Citation for final published version:

Jones, Andrew C., Nicholson, William I., Leitch, Jamie A. and Browne, Duncan L. ORCID: https://orcid.org/0000-0002-8604-229X 2021. A ball-milling-enabled cross-electrophile coupling. Organic Letters 23 (16) , 6337–6341. 10.1021/acs.orglett.1c02096 file

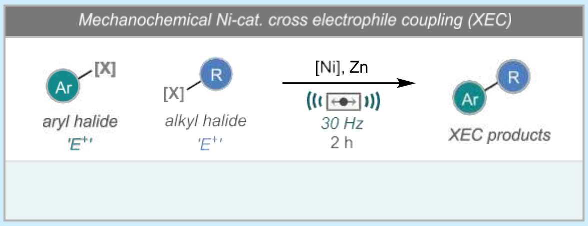
Publishers page: http://dx.doi.org/10.1021/acs.orglett.1c02096 <http://dx.doi.org/10.1021/acs.orglett.1c02096>

A Ball-Milling-Enabled Cross-Electrophile Coupling

Andrew C. Jones, William I. Nicholson, Jamie A. Leitch, and Duncan L. Browne*

ACCESS | Metrics & More | Article Recommendations | Supporting Information

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 setups, in reaction times of 2 h. 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.

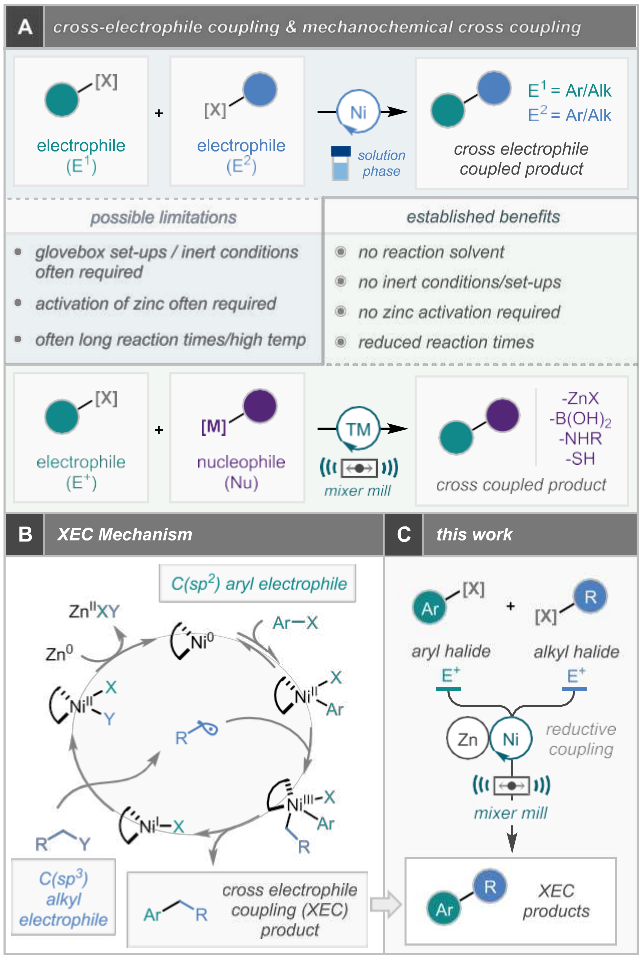


Owing to the ability to rapidly assemble molecules and related analogues, transition-metal-catalyzed cross-coupling methodology has become a stalwart approach in both industrial and academic settings.[1] Cross electrophile coupling (XEC), pioneered in contemporary synthesis by Weix and coworkers,[2,3] 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 $C(sp^2)$ aryl electrophile and a $C(sp^3)$ 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 setups.[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.

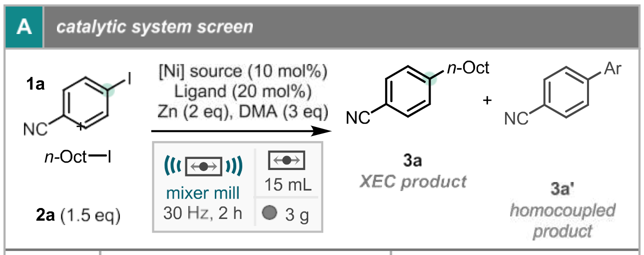
While mechanochemistry has held a key role in crystal engineering and formulation science for decades,[7] in recent years rapid and wide-ranging developments have established mechanochemistry as a powerful enabling technology in sustainable synthetic method development.[8] This is primarily due to the 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 setups 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 intensity,[12] which are of increasing importance in industrial route design and development. Advances in mechanochemical cross coupling[13] 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 thiols[18] (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 prefunctionalized 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, Scheme 2A) and 1-iodooctane (2a) with a variety of nickel-based catalyst systems using zinc metal as the reductant. Preliminary optimization 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 h (compared to 12 h + routinely used in XEC coupling methodology)[2] by

