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Fast and Selective Dehydrogenative C−H/C−H Arylation Using Mechanochemistry

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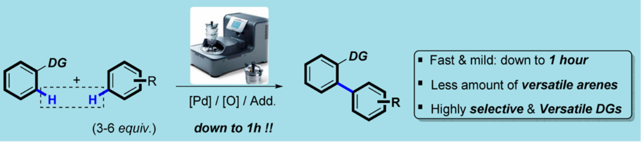
Supporting Information

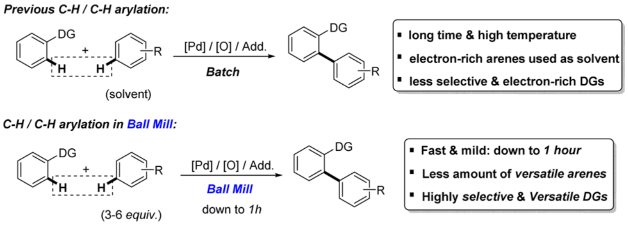


ABSTRACT: A fast and site-selective biaryl synthesis via dehydrogenative C−H/C−H arylation in a ball mill was developed. In this paper, both electron-deficient oximes and electron-rich anilides quickly and under mild conditions provided arylation with various arenes to give the biaryl products in high-level selectivity. Given the solventless mechanochemical conditions, the transformation obviated the use of large amounts of arene coupling partners as solvents and allowed utilization of more-complicated and more-expensive arenes as coupling partners, which may dramatically enhance the application prospect of the C−H/C−H arylation strategy.

KEYWORDS: *mechanochemistry, C−H bond activation, selective arylation, biaryls, ball milling*

Preparation of biaryl compounds has consistently been of great interest to the chemical community, because of their wide applications in pharmaceuticals and agrochemicals.[1] Despite the classic coupling reactions, transition-metal-catalyzed dehydrogenative C−H/C−H activation arylation has emerged as the most efficient way to access the biaryl scaffold.[2] Great effort has been exerted and various systems have been developed in the past decade.[3] However, several challenges still must be overcome. First, let us examine regioselective cross-coupling between substituted arenes and substrates. Most examples in C−H/C−H bond arylation were less selective, especially for the monosubstituted aromatic coupling partners. The Yu group reported a paraselective C−H bond arylation of monosubstituted arenes, in which the specific directing group as well as the external oxidants were crucial for the unique selectivity.[3d] Very recently, a ligand-controlled strategy was developed to achieve high-level paraselectivity.[3a] Second, a large excess amount of coupling partner must be considered (usually, simple arenes were used as solvents, which were difficult to handle and were not eco-friendly, *especially for the high boiling point and expensive arenes*). Third, the reactions required a long period of time and were less efficient for the electron-deficient arenes. With these considerations in mind, we envisioned developing a novel and efficient C−H/C−H arylation, using a ball mill to overcome the aforementioned problems (see Scheme 1).

Scheme 1. Biaryl Synthesis via Mechanochemical C−H/C−H Arylation in This Work Versus in Batch



Ball milling, as a mechanochemical technique in synthetic chemistry, has been receiving great attention, because of their environmentally friendly and solventless synthesis approaches, which remarkably enhance the efficiency of the reactions.[4] Several metal-catalyzed relevant reactions have been realized using ball-milling techniques in the past few years.[5] However, application of mechanochemical technique in C−H bond functionalization is less studied. First, ball-milling transition-metal-catalyzed C−H bond activation was detected by Ćúric and co-workers using solid-state Raman spectroscopy.[6] Very recently, practical examples of mechanochemically Rh-catalyzed C−H bond olefination and Ir-catalyzed C−H bond amidation were developed by Bolm and co-workers.[7] This work has revealed that C−H bond activation in a ball mill will be applicable for the reduction of solvent amount and reaction time. Given our continued interest in the C−H bond functionalization and green synthesis in a ball mill, we herein reported the first Pd-catalyzed mechanochemical biaryl synthesis via dehydrogenative C−H/C−H arylation under a liquid-assisted grinding (LAG)[8] process. In our previous nitrate-promoted C−H bond fluorination of ketone oximes, a small amount of biaryl product was detected when using toluene as a solvent.[9] Given the synthetic and economic potential of ketoxime ethers,[10] arylation of oximes with simple arenes is of great importance for the synthesis of useful biaryl skeletons.[11] With slight modification of the reaction condition, we found that arylated product **3a** was formed in 33% GC-MS

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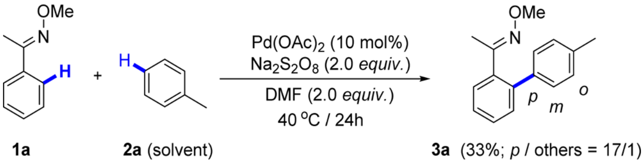
yield along with good paraselectivity at 40 °C for 24 h (see Scheme 2). Given the unique advance in mechanochemistry, we expected that such an arylation in the ball mill would be more efficient and require much less arene coupling partners in comparison with the traditional batch process.

