NJC

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
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Cite this: *New J. Chem.*, 2021, **45**, 11269

Mechanical metal activation for Ni-catalyzed, Mn-mediated cross-electrophile coupling between aryl and alkyl bromides†

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Received 9th April 2021,
Accepted 21st May 2021

DOI: 10.1039/d1nj01732b

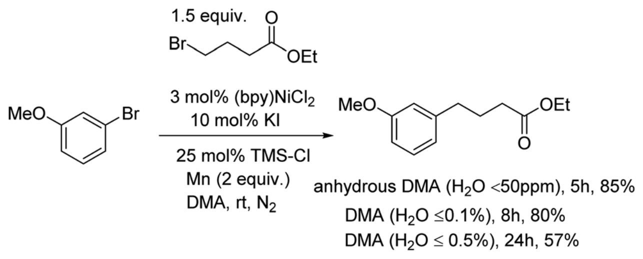
rsc.li/njc

Liquid-assisted grinding has been successfully applied to eliminate the requirements of chemical activators and anhydrous solvents in nickel-catalyzed, manganese-mediated cross-electrophile coupling between aryl and alkyl bromides. In addition to the traditional reaction parameters, mechanical ones, *e.g.* the rotational speed of mill, the filling degree of jar and ball size, have been found to affect the catalytic efficiency remarkably, implying the involvement of the regeneration of nickel(0) species in the rate-determining steps. A combined evaluation of the reaction and mechanical parameters led to an optimal condition under which a variety of *n*-alky aromatics with various functional groups could be readily obtained in good yields with a 1 mol% catalyst loading. The practical application of liquid-assisted grinding-enabled aryl/alkyl cross-electrophile coupling has been demonstrated in the gram-scale synthesis of 6-methoxytetralone.

Introduction

Transition-metal catalyzed cross-coupling of aryl halides represents the most reliable protocol for site-specific introduction of alkyl groups into aromatic rings. Compared with the traditional cross-coupling with organometallic reagents, the emerging nickel-catalyzed aryl/alkyl cross-coupling of electrophiles, in particular halides (XEC),[1] eliminates the requirement of preformation of organometallics, promising more cost-effective processes and/or higher functional group compatibility. Therefore, many efforts have been devoted to improving nickel catalyzed aryl/alkyl XEC since the pioneering work by the Weix group in 2010.[2] Although the past few years have witnessed a number of advances in XEC with respect to substrate scope,[3] catalysts,[4] reductants,[5] and mechanistic elucidation,[6] the requirement of anhydrous yet strong hydroscopic solvents, *e.g.* *N*,*N*′-dimethylpropyleneurea (DMPU), *N*,*N*′-dimethylacetamide (DMA), *etc.*, is still a challenge in practical applications. In sharp contrast to solvents, nickel catalyzed aryl/alkyl XEC processes appear to be compatible with a small amount of water in substrates, reagents and even vehicles. For example, hydrous catalyst precursors, *e.g.* $NiI_2{\cdot}xH_2O$, can be used in some cases.[2,7] Even, vehicles can be used without the rigorous drying procedure if anhydrous chemicals are used.[7] During the development of 6-methoxytetralone, we found that the addition of a small amount of water to anhydrous DMA would mainly make the XEC reaction between 3-bromoanisole and ethyl 4-bromobutyrate slow rather than quench in the presence of an activator, trimethylsilyl chloride (TMSCl) (Scheme 1).

These facts imply that the deleterious effects of non-anhydrous solvents can be attributed to their high water content as well as the requirement of a large volume in the traditional solution synthesis. We anticipate that, if solvent-free or liquid-assisted-grinding (LAG) mechanochemical synthesis *via* ball milling is applied,[8] it is possible to conduct nickel-catalyzed aryl/alkyl XEC without anhydrous solvents since only minimal amounts of solvents are required under LAG conditions. In addition, ball milling features mechanical activation of the metal surface for synthesis,[9] thus eliminating the need for chemical activators. In fact, Browne *et al.* have elegantly demonstrated the applications of mechanical activation of zinc



Scheme 1 Effects of a small amount of water on the Ni-catalyzed, Mn-mediated XEC between 3-bromoanisole and ethyl 4-bromobutyrate.

