A Ball Milling-Enabled Cross-Electrophile Coupling

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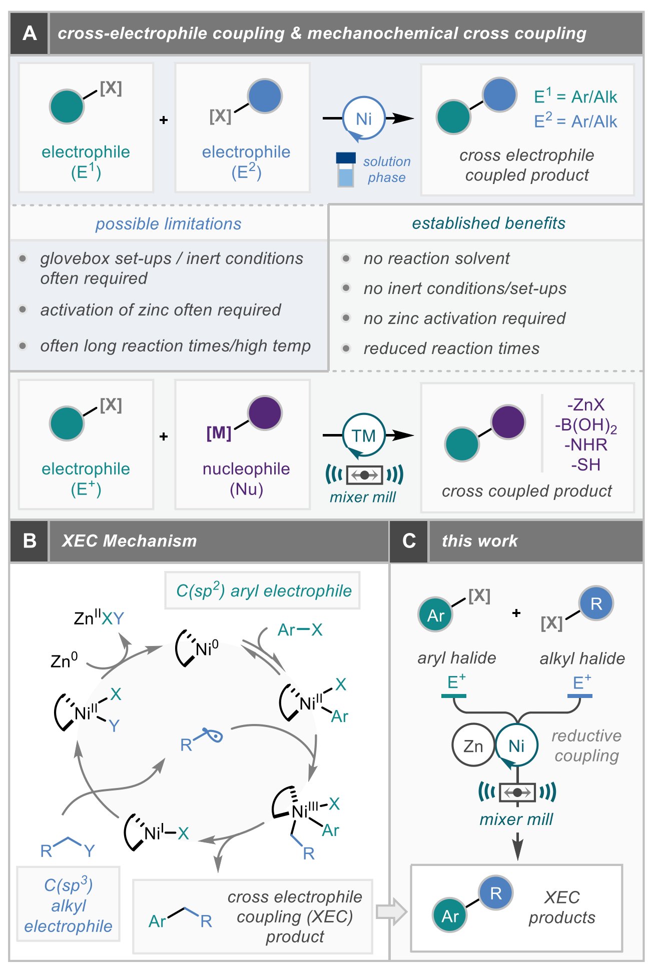
ABSTRACT: The nickel-catalyzed cross-electrophile coupling of aryl (pseudo)halides and alkyl (pseudo)halides enabled by ball-milling is herein described. Under a mechanochemical manifold, the reductive C–C bond formation was achieved in the absence of bulk solvent and air/moisture sensitive set-ups, 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 catalytic cycle of nickel. A library of 28 cross-electrophile coupled building blocks has been constructed to exemplify this technique,

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 established 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]

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



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[12] and process mass intensity[13], which are of increasing importance in industrial route design and development. Advances in mechanochemical cross coupling[14] have established the fusion of electrophilic aryl halides and a variety of nucleophilic species including organozinc reagents,[15] boronic acids,[16] amines,[17] alkenes/alkynes,[18] and thiols[19] (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.

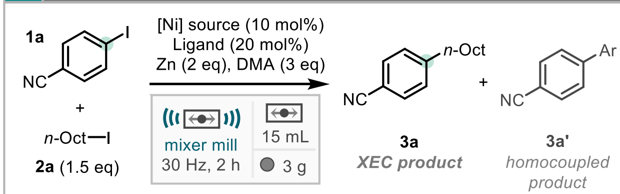
Accordingly, a mechanochemical approach to cross-electrophile coupling (XEC), negating the need for pre-functionalised regents, forging C–C bonds using a base-metal catalyst, under an air atmosphere, and all in the absence of bulk reaction solvent, would be of interest to synthetic communities and facilitate further implementation of this synthetic transformation in both industrial and academic settings and herein we wish to report our findings (Scheme 1C).

Our investigations into mechanochemical cross-electrophile coupling began *via* assessing the reaction of 4-iodobenzonitrile (**1a**, Table 1A) 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 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%, Table 1, entry 1).[20] Further screening of pre-catalysts and ligand systems uncovered that – whilst $NiCl_2(PPh_3)_2$ provided increased yields (85%, entry 2) – inexpensive, readily available salt $NiCl_2{\cdot}6H_2O$ 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). Alternative nickel catalyst precursor salts were then investigated in conjunction with **L4** (entries 10-13). Despite all nickel complexes showing modest to good reactivity in the cross- coupling reaction, $NiCl_2{\cdot}6H_2O$ remained the most active (entry 5).