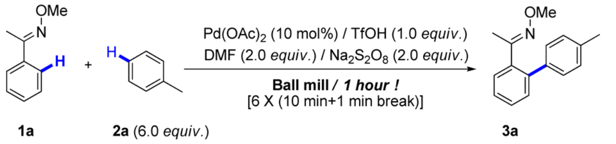
Scheme 2. C−H/C−H Bond Arylation of Oxime in Batch



1a **2a** (solvent) **3a** (33%; *p* / others = 17/1)

To our delight, cross-coupling product **3a** was obtained in 61% yield with 6.0 equiv toluene after 1 h of milling [6 × (10 min + 1 min break)]. Notably, high paraselectivity was observed under this condition [*p*/(*o* + *m*) = 25/1] (Table 1, entry 1). Pleasingly, the yield was significantly enhanced to 85% when 1.0 equiv of trifluoromethanesulfonic acid (TfOH)[3,12] was added (Table 1, entries 2 and 3), whereas the selectivity remained unchanged.[13] Various combinations of Pd catalysts and oxidants were then surveyed. Pd(OAc)$_2$ was selected as the best catalyst. Other peroxides, such as K$_2$S$_2$O$_8$, (NH$_4$)S$_2$O$_8$, and oxone could also deliver the desired product, albeit in lower yields (Table 1, entries 4−8). Electrophilic fluorinating agents such as SELECTFLUOR and *N*-fluorobenzenesulfonimide (NFSI) were good external oxidants to give comparable results.[3,14] PhI(OAc)$_2$, benzoquinone (BQ), or Cu(OAc)$_2$ were inefficient oxidants for this transformation (Table 1, entries 9−13). Furthermore, dimethylformamide (DMF), as an additive, might play the crucial role of ligand during the process, according to the previous report.[3] Omission of Pd catalyst, oxidant, or DMF led to negative results (Table 1, entries 14−16). To the best of our knowledge, this is the first time to use a ball-milling technique to promote the C−H/C−H bond arylation, which represented a highly efficient and selective cross-coupling protocol for the biaryl skeleton construction.

Table 1. Screening of Reaction Conditions[a]