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† Electronic supplementary information (ESI) available: Experimental procedure, characterization data for products, and copies of NMR and HRMS spectra. See DOI: 10.1039/d1nj01732b

powders in Reformatsky reaction and Negishi coupling.[10] Herein we report a liquid-assisted grinding-enabled cross-electrophile coupling between aryl and alkyl bromides to access alkyl aromatics without chemical activators under non-anhydrous conditions.

Results and discussion

Ball-milling is a well-known top-down protocol to increase the specific surface area and freshness of the surface for particles of hard materials. For metal powders, the morphological changes of particles, which strongly depend on the malleability of the corresponding metals, can directly reflect the effects of mechanochemical metal activation *via* ball-milling. In fact, the size of iron and manganese particles reduced after ball-milling at 525 rpm for 30 minutes, while the particles of zinc and aluminum are obviously merged by the force of ball-milling after the removal of oxide layers (Fig. 1) (see the ESI† for the original photographs). These results promise the potential to eliminate the need for a chemical activator in the activation of metal powders in the nickel-catalyzed, metal-mediated aryl/alkyl XEC process.

The coupling between 3-bromoanisole (**1a**) and 1.5 equiv. of ethyl 4-bromobutyrate (**2a**) was taken as the model reaction to explore the mechanical metal activation strategy in the Ni-catalyzed XEC process. Under solvent-free ball-milling (525 rpm) in a 50 mL stainless-steel jar and 8 balls ($\varnothing$ = 7 mm), only a trace amount of the desired product (**3aa**) was detected in 4 h using a catalyst system, 3 mol% (bpy)NiCl$_2$, 10 mol% KI and Mn (2 equiv.) under nitrogen (Table 1, entry 1). When a small amount of analytical grade (99%) non-anhydrous DMA, that is, 0.5 μL mg^{-1} (η = 0.5), was used as the assisting liquid,[11] **3aa** was isolated in 75% yield, implying a key role played by strong polar solvents. A decrease in KI loading (5 mol%) led to a lower yield (56%), while a higher loading (50 mol% KI) failed to increase the yield (Table 1, entries 3 and 4). In contrast, the yields increased to 82–84% when increasing the loading of DMA (η = 1, 2) (Table 1, entries 5 and 6). In fact, the reaction completed in 1.5 h with 1 μL mg^{-1} of DMA loading (η = 1).

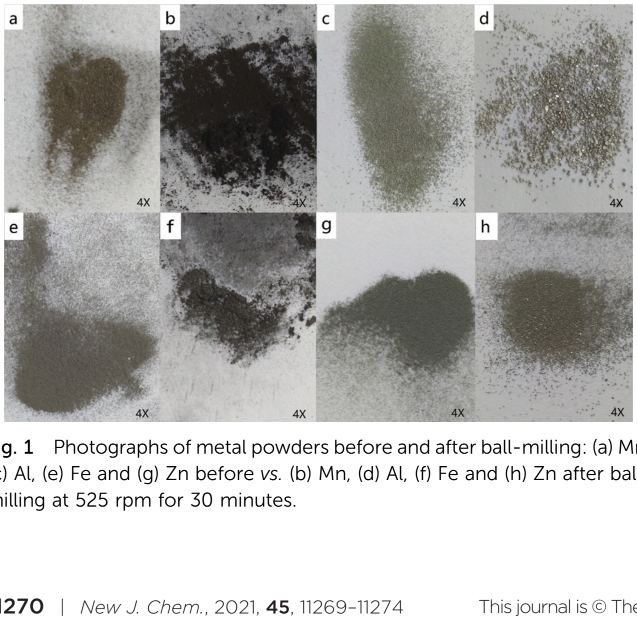


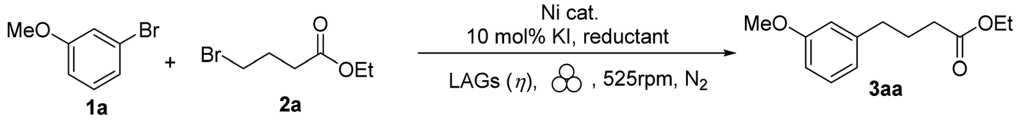
Fig. 1 Photographs of metal powders before and after ball-milling: (a) Mn, (c) Al, (e) Fe and (g) Zn before *vs.* (b) Mn, (d) Al, (f) Fe and (h) Zn after ball-milling at 525 rpm for 30 minutes.