To probe the reaction further, several control reactions were performed (Table 1B). 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**).[21] Furthermore, an alternative reductant frequently used in cross-electrophile coupling is manganese metal.[2,3] Under the reaction conditions, the use of manganese pieces in the place of zinc maintained excellent reactivity affording the XEC product **3a** in 78% yield.

Table 1. Optimization of the mechanochemical cross-electrophile coupling of aryl iodides and alkyl iodides

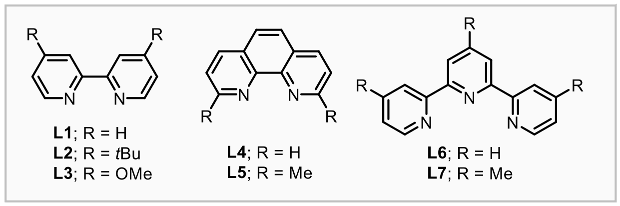
A *catalytic system screen*



entry	[Ni] source	Ligand	3a (%)[a]	4a (%)[a]
1	$NiCl_2{\cdot}6H_2O$	**L1**	64	10
2	$NiCl_2(PPh_3)_2$	-	85 (80)[b]	trace
3	$NiCl_2{\cdot}6H_2O$	**L2**	83	trace
4	$NiCl_2{\cdot}6H_2O$	**L3**	51	12
5	**$NiCl_2{\cdot}6H_2O$**	**L4**	**91 (85)[b]**	**trace**
6	$NiCl_2{\cdot}6H_2O$	**L5**	27	4
7	$NiCl_2{\cdot}6H_2O$	**L6**	47	23
8	$NiCl_2{\cdot}6H_2O$	**L7**	52	42
9	$NiCl_2{\cdot}6H_2O$	-	0	0
10	$NiCl_2$ (anhyd.)	**L4**	31	0
11	$NiCl_2{\cdot}DME$	**L4**	78	2
12	$NiBr_2{\cdot}DME$	**L4**	42	9
13	NiI_2	**L4**	11	4

B ***control reactions*** *- variation from entry 5* - **3a** (%)[a]