Scheme 1. Mechanochemistry in Transition-Metal-Catalyzed Cross-Coupling



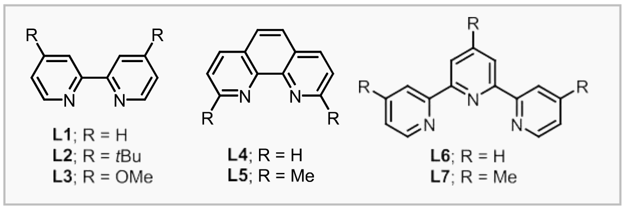
Scheme 2. Optimization of the Mechanochemical Cross-Electrophile Coupling of Aryl Iodides and Alkyl Iodides



entry	[Ni] source	Ligand	**3a** (%)[a]	**4a** (%)[a]
1	$NiCl_2·6H_2O$	**L1**	64	10
2	$NiCl_2(PPh_3)_2$	-	85 (80)[b]	trace
3	$NiCl_2·6H_2O$	**L2**	83	trace
4	$NiCl_2·6H_2O$	**L3**	51	12
5	**$NiCl_2·6H_2O$**	**L4**	**91 (85)[b]**	**trace**
6	$NiCl_2·6H_2O$	**L5**	27	4
7	$NiCl_2·6H_2O$	**L6**	47	23
8	$NiCl_2·6H_2O$	**L7**	52	42
9	$NiCl_2·6H_2O$	-	0	0