Although there is always some metallic manganese observed after the reaction, when 1.2–1.5 equiv. of Mn powders were used **3aa** was obtained in lower yields (71–80%). The other common metals, *i.e.* Zn, Al and Fe, were also examined as reductants to regenerate catalytically active nickel species since the reducing agent has proven to be vital for nickel-catalyzed cross-electrophile coupling. Zinc powders, commonly used as the reducing agent in organic reactions, led to only a 38% yield, while Al and Fe provided no reaction (Table 1, entries 12–14). Screening of the other common polar solvents, *e.g.* DMF, DMPU, DMSO, THF, dioxane and acetonitrile, showed that only expensive DMPU performed similarly to DMA, while less-polar dioxane and THF failed completely (Table 1, entries 15–20). A slight excess (1.2–1.5 equiv.) of the alkyl counterpart appeared to be necessary to obtain good yields. In fact, a larger excess (2.0 equiv.) of ethyl 4-bromobutyrate (**2a**) made it difficult to obtain analytically pure **3aa** (^{1}H NMR) although the yield of the impure product was $>$90% (Table 1, entries 21–24). When the catalyst (bpy)NiCl$_2$ loading was reduced to 1 mol%, the model reaction became slow and required 9 h to complete, but still gave **3aa** in a comparable yield (Table 1, entry 25).

In addition to the reaction parameters, mechanical ones often play an important role in mechanochemical synthesis. It is well known that the rotational speed of mill, the filling degree of jar and even ball size could affect the energy input, impact force and mixing efficiency in ball milling. Indeed, the filling degree of jar and the rotational speed of mill have proven to affect the model reaction rate remarkably. When the number of balls was increased from 8 to 16, the reaction proceeded faster and could complete within 2 h with a 1 mol% catalyst loading, affording **3aa** in 86% yield, while the use of larger balls ($\varnothing$ = 10 mm) led to a slight decrease in the yield of **3aa** due to an increase in homo-coupling of **1a**. The reaction took a longer time (4 h) to complete with a lower rotational speed (300 rpm) (Table 1, entries 27 and 28). Namely, the higher rotational speed of mill and the filling degree of jar provided a higher catalytic efficiency. Obviously, these results are consistent with the mechanical activation of manganese powders, implying that the activation of manganese and the corresponding reduction of Ni(II) to Ni(0) by active Mn(0) should be involved in the rate-determining steps in the catalytic cycle. When 0.1 equiv. of Tempo was added to the reaction mixture, the coupling could be suppressed remarkably (36%, 2 h). Further, 0.5 equiv. of Tempo blocked the reaction completely. Unfortunately, similar to a report by Weix *et al.*,[6a] attempts to isolate the *O*-alkyl Tempo derivative failed. However, coupling of the radical probe, (bromomethyl)cyclopropane, gave a mixture of 1-(but-3-enyl)-3-methoxybenzene in 55% yield (GC) and its internal isomers (7%) as major products along with 10% (GC) normal coupling product 1-(cyclopropylmethyl)-3-methoxybenzene in 72% total yield (Scheme 2) (see the ESI† for GC-MS and ^{1}H NMR spectra).

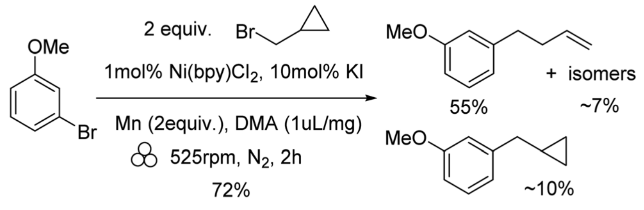
These results indicate that coupling under LAG conditions should also mainly follow a radical-involved mechanism established by Weix *et al.* (Scheme 3). However, given the

Table 1 Optimization of Ni-catalyzed XEC between 3-bromoanisole **1a** and ethyl 4-bromobutyrate **2a** under LAG conditions[a]