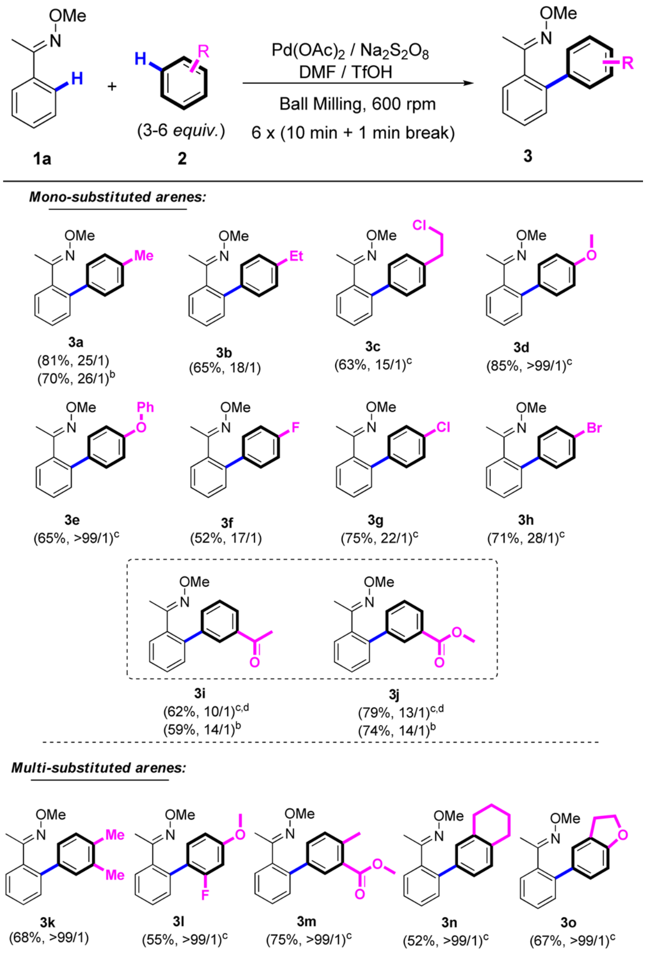


entry	variation from “standard condition”	conversion of **1a** (%)	yield of **3a** (%)[b]
1	without TfOH	68	61
2	none	96	**85**
3	TsOH·H$_2$O instead of TfOH	93	80
4	Pd(TFA)$_2$ instead of Pd(OAc)$_2$	94	84
5	Pd$_2$(dba)$_3$ instead of Pd(OAc)$_2$	80	76
6	Pd(PPh$_3$)$_4$ instead of Pd(OAc)$_2$	74	66
7	K$_2$S$_2$O$_8$ instead of Na$_2$S$_2$O$_8$	44	36
8	(NH$_4$)$_2$S$_2$O$_8$ instead of Na$_2$S$_2$O$_8$	74	63
9	oxone instead of Na$_2$S$_2$O$_8$	62	54
10	BQ instead of Na$_2$S$_2$O$_8$	6	0
11	Cu(OAc)$_2$ instead of Na$_2$S$_2$O$_8$	2	0
12	PhI(OAc)$_2$ instead of Na$_2$S$_2$O$_8$	62	0
13	SELECTFLUOR instead of Na$_2$S$_2$O$_8$	88	80
14	NFSI instead of Na$_2$S$_2$O$_8$	52	35
15	without Pd(OAc)$_2$	3	0
16	without Na$_2$S$_2$O$_8$	2	0
17	without DMF	5	0

[a] **1a** (0.3 mmol), **2a** (6.0 equiv), Pd(OAc)$_2$ (10 mol %), Na$_2$S$_2$O$_8$ (2.0 equiv), DMF (2.0 equiv), TfOH (1.0 equiv), 600 rpm in ball mill [6(10 min +1 min break)], 60 stainless steel grinding balls (2 mm diameter); DMF = *N*,*N*-dimethylformamide, Selectfluor = F-TEDA-BF$_4$, NFSI = *N*-fluorobenzenesulfonimide. [b] Determined by GC-MS using dodecane as an internal standard.

With the optimized condition in hand, we then investigated the scope and limitation of the present mechanochemical arylation. Various arenes including monosubstituted and disubstituted arenes were subjected to the system and excellent regioselectivity was obtained (Table 2). Monosubstituted arenes bearing electron-donating functional groups, e.g., alkyl, alkyloxy, and aryloxy underwent C−H/C−H cleavage cross-coupling smoothly to give the biaryl products in moderate to

Table 2. Mechanochemical C−H/C−H Arylation with Various Arenes[a]



[a] **1a** (0.3 mmol), **2** (1.80 mmol, 6.0 equiv), Pd(OAc)$_2$ (10 mol %), Na$_2$S$_2$O$_8$ (0.6 mmol, 2.0 equiv), DMF (2.0 equiv), TfOH (0.3 mmol, 1.0 equiv), 600 rpm in ball mill [6(10 min + 1 min break)], 60 stainless steel grinding balls (2 mm diameter); isolated yields and regioselectivity (p/others) determined by gas chromatography (GC), unless otherwise noted. [b] **1a** (0.3 mmol), **2** (1.5 mL), Pd(OAc)$_2$ (10 mol %), Na$_2$S$_2$O$_8$ (0.6 mmol, 2.0 equiv), DMF (2.0 equiv), TfOH (0.3 mmol, 1.0 equiv), 40 °C, 24 h. [c] **2** (0.9 mmol, 3.0 equiv). [d] Isolated yields and regioselectivity (*m*/others) determined by GC.

good yields, along with excellent paraselectivity (**3a**−**3e**). Aromatic halides are also good coupling partners and gave excellent paraselectivity as well, which might provide opportunities for further decorations of the C−X (X = Cl or Br) bonds (**3f**−**3h**). Electron-deficient arenes as C−H/C−H arylation coupling partners were less studied in the previous reports, because of their lower reactivity. Notably, in this case, the electron-deficient aromatics such as acetophenone and methyl benzoate were also found reactive under the present mechanochemical condition, and a high *meta*-selectivity was observed (**3i**, **3j**), presumably because of the *meta*-C−H site of acetophenone and methyl benzoate are more reactive for the electrophilic substitution (SEAr).[15] Furthermore, several disubstituted arenes were investigated. Highly site-selective C−H/C−H arylation were delivered at the electronic-favored and less sterically hindered C−H bonds of the arenes respectively (**3k**−**3o**). Note that only 3.0−6.0 equiv of arene coupling partners (6.0 equiv for volatile arenes and 3.0 equiv for less-volatile arenes) were required in all cases and arenes that were hardly used in the previous solvent-based C−H/C-H arylation were now possible, to serve as successful coupling partners, which would dramatically enhance the application prospect of the C−H/C−H arylation strategy.