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

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

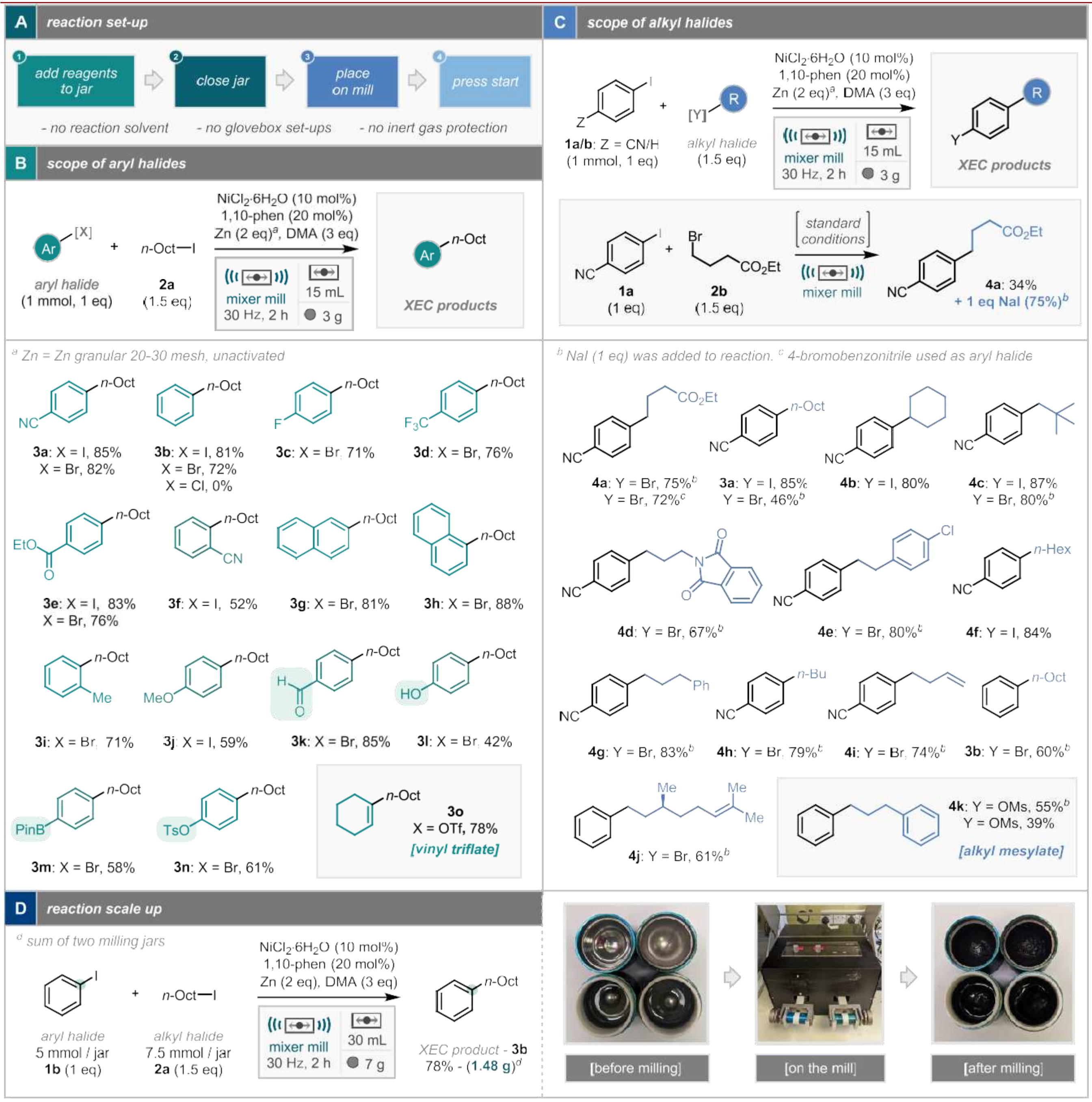


General reaction conditions: 4-iodobenzonitrile (1a, 1.0 mmol), 1-iodooctane (2a, 1.5 mmol), [Ni] catalyst (10 mol %, 0.1 mmol), Ligand (20 mol %, 0.2 mmol), Zn (granular 20−30 mesh, 2.0 mmol), *N*,*N*-dimethylacetamide (3.0 mmol), under an air atmosphere. The reaction was milled at 30 Hz for 2 h in 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.

employing 1.5 equiv of alkyl halide, 2 equiv of zinc metal as a reductant, and 3 equiv of DMA as a liquid-assisted grinding (LAG) agent (64%, Scheme 2A, entry 1).[19] Further screening of precatalysts and ligand systems uncovered that while $NiCl_2(PPh_3)_2$ provided increased yields (85%, entry 2), inexpensive, readily available salt $NiCl_2·6H_2O$ provided further improved yields, when coupled with bipyridyl-based ligand sets, with 1,10-phenanthroline (L4) proving optimal (91%, entry 5). Interestingly, the use of tridentate ligand systems substantially increased the observation of homocoupled biaryl 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]

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), electron-rich (3i−j) and 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 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

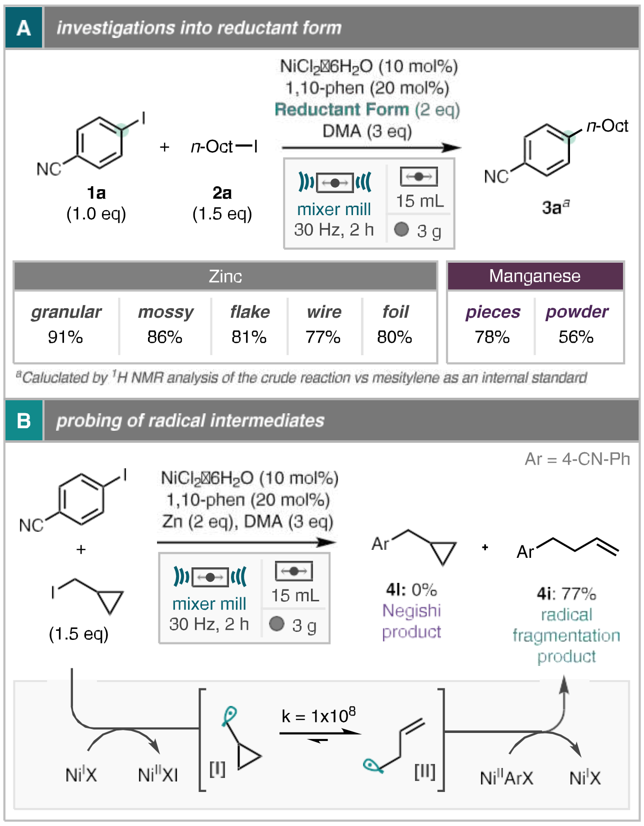
Scheme 3. Scope of the Reductive Cross-Electrophile Coupling of Aryl and Alkyl Halides Enabled by Ball-Milling



derivative afforded the desired product in excellent yield (78%, 3o). Following this, attention turned to investigating the variation of the alkyl halide partner (Scheme 3C). A convenient solution for low-yielding alkyl bromide substrates (2b) was found in the addition of 1 equiv 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-iodobenzontrile (3a). Citronellyl bromide was also successfully coupled with iodobenzene in 61% yield (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. This 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 Zn^0 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 the unique reaction environment of the mixer mill enables the use of a wide range of zinc forms without substantial yield variations and, critically, with excellent reproducilbity.[10] Pleasingly, in this methodology, excellent reactivity was maintained when using granular, mossy, flake, wire, or foil forms of Zn^0 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 Zn^0 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