without Zn	without DMA	1 h reaction	Mn as reductant
0%	4%	72%	78%



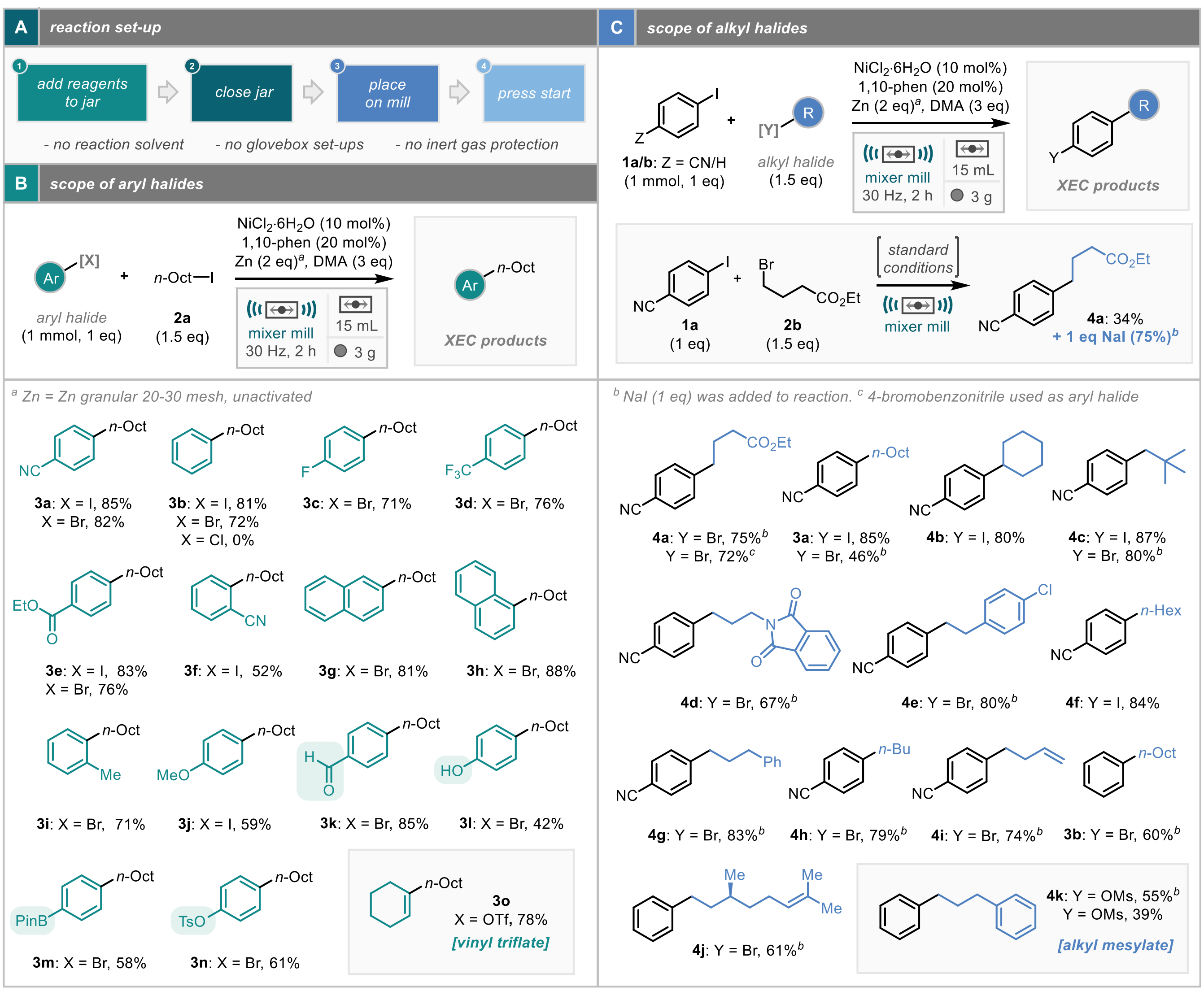
General reaction conditions: 4-iodobenzonitrile (**1a**, 1.0 mmol), 1-iodooctane (**2a**, 1.5 mmol), [Ni] catalyst (10 mol%, 0.1 mmol), Ligand (20 mol%, 0.2 mmol), Zn (granular 20-30 mesh, 2.0 mmol), *N,N*-dimethylacetamide (3.0 mmol), under an air atmosphere. The reaction was milled at 30 Hz for 2 hours in a stainless steel 15 mL milling jar using a 3 g 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 2A) to a range of aryl halide fragments was explored (Scheme 2B). To our delight, the reaction system could be readily translated to bromoarenes with no appreciable drop in efficiency (**3a-b**).[22] 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**). Notably, 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. This allows for the successful coupling of substrates with acidic sites such as free phenols (**3l**).[23] Importantly, aryl halides bearing boronate esters and tosylates 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**). To our delight, it was also shown that pseudohalides were compatible with our mechanochemical system, exemplified by the reaction of cyclohex-1-en-1-yl trifluoromethanesulfonate – a vinyl triflate derivative –, which afforded desired XEC product in excellent yield (78%, **3o**).

Following this, our attention turned to investigating the varying alkyl halides (Scheme 2C). Preliminary explorations showed that whilst alkyl iodides performed well in the rection, alkyl bromides proceeded in diminished yields owing to lower conversion from the alkyl bromide starting material. This observation is illustrated by the low yield achieved upon coupling 4-iodobenzontirile (**1b**) with ethyl 4-bromo butyrate (**2b**). A convenient solution to this was found in the addition of 1 equivalent of sodium iodide to facilitate an *in-situ* Finkelstein reaction.[24,2b] 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.[25]

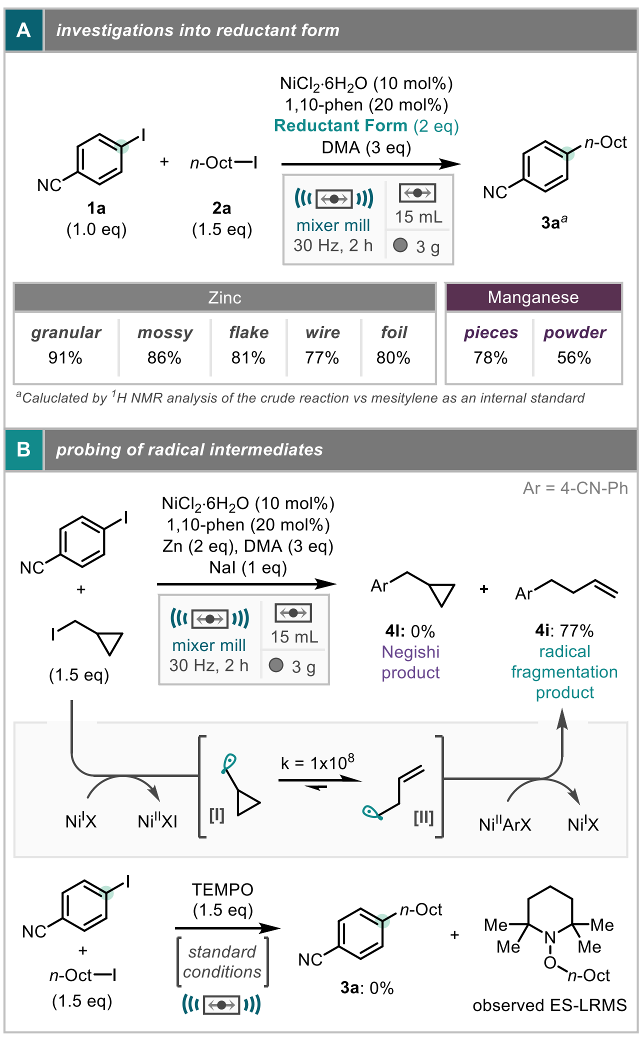
Using this methodology, a range of alkyl halides were coupled to model aryl halides 4-iodobenzonitrile (**1a**) and 4-iodobenzene (**1b**). Carboxylic ester (**4a**), protected amine (**4d**), and chloroarene (**4e**) functionality were tolerated with great efficiency alongside a selection of skeletal 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**). Alkene functionality was also tolerated in the case of 4-bromo-1-butene (**4i**).