We then explored the reactivity of oximes with different functional groups. Electronic-rich acetophenone *O*-methyl oximes were more reactive, whereas electron-deficient oximes were less effective and required longer reaction time to obtain compromised yields. No obstacles were occurred when other carbonyl *O*-methyl oximes were subjected to the present condition (Table 3).

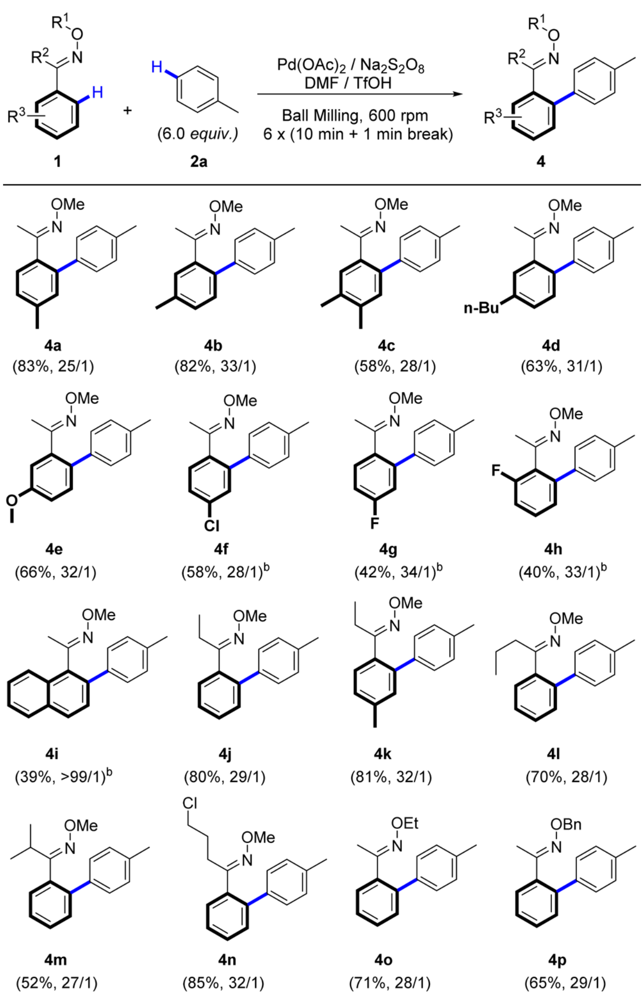
Moreover, olefinic sp^2 C−H bond could also be arylated with different arenes (e.g., toluene, anisole, or aromatic fluoride) to afford the excellent paraselective products in good yields under the mechanochemical conditions (Scheme 3).[16]

Apart from the electron-deficient oxime substrates, electron-rich anilide derivatives, which were widely used in this type of C−H/C−H arylation,[3] were also carried out to evaluate the universality of this method. Anilides including urea and acetanilide could couple with different arenes to form various useful biarylaniline products in good yields, along with consistent high-level selectivity (Table 4).

Finally, both biaryl oximes and anilides could undergo removal of directing groups using simple workup, which enhanced the application prospect of this method.[14]

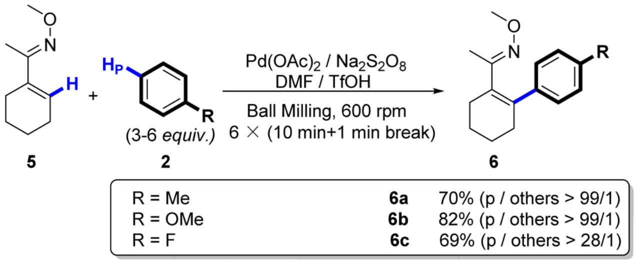
To gain mechanistic insight of this mechanochemical process, kinetic isotope effects (KIE) experiments were performed using deuterated substrate [D$_5$]**1a** and coupling partner [D$_8$]**2a**, respectively. Intermolecular H/D competition between [D$_5$]**1a** and **1a** with **2a** had a significant KIE value of 3.0, which indicated that the initial step of oximyl-directing-group-assisted C−H bond activation might be involved in the rate-determined step (Scheme 4a). However, a competition between **2a** and [D$_8$]**2a** gave a H/D isotope effect of 1.0, which suggested that the C−H bond activation of arene coupling partner is not the slow step in the catalytic cycle (Scheme 4b). The KIE values under the present mechanochemical condition are consistent with the data reported in the similar transformation using arenes as solvents.[3] Based on the preliminary mechanism study and the previous report, two sequential C−H bond activations, including the initial cyclopalladation of oximes or amides and the fast C−H bond activation of arene substrates at the Pd^{IV} center, might be responsible for the high-level selectivity.[17] In addition, the solventless condition significantly promoted the transformation by reducing the coupling partner content and reaction time.