Zinc					Manganese	
granular	*mossy*	*flake*	*wire*	*foil*	*pieces*	*powder*
91%	86%	81%	77%	80%	78%	56%

[a]*Caluclated by ^{1}H NMR analysis of the crude reaction vs mesitylene as an internal standard*

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 setups, 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

Supporting Information

Synthetic procedures and characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

Duncan L. Browne − *Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, London WC1N 1AX, United Kingdom;* orcid.org/0000-0002-8604-229X; Email: Duncan.Browne@ucl.ac.uk

Authors

Andrew C. Jones − *Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Cardiff CF10 3AT, United Kingdom*

William I. Nicholson − *Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Cardiff CF10 3AT, United Kingdom*

Jamie A. Leitch − *Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, London WC1N 1AX, United Kingdom;* orcid.org/0000-0001-6997-184X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge T. Linford-Wood and C. Parsons (both Cardiff University) for preliminary experiments. D.L.B. is grateful to the European Union, WEFO and Cardiff University for a Knowledge Economy and Skills Scholarship (KESS2) to A.C.J. W.I.N. thanks Cardiff University for a studentship. J.A.L. thanks the Leverhulme Trust (RPG-2019-260) for a research fellowship.

REFERENCES

(1) 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 (and citing references), 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) 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.

(3) For a review (and references therein), see: Everson, D. A.; Weix, D. J. Cross-electrophile coupling: principles of reactivity and selectivity. *J. Org. Chem.* 2014, *79*, 4793−4798.

(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) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* 2015, *48*, 1767−1775. (c) 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.

(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, *138*, 5016−5019.

(6) During the final preparation of this manuscript, Shi and Zou reported a similar transformation under solvent-free mechanochemical conditions 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, *45*, 11269.

(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.; Streletskii, 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.

(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) Ardila-Fierro, K. J.; Hernández, J. G. Sustainability Assessment of Mechanochemistry Using the Twelve Principles of Green Chemistry. *ChemSusChem* 2021, *14*, 2145. (b) Colacino, E.; Isoni, V.; Crawford, D.; García, F. Upscaling Mechanochemistry: Challenges and Opportunities for Sustainable Industry. *Trends Chem.* 2021, *3*, 335−339.

(12) 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.

(13) (a) Kubota, K.; Ito, H. Mechanochemical Cross-Coupling Reactions. *Trends Chem.* 2020, *2*, 1066−1081. (b) Porcheddu, A.; Colacino, E.; De Luca, L.; Delogu, F. Metal-Mediated and Metal-Catalyzed Reactions Under Mechanochemical Conditions. *ACS Catal.* 2020, *10*, 8344−8394. (c) Effaty, F.; Ottenwaelder, X.; Friščić, T. Mechanochemistry in transition metal catalyzed reactions. *Curr. Opin. Green Sustain. Chem.* 2021, *32*, 100524. For a review on mechanochemical C−H functionalization, see: (d) Hernández, J.G. C−H Bond Functionalization by Mechanochemistry. *Chem. - Eur. J.* 2017, *23*, 17157−17165.

(14) (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) 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.

(15) (a) Nielsen, S. F.; Peters, D.; Axelsson, O. The Suzuki Reaction Under Solvent-Free Conditions. *Synth. Commun.* 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 Res. Dev.* 2009, *13*, 44−48.

(16) (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.

(17) (a) Tullberg, E.; Peters, D.; Frejd, T. *J. Organomet. Chem.* 2004, *689*, 3778−3781. (b) Tullberg, 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) 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. (d) Thorwirth, R.; Stolle, A.; Ondruschka, B. Fast copper-, ligand- and solvent-free Sonogashira coupling in a ball mill. *Green Chem.* 2010, *12*, 985−981.

(18) 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.

(19) Ying, P.; Yu, J.; Su, W. Liquid-Assisted Grinding Mechanochemistry in the Synthesis of Pharmaceuticals. *Adv. Synth. Catal.* 2021, *363*, 1246−1271.

(20) The crucial addition of DMA in zinc-mediated mechanochemistry has been noted in a previous study; see ref 10a.

(21) Unfortunately, under these conditions aryl chlorides and tertiary alkyl halides were not compatible coupling partners.

(22) Mechanochemical mixing of alkyl bromide 2b with NaI with/without the presence of DMA leads to good conversion to the corresponding alkyl iodide.

(23) The addition of sodium iodide had no positive/negative effect on the reaction of alkyl iodides.

(24) A pre-print of an earlier version of this manuscript is available at: Jones, A. C.; Nicholson, W. I.; Leitch, J. A.; Browne, D. L. A Ball Milling Enabled Cross-Electrophile Coupling. *Chem. Rxiv* 2021, DOI: 10.26434/chemrxiv.14770740.v1.