Scheme 2. Scope of the reductive cross-electrophile coupling of aryl and alkyl halides enabled by ball-milling



For longer chain alkyl bromides, it was shown that higher yields were achieved using electron-neutral iodobenzene (**3b**) when compared to 4-iodobenzontrile (**3a**). In the latter of these cases, propensity for electron poor iodoarenes to afford undesired homo-coupled biaryl products (4,4'-biphenyldicarbonitrile, Table 1, **3a'**) in significant quantities (28%) was noted. This issue was shown to be much less pronounced with iodobenzene leading to increased yields of cross-electrophile coupled product **3b**. Citronellyl bromide was also successfully coupled with iodobenzene in 61% again demonstrating tolerance for alkene functionality (**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** was delivered upon reaction of iodobenzene with 3-phenylpropyl methanesulfonate. The yield of this reaction was again shown to be increased with the addition of 1 equivalent of sodium iodide (55%).

Scheme 3. Studies into the form of the reductant and the presence of radical intermediates.



The use of Zn° 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 reproducibilty.[10] Pleasingly, in this methodology, excellent reactivity was maintained when using granular, mossy, flake, wire, or foil forms of Zn° metal (Scheme 3A). Notably exchanging for the alternative reductant of manganese pieces (78%) for 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 that single electron transfer activation followed by radical capture by a Ni(II) species and subsequent reductive elimination forges the C–C bond. Despite this, we were aware that, *via in-situ* generation of an alkyl organozinc intermediate (through mechanochemical reaction of Zn° and the alkyl iodide), a tandem Negishi-type coupling may also be in operation. The presence of a key alkyl open-shell intermediate can be probed through radical clock experiments.[26] Here, through employing cyclopropylmethyl iodide as the alkyl halide substrate, 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 3B). Interestingly, the latter radical fragmentation product was formed exclusively in excellent yield (77%) in the reaction mixture. Further radical trapping studies showed that the addition of TEMPO (2,2,6,6-tetramethylpiperidinyloxy) nullified reactivity for cross coupling and the *n*-octyl TEMPO adduct (derived from the *n*-octyl radical) was observed by ES-LRMS analysis of the crude reaction mixture. For these reasons, it is suggested that this mechanochemical manifold operates under the unified mechanism observed in the analogous solution-phase transformations.

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. A library of 28 examples has been demonstrated using this methodology, highlighting the robust transformation especially noted in the tolerance of traditionally fragile functionality such as aryl boronates, aldehydes and tosylates. Initial mechanistic investigations align the mechanochemical process with solution-phase mechanisms, proceeding via an intermediary alkyl radical, operating within a nickel-based catalytic cycle. Work is currently ongoing to unlock aryl chlorides as inexpensive feedstocks for this mechanochemical cross electrophile coupling methodology.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at:

- Experimental procedures and characterization data

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REFERENCES

(1) (a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564-12649. (b) Buskes, M. J.; Blanco, M.-J. Impact of Cross-Coupling Reactions in Drug Discovery and Development. *Molecules* **2020**, *25*, 3493. (c) Campeau, L.-C.; Hazari, N. *Organometallics* **2019**, *38*, 3-35. (d) Torborg, C.; Beller, M. Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries. *Adv. Synth. Catal.* **2009**, *351*, 3027-3043. (e) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.