Table 3. Mechanochemical C−H/C−H Arylation of Oximes[a]



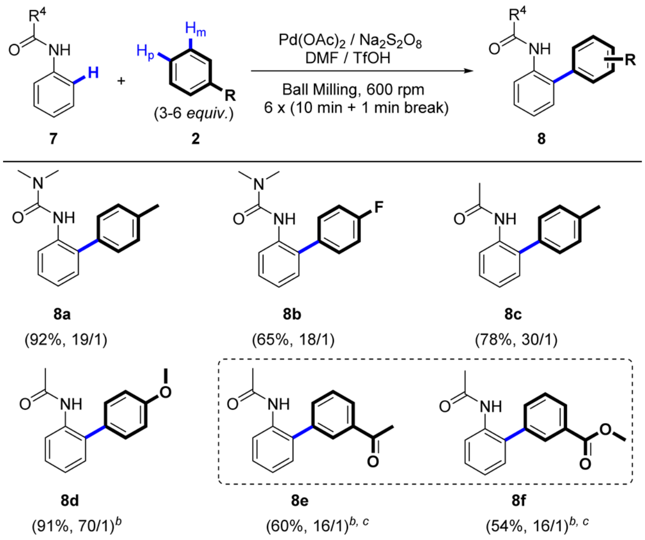
[a] **1** (0.3 mmol), **2a** (1.80 mmol, 6.0 equiv), Pd(OAc)$_2$ (10 mol %), Na$_2$S$_2$O$_8$ (0.6 mmol, 2.0 equiv), DMF (2.0 equiv), TfOH (0.3 mmol, 1.0 equiv), 600 rpm in ball mill [6(10 min +1 min break)], 60 stainless steel grinding balls (2 mm diameter); isolated yields and regioselectivity (*p*/others) determined by GC. [b] 600 rpm in ball mill [9(10 min + 1 min break)].

Scheme 3. Mechanochemical Olefinic C−H Arylation with Simple Arenes



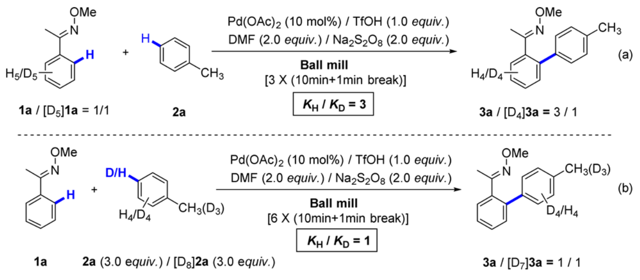
In conclusion, we have developed an efficient mechanochemical dehydrogenative C−H/C−H arylation of both electron-deficient oximes and electron-rich anilides. Notably, the solventless conditions allowed us to use various simple arenes including monosubstituted and disubstituted arenes with

Table 4. Mechanochemical C−H/C−H Arylation of Anilides[a]



[a] **7** (0.3 mmol), **2** (1.80 mmol, 6.0 equiv), $Pd(OAc)_2$ (10 mol %), $Na_2S_2O_8$ (0.6 mmol, 2.0 equiv), DMF (2.0 equiv), TfOH (0.3 mmol, 1.0 equiv), 600 rpm in ball mill [6(10 min + 1 min break)], 60 stainless steel grinding balls (2 mm diameter); isolated yields and regioselectivity (*p*/others) determined by GC; unless otherwise noted. [b] **2** (0.9 mmol, 3.0 equiv). [c] Isolated yields and regioselectivity (m/others) determined by GC.

Scheme 4. Kinetic Isotope Effects (KIE) Experiments



different electronic characteristics as the coupling partners. Under the present mechanochemical conditions, fast arylation occurred and gave the biaryl products with high-level selectivity. KIE experiments indicated that the transformation might undergo a Pd(II/IV) catalytic cycle involving sequential two-step C−H bond activation. Attempt to apply this efficient and selective arylation for the preparing of more useful and complicated biaryl frameworks are still ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00861.

> General experimental details, including procedures, the kinetic isotope effect experiment, syntheses, and characterization data of new products (PDF)

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Notes

The authors declare no competing financial interest.

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