Entry	Ball no.	Ni cat. (mol%)	LAGs (η)	Red. (equiv.)	**2a** (equiv.)	Time (h)	Yield[b] (%)
1	8	(bpy)NiCl$_2$ (3)	—	Mn (2)	1.5	4	Trace
2	8	(bpy)NiCl$_2$ (3)	DMA (0.5)	Mn (2)	1.5	4	75
3	8	(bpy)NiCl$_2$ (3)	DMA (0.5)	Mn (2)	1.5	4	74[c]
4	8	(bpy)NiCl$_2$ (3)	DMA (0.5)	Mn (2)	1.5	4	56[d]
5	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	1.5	4	82(21[e])
6	8	(bpy)NiCl$_2$ (3)	DMA (2)	Mn (2)	1.5	4	84
7	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	1.5	1	62
8	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	1.5	1.5	84
9	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (1.5)	1.5	1.5	80
10	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (1.2)	1.5	1.5	71
11	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2.5)	1.5	1.5	83
12	8	(bpy)NiCl$_2$ (3)	DMA (1)	Al (2)	1.5	1.5	Trace
13	8	(bpy)NiCl$_2$ (3)	DMA (1)	Zn (2)	1.5	1.5	38
14	8	(bpy)NiCl$_2$ (3)	DMA (1)	Fe (2)	1.5	1.5	Trace
15	8	(bpy)NiCl$_2$ (3)	DMPU (1)	Mn (2)	1.5	1.5	83
16	8	(bpy)NiCl$_2$ (3)	DMF (1)	Mn (2)	1.5	1.5	64
17	8	(bpy)NiCl$_2$ (3)	DMSO (1)	Mn (2)	1.5	1.5	67
18	8	(bpy)NiCl$_2$ (3)	MeCN (1)	Mn (2)	1.5	1.5	17
19	8	(bpy)NiCl$_2$ (3)	Dioxane (1)	Mn (2)	1.5	1.5	Trace
20	8	(bpy)NiCl$_2$ (3)	THF (1)	Mn (2)	1.5	1.5	Trace
21	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	1.0	1.5	75
22	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	0.8	1.5	53
23	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	1.2	1.5	77
24	8	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	2.0	1.5	84(92)[f]
25	8	(bpy)NiCl$_2$ (1)	DMA (1)	Mn (2)	1.5	9	85
26	16	(bpy)NiCl$_2$ (3)	DMA (1)	Mn (2)	1.5	0.5	84
27	16	(bpy)NiCl$_2$ (1)	DMA (1)	Mn (2)	1.5	2	86[g]
28	16	(bpy)NiCl$_2$ (1)	DMA (1)	Mn (2)	1.5	4	83[h]
29	16	(bpy)NiCl$_2$ (1)	DMA (1)	Mn (2)	1.5	1.5	71[i]
30	16	(bpy)NiCl$_2$ (1)	DMA (1)/6 μL H_2O	Mn (2)	1.5	3	86
31	16	(bpy)NiCl$_2$ (1)	DMA (1)/50 μL H_2O	Mn (2)	1.5	6	84
32	16	(bpy)NiCl$_2$ (1)	DMA (1)/100 μL H_2O	Mn (2)	1.5	6	Trace
33	16	(bpy)NiCl$_2$ (1)	DMA (1)	Mn (2)	1.5	8	54[e]
34	16	NiCl$_2$ (1)	DMA (1)	Mn (2)	1.5	4	Trace
35	16	NiCl$_2$/bpy (1)	DMA (1)	Mn (2)	1.5	4	82
36	16	NiCl$_2$/Phen (1)	DMA (1)	Mn (2)	1.5	4	81
37	16	NiCl$_2$/Py (1)	DMA (1)	Mn (2)	1.5	4	Trace
38	16	NiCl$_2$/8-HQ (1)	DMA (1)	Mn (2)	1.5	4	10

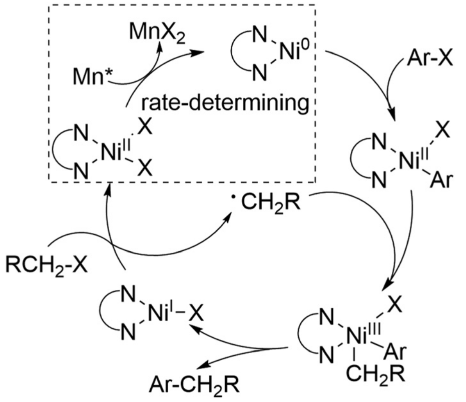
[a] Reaction run on a 1.0 mmol scale (**1a**), 8 stainless-steel balls (∅ = 7 mm), 525 rpm. [b] Isolated yields. [c] Used KI (50 mol%). [d] Used KI (5 mol%). [e] In air. [f] Impure. [g] No reaction in solution. [h] At 300 rpm. [i] 16 stainless-steel balls (∅ = 10 mm).