(2) For key references on catalytic cross-electrophile coupling from Weix and co-workers, see: (a) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 920-921. (b) Everson, D. A.; Jones, B. A.; Weix, D. A. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146-6159. (c) Ackerman, L. K. G.; Lovell, M. M.; Weix, D. J. Multimetallic catalysed cross-coupling of aryl bromides with aryl triflates. *Nature* **2015**, *524*, 454-457. (d) Kim, S.; Goldfogel, M. J.; Gilbert, M. M.; Weix, D. J. Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Chlorides with Primary Alkyl Chlorides. *J. Am. Chem. Soc.* **2020**, *142*, 9902-9907. (e) Olivares, A. M.; Weix, D. J. Multimetallic Ni- and Pd-Catalyzed Cross-Electrophile Coupling To Form Highly Substituted 1,3-Dienes. *J. Am. Chem. Soc.* **2018**, *140*, 2446-2449; (f) Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J. Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem.* **2017**, *82*, 7085-7092. (g) Kang, K.; Huang, L.; Weix, D. J. Sulfonate Versus Sulfonate: Nickel and Palladium Multimetallic Cross-Electrophile Coupling of Aryl Triflates with Aryl Tosylates. *J. Am. Chem. Soc.* **2020**, *142*, 10634-10640.

(3) For reviews see: (a) Everson, D. A.; Weix, D. J. Cross-electrophile coupling: principles of reactivity and selectivity. *J. Org. Chem.* **2014**, *79*, 4793-4798. (b) Poremba, K. E.; Dibrell, S. E.; Reisman, S. E. Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions. *ACS Catal.* **2020**, *10*, 8237-8246. (c) Kaga, A.; Chiba, S. Engaging Radicals in Transition Metal-Catalyzed Cross-Coupling with Alkyl Electrophiles: Recent Advances. *ACS Catal.* **2017**, *7*, 4697-4706. For selected other reports, see: (d) Kwa, T. L.; Boelhouwer, Wurtz-Fittig syntheses of mixed trideuteromethyl and methyl derivatives of benzene. *Tetrahedron* **1969**, *25*, 5771-5776. (e) Gomes, P.; Fillon, H.; Gosmini, C.; Labbé, E.; Périchon, J. Synthesis of unsymmetrical biaryls by electroreductive cobalt-catalyzed cross-coupling of aryl halides. *Tetrahedron* **2002**, *58*, 8417-8424. (f) Amatore, M.; Gosmini, C. Efficient Cobalt-Catalyzed Formation of Unsymmetrical Biaryl Compounds and Its Application in the Synthesis of a Sartan Intermediate. *Angew. Chem. Int. Ed.* **2008**, *47*, 2089-2092. (g) Hassan, J.; Hathroubi, C.; Gozzi, C.; Lemaire, M. Synthesis of unsymmetrical biaryls via palladium-catalyzed coupling reaction of aryl halides. *Tetrahedron Lett.* **2000**, *41*, 8791-8794. (h) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. Nickel-Catalyzed Reductive Cross-Coupling of Unactivated Alkyl Halides. *Org. Lett.* **2011**, *13*, 2138-2141. (i) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. Nickel-catalyzed cross-coupling of unactivated alkyl halides using bis(pinacolato)diboron as reductant. *Chem. Sci.* **2013**, *4*, 4022-4029. (j) Li, Z.; Sun, W.; Wang, X.; Li, L.; Zhang, Y.; Li, C. Electrochemically Enabled, Nickel-Catalyzed Dehydroxylative Cross-Coupling of Alcohols with Aryl Halides. *J. Am. Chem. Soc.* **2021**, *143*, 3536-3543. (k) Dorval, C.; Tricoire, M.; Begouin, J.-M.; Gandon, V.; Gosmini, C. Cobalt-Catalyzed C(sp^2)–CN Bond Activation: Cross-Electrophile Coupling for Biaryl Formation and Mechanistic Insight. *ACS Catal.* **2020**, *10*, 12819-128927. (l) Truesdell, B. L.; Hamby, T. B.; Sevov, C. S. General C(sp^2)–C(sp^3) Cross-Electrophile Coupling Reactions Enabled by Overcharge Protection of Homogeneous Electrocatalysts. *J. Am. Chem. Soc.* **2020**, *142*, 5884-5893. (m) Cherney, A. H.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles. *J. Am. Chem. Soc.* **2014**, *136*, 14365-14368. (n) Wright, A. C.; Stoltz, B. M. Enantioselective construction of the tricyclic core of curcusones A–D via a cross-electrophile coupling approach. *Chem. Sci.* **2019**, *10*, 10562-10565.

