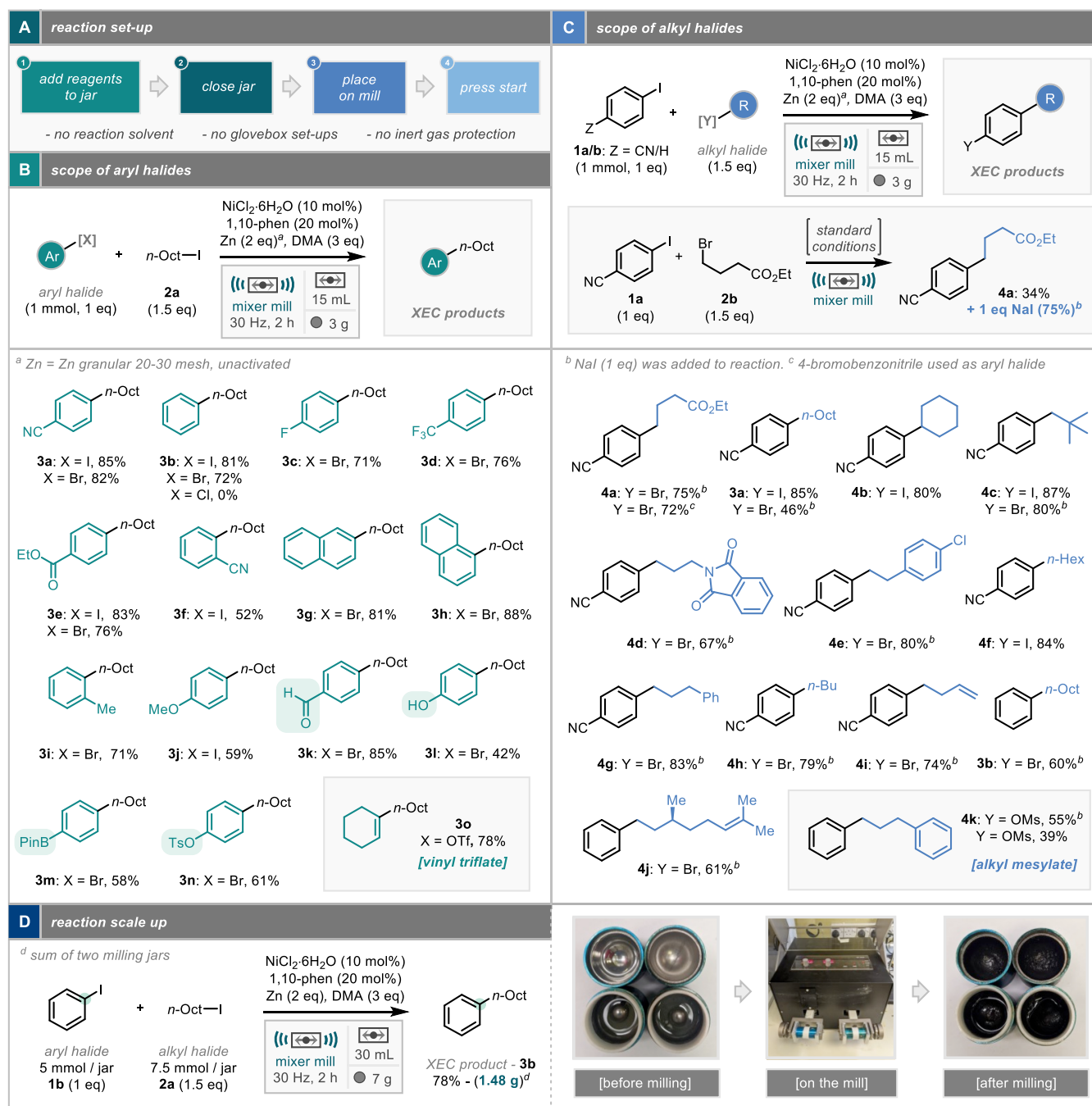


General reaction conditions: 4-iodobenzonitrile (**1a**, 1.0 mmol), 1-iodooctane (**2a**, 1.5 mmol), [Ni] catalyst (10 mol%, 0.1 mmol), Ligand (20 mol%, 0.2 mmol), Zn (granular 20-30 mesh, 2.0 mmol), *N,N*-dimethylacetamide (3.0 mmol), under an air atmosphere. The reaction was milled at 30 Hz for 2 hours in a stainless steel 15 mL milling jar using a 3 g (7 mm diameter) stainless steel milling ball (see supporting information for more details). ^a yield determined by ¹H NMR using mesitylene (0.33 mmol) as an internal standard. ^b isolated yield after silica gel column chromatography

With optimal conditions in hand, application of our operationally simple method (Scheme 3A) to a range of aryl halide fragments was explored (Scheme 3B). To our delight, the reaction system could be readily translated to bromoarenes with no appreciable drop in efficiency (**3a-b**).²¹ Furthermore, the reductive mechanochemical methodology was shown to be efficient across a spectrum of haloarene electronics, showcasing reactivity with both electron poor

(**3d**, **3e**), and electron rich (**3i-j**) as well as unactivated electron neutral systems (**3b**, **3c**, **3g-h**) when a selection of iodo/bromoarenes were employed. Moreover, sterically hindered *ortho*-substituted arenes also proceeded with negligible suppression of reaction efficiency (**3g**, **3h**). Substrates containing highly electrophilic sites such as aldehydes selectively underwent cross-coupling and showed no undesired reactivity of the carbonyl functionality (**3k**). A well-established advantage of cross-electrophile coupling is the lack of requirement for a stoichiometric base in the reaction medium, as would typically be seen with an analogous Suzuki coupling, allowing for the successful coupling of substrates with acidic sites such as free phenols (**3l**). Importantly, aryl halides bearing boronate esters and tosylates

Scheme 3. Scope of the reductive cross-electrophile coupling of aryl and alkyl halides enabled by ball-milling

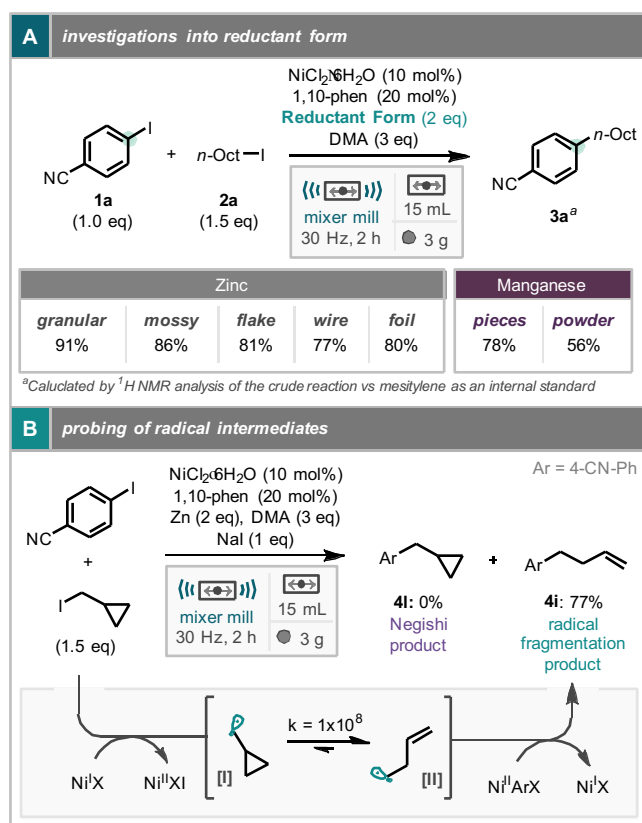


were entirely selective for coupling at the halide site affording products with important functional handles for orthogonal downstream derivatization through subsequent coupling reactions (**3m**, **3n**). In addition, pseudohalides were shown to be compatible with our mechanochemical system, where coupling of a vinyl triflate derivative afforded the desired product in excellent yield (78%, **3o**). Following this, our attention turned to investigating the varying alkyl halides (Scheme 3C). A convenient solution for low-yielding alkyl bromide substrates (**2b**) was found in the addition of 1 equivalent of sodium iodide to facilitate an *in-situ* Finkelstein reaction.^{22,2b}