Scheme 2 Evidence for a radical-involved pathway.

extremely fast ring-opening rearrangement of a cyclopropylcarbinyl radical, the formation of a small amount of normal product implied that some minor non-radical pathways should not be excluded under LAG conditions.

Control experiments on the influence of water content in the system showed a much better water-compatibility under LAG



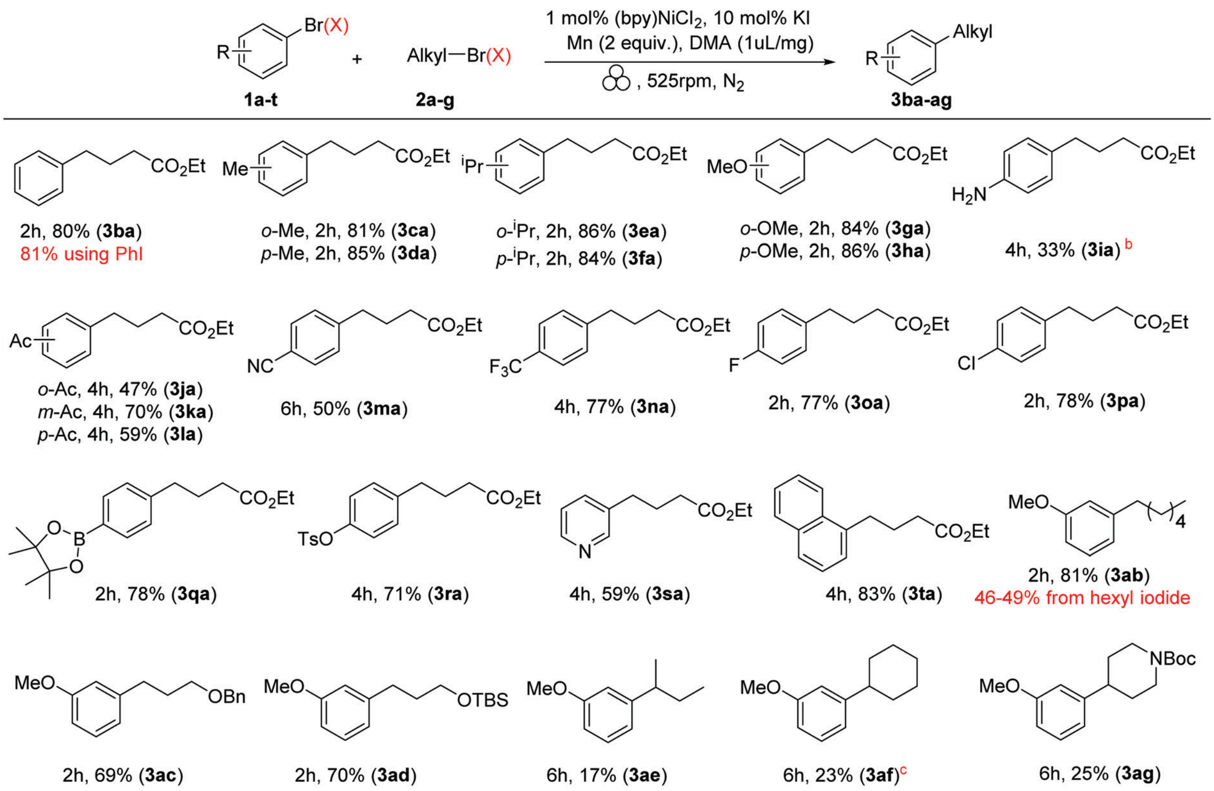
Scheme 3 The catalytic cycle proposed by Weix *et al.*