(4) (a) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197. (b) Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767-1775. (c) Anka-Lufford, L.; Huihui, K. M. M.; Gower, N. J.; Ackerman, L. K. G.; Weix, D. J. Nickel-Catalyzed Cross-Electrophile Coupling with Organic Reductants in Non-Amide Solvents. *Chem. Eur. J.* **2016**, *22*, 11564-11567. (d) Charboneau, D. J.; Barth, E. L.; Hazari, N.; Uehling, M. R.; Zultanski, S. L. A Widely Applicable Dual Catalytic System for Cross-Electrophile Coupling Enabled by Mechanistic Studies. *ACS Catal.* **2020**, *10*, 12642-12656. (e) Paul, A.; Smith, M. D.; Vannucci, A. K. Photoredox-Assisted Reductive Cross-Coupling: Mechanistic Insight into Catalytic Aryl–Alkyl Cross-Couplings. *J. Org. Chem.* **2017**, *82*, 1996-2003.

(5) (a) Ackerman, L. K. G.; Anka-Lufford, L.; Naodovic, M.; Weix, D. J. Cobalt co-catalysis for cross-electrophile coupling: diarylmethanes from benzyl mesylates and aryl halides. *Chem. Sci.* **2015**, *6*, 1115-1119. (b) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. Decarboxylative Cross-Electrophile Coupling of *N*-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *136*, 5016-5019. (c) Everson, D. A.; Buonomo, J. A.; Weix, D. J. Nickel-Catalyzed Cross-Electrophile Coupling of 2-Chloropyridines with Alkyl Bromides. *Synlett* **2014**, *25*, 233-238. (d) Zhao, Y.; Weix, D. J. Enantioselective Cross-Coupling of meso-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015**,*137*, 3237-3240.

(6) During the final preparation of this manuscript, Shi and Zou reported a similar transformation using a planetary mill and inert atmosphere protection: Wu, S.; Shi, W.; Zou, G. Mechanical metal activation for Ni-catalyzed, Mn-mediated cross-electrophile coupling between aryl and alkyl bromides. *New J. Chem.* **2021**, DOI: 10.1039/D1NJ01732B.

(7) (a) Baláž, P.; Achimovičová, M.; Baláž, M.; Billik, P.; Cherkezova-Zheleva, Z.; Criado, J. M.; Delogu, F.; Dutková, E.; Gaffet, E.; Gotor, F. J.; Kumar, R.; Mitov, I.; Rojac, T.; Senna, M.; Stre-

letskii, A.; Wieczorek-Ciurowa, K. Hallmarks of mechanochemistry: from nanoparticles to technology. *Chem. Soc. Rev.* **2013**, *42*, 7571-7637. (b) Boldyreva, E. Mechanochemistry of inorganic and organic systems: what is similar, what is different? *Chem. Soc. Rev.* **2013**, *42*, 7719-7738.

(8) (a) Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B. Ball milling in organic synthesis: solutions and challenges. *Chem. Soc. Rev.* **2011**, *40*, 2317-2329. (b) Andersen, J.; Mack, J. Mechanochemistry and organic synthesis: from mystical to practical. *Green Chem.* **2018**, *20*, 1435-1443. (c) Egorov, I. N.; Santra, S.; Kopchuk, D. S.; Kovalev, I. S.; Zyryanov, G. V.; Majee, A.; Ranu, B. C.; Rusinov, V. L.; Chupakhin, O. N. Ball milling: an efficient and green approach for asymmetric organic syntheses. *Green Chem.* **2020**, *22*, 302-315. (d) Friščić, T.; Mottillo, C.; Titi, H. M. Mechanochemistry for Synthesis. *Angew. Chem. Int. Ed.* **2020**, *59*, 1018-1029. (e) Hernández, J. G. C–H Bond Functionalization by Mechanochemistry. *Chem. Eur. J.* **2017**, *23*, 17157-17165. (f) Wang, G.-W. Mechanochemical organic synthesis. *Chem. Soc. Rev.* **2013**, *42*, 7668-7700. (g) Kubota, K.; Ito, H. Mechanochemical Cross-Coupling Reactions. *Trends Chem.* **2020**, *2*, 1066-1081. (h) Leitch, J. A.; Browne, D. L. *Chem. Eur. J.* **2021.** DOI: 10.1002/chem.202100348

(9) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, *9*, 3080-3094.