This modification to the reaction conditions provided a remarkable increase in yield from 34% to 75%, and throughout the remaining scope, this technique was used for alkyl bromide coupling partners.²³ Using these conditions, a range of alkyl halides were coupled to model aryl halides 4-iodobenzonitrile (**1a**) and 4-iodobenzene (**1b**). Carboxylic ester (**4a**), protected amine (**4d**), and chloroarene (**4e**) functionality were tolerated with great efficiency alongside a selection of skeletal aliphatic side chains. Notably, secondary alkyl iodides were demonstrated to be excellent coupling partners in this methodology (**4b**, 80%), in conjunction with the smooth introduction of sterically demanding neopentyl chains (**4c**). For longer chain alkyl bromides, it was shown that higher yields were achieved using electron-neutral iodobenzene (**3b**) when compared to 4-iodobenzonitrile (**3a**). Citronellyl bromide was also successfully coupled with iodobenzene in 61% (**4k**). Coupling of alkyl mesylates is particularly desirable as it provides an efficient, indirect route from commodity alcohols.^{5a} Exploring this concept, under our conditions, 39% of **4k** (55% on addition of NaI) was delivered upon reaction of iodobenzene with 3-phenylpropyl methanesulfonate. Pleasingly the transformation was readily scaled up to gram-scale, where using 30 mL milling jars and 7 g milling balls, 1.48 g of the cross electrophile-coupled product **3b** could be achieved using the two milling jars, in comparable yields to previously achieved (78%, Scheme 3D)

The use of Zn⁰ metal as a reagent can lead to variation in reproducibility and performance of reactions. It is critical to achieve effective activation of the zinc and this in turn is highly dependent on the physical form of the zinc metal employed. Our previous reports on the mechanochemical generation and downstream reactivity of organozinc species have denoted that in the unique reaction environment of the mixer mill enables the use of a wide range of zinc forms without substantial yield variations and, critically, excellent reproducibility.¹⁰ Pleasingly, in this methodology, excellent reactivity was maintained when using granular, mossy, flake, wire, or foil forms of Zn⁰ metal (Scheme 4A). Notably exchanging for the alternative reductant of manganese pieces (78%) or manganese powder (56%) was also possible. Cross-electrophile coupling mechanisms have been extensively explored in previous studies.¹⁵ The overall mechanism (exemplified above in Scheme 1B) details a single electron transfer mechanism for the activation of the alkyl halide. Despite this, *via in-situ* generation of an alkyl organozinc intermediate (through mechanochemical reaction of Zn⁰ and the alkyl iodide), a Negishi-type coupling may also be in operation. This was probed through employing cyclopropylmethyl iodide as the alkyl halide substrate, where a two-electron Negishi-type process would lead to the ring closed product, and a single-electron process (akin to those detailed by Weix)⁴ would lead to the ring opened homoallylarene structure (*via* the well-established cyclopropylmethyl radical fragmentation of [I] to [II], Scheme 4B). To this end, the latter radical fragmentation product was formed exclusively in excellent yield (77%) in the reaction mixture, suggesting that this mechanochemical manifold operates under the unified mechanism observed in the solution-phase transformations.²⁴

Scheme 4. Studies into the form of the reductant and the presence of radical intermediates.



In conclusion, the mechanochemical cross-electrophile coupling of aryl halides and alkyl halides has been described. Negating the use of bulk reaction solvent and air/moisture sensitive reaction set-ups, the coupling of two electrophilic species through a reductive nickel catalytic cycle is achieved. Perhaps most notable is the ability to render the reaction with increased robustness owing to mechanical activation of zinc or manganese metal in a variety of physical forms. Moreover, the reaction methodology was then demonstrated on gram-scale with maintained efficiency.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at:

- Synthetic procedures and characterization data

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