conditions than that in the traditional solution. The reaction could still proceed well when 1–8% volume (6–50 μL) of water with respect to DMA (0.6 mL) was added to the system (Table 1, entries 30–32), while the 0.5% water content in DMA made the reaction rather slow (24 h, 57% yield) in solution even in the presence of 25 mol% TMSCl as an activator (see Scheme 1). In fact, no reaction occurred in non-anhydrous DMA without the activator TMSCl in solution (Table 1, entry 27). The reaction could proceed slowly to give **3aa** in 54% yield even in air (Table 1, entry 33). A direct combination of $NiCl_2$ with 2,2′-bipyridine (bpy) or 1,10-phenanthroline (phen) appeared to work, while pyridine itself failed (Table 1, entries 35–38). Therefore, after combined evaluation of the reaction and mechanical parameters, the optimal conditions were obtained as follows: 1.5 molar ratio of alkyl/aryl bromides, 2 equiv. of manganese powders, 1 mol% (bpy)$NiCl_2$ catalyst and 10 mol% KI as the additive, with 16 stainless-steel balls (∅ = 7 mm) at 525 rpm under N_2.

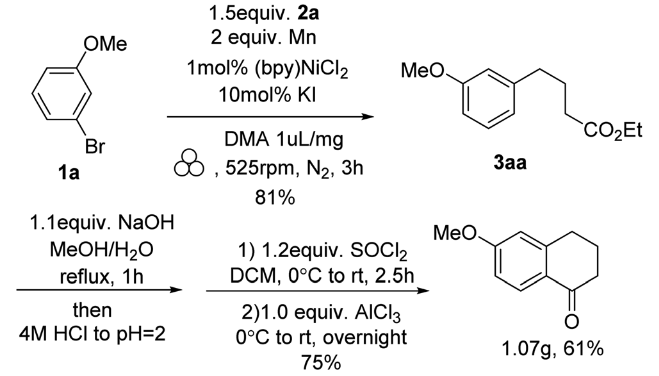
The scope and limitations of the LAG-enabled, Ni-catalyzed, Mn-mediated cross-electrophile coupling between aryl and alkyl bromides/(pseudo)halides were briefly explored under the optimal conditions (Table 2).

Phenyl bromide (**1b**) reacted smoothly with **2a** to give **3ba** in 80% yield. No reaction was observed for phenyl chloride (PhCl), phenyl tosylate (PhOTs) and triflate (PhOTf), while phenyl iodide reacted similarly to bromide (**1b**). The electronic factors from aryl bromides affected their cross-coupling more significantly than steric ones, albeit sterically demanding 2,4,6-trimethyl bromobenzene completely failed. For example, aryl bromides bearing an electron-donating group, *e.g.* Me (**1c** and **1d**), ^{i}Pr (**1e** and **1f**) and OMe (**1g** and **1h**), at the *ortho*- or *para*-position of the phenyl ring, except for NH_2 which gave a low yield (33%) due to *N*-alkylation, reacted with **2a** smoothly, affording *n*-alkyl aromatics **3ca–3ha** in good yields (81–86%), while those bearing an electron-withdrawing group, *e.g.* Ac(**1j–1l**), CN (**1m**), CF_3 (**1n**), F (**1o**) and Cl (**1p**), gave lower yields (47–78%) of the desired products **3ja–3pa**. 3-Bromopyridine (**1s**) also gave a lower yield than its phenyl analog (**1a**), while no reaction was observed for 1-bromo-4-nitrobenzene. In particular, *m*-bromoacetophenone (**1k**) reacted to give the desired product **3ka** in 70% yield, remarkably higher than its *ortho*- and *para*-isomers (**1j**, 47% and **1l**, 59%), clearly reflecting the electronic effect of aryl bromides, that is, electron-rich aryl bromides perform better than electron-deficient ones. It is worth noting that borate (**1q**, 78%) and tosylate (**1r**, 71%) groups which could be used in subsequent conventional cross-coupling reactions were tolerable. On the alkyl counterpart, primary bromides could be efficiently coupled, giving good yields of the corresponding *n*-alkyl products (81% for **3ab**, 69% for **3ac** and 70% for **3ad**), while no reaction was observed for *n*-hexyl chloride. Surprisingly,

Table 2 Scope of the Ni-catalyzed, Mn-mediated XEC between aryl and alkyl bromides/(pseudo)halides under LAG conditions[a]



[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), 1 mol% (bpy)$NiCl_2$, 10 mol% KI, Mn (2 equiv.), DMA (η = 1), 16 stainless-steel balls (∅ = 7 mm) under a N_2 atmosphere at 525 rpm in a planetary ball mill. [b] The *N*-alkylation product ethyl 4-(4-((4-ethoxy-4-oxobutyl)amino)phenyl)butanoate was also isolated in 31% yield. [c] No increase in yield (22–25%) with 3–5 mol% catalyst loadings.