(10) (a) Kubota, K.; Takahashi, R.; Ito, H. Mechanochemistry allows carrying out sensitive organometallic reactions in air: glove-box-and-Schlenk-line-free synthesis of oxidative addition complexes from aryl halides and palladium (0). *Chem. Sci.* **2019**, *10*, 5837-5842. (b) Kubota, K.; Takahashi, R.; Uesugi, M.; Ito, H. A Glove-Box- and Schlenk-Line-Free Protocol for Solid-State C–N Cross-Coupling Reactions Using Mechanochemistry. *ACS Sustainable Chem. Eng.* **2020**, *8*, 16577-16582.

(11) (a) Ardilla-Fierro, K. J.; Hernández, J. G. Sustainability Assessment of Mechanochemistry Using the Twelve Principles of Green Chemistry. *ChemSusChem* **2021**; DOI: 10.1002/cssc.202100478 (b) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301-312; (c) Sheldon, R. A. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.

(12) (a) Trost, B. M. The atom economy--a search for synthetic efficiency. *Science* **1991**, *254*, 1471-1477; (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3010-321.

(13) Kjell, D. P.; Watson, I. A.; Wolfe, C. N.; Spitler, J. T. Complexity-Based Metric for Process Mass Intensity in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2013**, *17*, 169-174.

(14) (a) Kubota, K.; Ito, H. Mechanochemical Cross-Coupling Reactions. *Trends Chem.* **2020**, *2*. 1066-1081; (b) Porcheddu, A.; Calacino, E.; De Luca, L.; Delogu, F. Metal-Mediated and Metal-Catalyzed Reactions Under Mechanochemical Conditions. *ACS Catal.* **2020**, *10*, 8344-8394.

(15) (a) Cao, Q.; Howard, J. L.; Wheatley, E.; Browne, D. L. Mechanochemical Activation of Zinc and Application to Negishi Cross-Coupling. *Angew. Chem. Int. Ed.* **2018**, *57*, 11339-11343. (b) Cao, Q.; Stark, R. T.; Fallis, I. A.; Browne, D. L. *ChemSusChem* **2019**, *12*, 2554-2557. (c) Yin, J.; Stark, R. T.; Fallis, I. A.; Browne, D. L. A Mechanochemical Zinc-Mediated Barbier-Type Allylation Reaction under Ball-Milling Conditions. *J. Org. Chem.* **2020**, *85*, 2347-2354.

(16) (a) Nielsen, S. F.; Peters, D.; Axelsson, O. The Suzuki Reaction Under Solvent-Free Conditions. *Synth. Comm.* **2000**, *30*, 3501-3509. (b) Klingensmith, L. M.; Leadbeater, N. E. Ligand-free palladium catalysis of aryl coupling reactions facilitated by grinding. *Tetrahedron Lett.* **2003**, *44*, 765-768. (c) Schneider, F.; Ondruschka, B. *ChemSusChem* **2008**, *1*, 622-625. (d) Schneider, F.; Stolle, A.; Ondruschka, B.; Hopf, H. The Suzuki–Miyaura Reaction under Mechanochemical Conditions. *Org. Process Rev. Dev.* **2009**, *13*, 44-48. (e) Jiang, Z.-J.; Li, Z.-H.; Yu, J.-B.; Su, W.-K. Liquid-Assisted Grinding Accelerating: Suzuki–Miyaura Reaction of Aryl Chlorides under High-Speed Ball-Milling Conditions. *J. Org. Chem.* **2016**, *81*, 10049-10055. (f) Seo, T.; Ishiyama, T.; Kubota, K.; Ito, H. Solid-state Suzuki–Miyaura cross-coupling reactions: olefin-accelerated C–C coupling using mechanochemistry. *Chem. Sci.* **2019**, *10*, 8202-8210. (g) Seo, T.; Kubota, K.; Ito, H. Selective Mechanochemical Monoarylation of Unbiased Dibromoarenes by in Situ Crystallization. *J. Am. Chem. Soc.* **2020**, *142*, 9884-9889. (h) Seo, T.; Toyoshima, N.; Kubota, K.; Ito, H. Tackling Solubility Issues in Organic Synthesis: Solid-State Cross-Coupling of Insoluble Aryl Halides. *J. Am. Chem. Soc.* **2021**, *143*, 6165-6175. (i) Báti, G.; Csókás, D.; Yong, T.; Tam, S. M.; Shi, R. R. S.; Webster, R. D.; Pápai, I.; Garcia, F.; Stuparu, M. C. *Angew. Chem. Int. Ed.* **2020**, *59*, 21620-21626.