Scheme 4 Synthesis of 6-methoxytetralone on a gram scale.

lower yields (46–49%) were obtained for *n*-hexyl iodide in experiments. Under the optimal conditions, *n*-hexyl tosylate reacted with **1a** to give **3ab** in a very low yield (8%), which could increase to 47% with 1 equiv. of KI, consistent with the conversion of alkyl tosylate into iodide. Unfortunately, the coupling of secondary acyclic (**2e**) and cyclic bromides (**2f** and **2g**) with **1a** under the LAG conditions was not satisfactory and a higher catalyst loading (3–5 mol%) appeared to fail in increasing the yields. Instead, self-coupling of **1a** took place to give 3,3′-dimethoxybiphenyl as the major isolated product.

To demonstrate the application of the LAG-enabled, Ni-catalyzed, Mn-mediated aryl/*n*-alkyl XEC, a gram-scale synthesis of 6-methoxytetralone, a key starting material for a synthetic progestogen, Norgestrel, was carried out (Scheme 4). Under the optimal conditions, the reaction of 3-bromoanisole (**1a**) with ethyl 4-bromobutyrate (**2a**, 1.5 equiv.) could be readily conducted on a gram scale at the same size (50 mL) and filling degree (16 ball, ∅ = 7 mm) of the jar for a 1 mmol substrate loading to afford **3aa** in 81% yield (5.39 g) in 3 h. Hydrolysis of the ester **3aa,** followed by subsequent treatment with $SOCl_2$ and $AlCl_3$, provided 6-methoxytetralone in 75% yield.

Conclusions

In summary, liquid-assisted grinding (DMA, η = 1) has been used to enable an efficient nickel-catalyzed, manganese-mediated cross-electrophile coupling between aryl and *n*-alkyl bromides without the requirement of chemical activators and anhydrous solvents. The catalytic efficiency has proven to correlate well with the mechanical activation of the metal surface and mixing of heterogeneous materials, implying that the reduction of Ni(II) to Ni(0) by active Mn(0) should be involved in the rate-determining steps. A variety of *n*-alky aromatics with various functional groups could be obtained in good yields with a low catalyst loading (1 mol%). Elimination of the need for chemical activators and compatibility with non-anhydrous solvents make the nickel-catalyzed manganese-mediated *n*-alkyl cross-electrophile coupling a further step towards practical use for the synthesis of *n*-alkyl aromatics.

Experimental

General information

Reactions were carried out under a nitrogen atmosphere unless otherwise stated. All mechanochemical reactions were conducted in a planetary ball mill (QM-3SP2) equipped with four (50 mL) milling jars made of stainless steel and 8 or 16 stainless-steel balls (∅ = 7 or 10 mm) at 300 rpm or 525 rpm. Chemicals obtained from commercial sources were used as received. (bpy)$NiCl_2$ was prepared according to a previously reported procedure.[12] The reaction progress was monitored by TLC. Column chromatography was performed on 300–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature. New compounds **3ba**, **3ka** and **3ca** were further characterized by HRMS.

Typical procedure

A mixture of aryl bromide (1.0 mmol), alkyl bromide (1.5 mmol), (bpy)$NiCl_2$ (1 mol%), Mn powder (2 equiv.), DMA (η = 1) and KI (10 mol%) were added in a 50 mL stainless steel milling jar. The milling jar was flushed with N_2 through the lid with a gas inlet, screwed tightly and then placed on the planetary ball mill at 525 rpm using 16 stainless-steel balls (∅ = 7 mm) for 2–6 h. After the elapsed time, the reaction mixture was transferred from the milling jar into a flask with the aid of CH_2Cl_2 (3 × 5 mL) and then concentrated by a rotavapor to afford the crude product, which was purified by flash column chromatography on silica gel using a gradient of ethyl acetate in petroleum ether (see the ESI† for details).

Author contributions

Supervision, G. Z.; conceptualization, W. S. & G. Z.; investigation, S. W. & W. S.; writing – original draft preparation, W. S.; writing – review & editing, G. Z. & W. S.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support provided by the National Natural Science Foundation of China (21472041).

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