(17) (a) Shao, Q.-L.; Jiang, Z.-J.; Su, W.-K. *Tetrahedron Lett.* **2018**, *59*, 2277-2280. (b) Cao, Q.; Nicholson, W. I.; Jones, A. C.; Browne, D. L. Robust Buchwald–Hartwig amination enabled by ball-milling. *Org. Biomol. Chem.* **2019**, *17*, 1722-726. (c) Kubota, K.; Seo, T.; Koide, K.; Hasegawa, Y.; Ito, H. Olefin-accelerated solid-state C–N cross-coupling reactions using mechanochemistry. *Nat. Commun.* **2019**, *10*, 111.

(18) (a) Tullberg, E.; Peters, D.; Frejd, T. *J. Organomet. Chem.* **2004**, *689*, 3778-3781. (b) Tullbergg, E.; Schacher, F.; Peters, D.; Frejd, T. Solvent-Free Heck–Jeffery Reactions under Ball-Milling Conditions Applied to the Synthesis of Unnatural Amino Acids Precursors and Indoles. *Synthesis* **2006**, *7*, 1183-1189. (c) Declerck, V.; Colacino, E.; Bantriel, X.; Martinez, J.; Lamaty, F. Poly(ethylene glycol) as reaction medium for mild Mizoroki–Heck reaction in a ball-mill. *Chem. Commun.* **2012**, *48*, 11778-11780. (d) Fulmer, D. A.; Shearouse, W. C.; Medonza, S. T.; Mack, J. Solvent-free Sonogashira coupling reaction via high speed ball milling. *Green. Chem.* **2009**, *11*, 1821-1825. (e) Thorwirth, R.; Stolle, A.; Ondruschka, B. Fast copper-, ligand- and solvent-free Sonogashira coupling in a ball mill. *Green. Chem.* **2010**, *12*, 985-981. (f) Zhu, X.; Liu, J.; Chen, T.; Su, W. *Appl. Organomet. Chem.* **2012**, *26*, 145-147.

(19) Jones, A. C.; Nicholson, W. I.; Smallman, H. R.; Browne, D. L. A Robust Pd-Catalyzed C–S Cross-Coupling Process Enabled by Ball Milling. *Org. Lett.* **2020**, *22*, 7433-7438.

(20) For further reading on the benefits of liquid-assisted grinding agent, see: (a) Ying, P.; Yu, J.; Su, W. Liquid-Assisted Grinding Mechanochemistry in the Synthesis of Pharmaceuticals. *Adv. Synth. Catal.* **2021**, *363*, 1246-1271. (b) Howard, J. L.; Sagatov, Y.; Repusseau, L.; Schotten, C.; Browne, D. L. *Green. Chem.* **2017**, *19*, 2798-2802.

(21) The crucial addition of DMA as an additive in zinc-mediated mechanochemical reactions has already been noted in a previous study, see reference 10a.

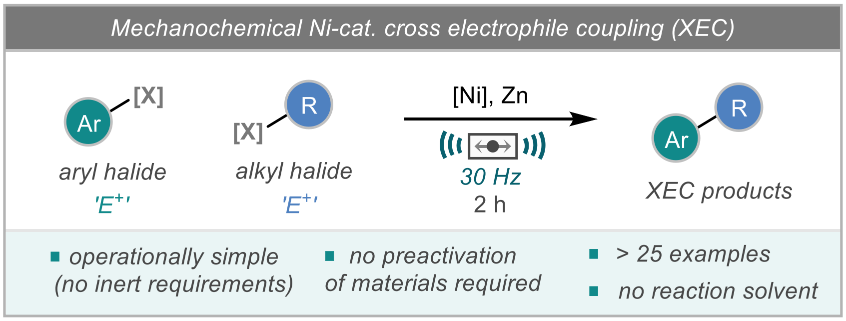
(22) Unfortunately, under these conditions aryl chlorides were not compatible coupling partners in this methodology

(23) Free anilines did not show any desired product, most likely due to coordination to the nickel catalyst leading to catalyst poisoning.

(24) Simple mechanochemical mixing of alkyl bromide **2b** with NaI with/without the presence of DMA leads to good conversion to the corresponding alkyl iodide.

(25) Control experiments demonstrated the addition of sodium iodide had no positive/negative effect on the reaction of alkyl iodides.

(26) Griller, D.; Ingold, K. U. Free-radical clocks. *Acc. Chem. Res.* **1980**, *13*, 317-323.


Mechanochemical Ni-cat. cross electrophile coupling (XEC)
Ar
[X]
aryl halide
'E+'
[X]
R
alkyl halide
'E+'
[Ni], Zn
30 Hz
2 h
Ar
R
XEC products
operationally simple (no inert requirements)
no preactivation of materials required
> 25 examples
no reaction solvent