Article

Cross-Electrophile Coupling of Aryl Chlorides with Alkyl Chlorides Using Rotating Magnetic Field and Metal Rods

Xiaomei Feng,[†] Xiangye Li,[†] Ning Zhang, Lizhi Zhang, Fenggang Sun, Hui Liu, Zengdian Zhao, and Xinjin Li[*]
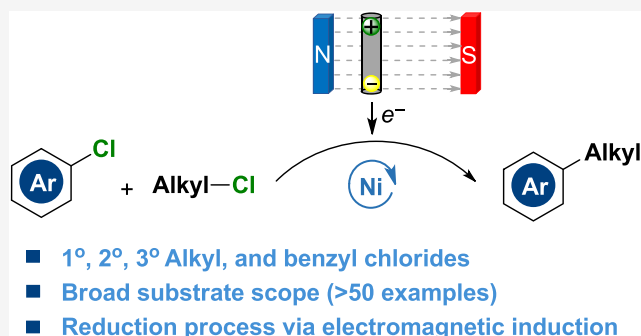
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The pursuit of sustainable and environmentally benign methods and techniques continues to challenge organic chemists. Herein, we report the development of a novel approach in which electromagnetic induction could participate in the coupling of organic chlorides using a rotating magnetic field and metal rods. In particular, we describe the application of this strategy to the nickel-catalyzed cross-electrophile coupling of aryl chlorides with alkyl chlorides. Using these abundant and commercially available organochlorides, such a system allows reactions to proceed with a broader scope than the current protocols under mild conditions.

■ 1º, 2º, 3º Alkyl, and benzyl chlorides
■ Broad substrate scope (>50 examples)
■ Reduction process via electromagnetic induction

■ INTRODUCTION

Nickel-catalyzed cross-electrophile coupling has become an important and powerful strategy for the construction of C(sp^2)−C(sp^3) bonds.[1−5] The foremost advantage of this strategy lies within the usage of diverse electrophiles (e.g., organohalides, carboxylates, and sulfonates), which are more stable than their organometallic counterparts.[6,7] Compared to organic bromides and iodides that are typically employed for C−C coupling reactions with Ni catalysts,[8−16] organochlorides are more attractive due to their greater commercial availability and lower cost.[17,18] However, in practice, engaging less reactive C−Cl bonds has proven challenging in cross-electrophile coupling reactions due to their strong bond dissociation energy.[19] Seminal studies have explored the nickel-catalyzed cross-coupling of organic chlorides.[20−24] Zhang reported couplings of a variety of aryl chlorides with ClCF$_2$H using Zn as the reductant with an excess of MgCl$_2$ to facilitate the reduction process.[20] Weix developed a selective ligand (PyBCam^{CN}) to achieve the cross-coupling of aryl chlorides with primary alkyl chlorides (Scheme 1a).[23] MacMillan reported coupling reactions of alkyl chlorides with aryl chlorides via the merger of photoredox, nickel catalyst and a silane reagent enabling chlorine atom transfer to form alkyl radicals (Scheme 1b).[24]

More recently, we have developed a novel approach that electromagnetic induction could induce the redox reaction of organic molecules using a rotating magnetic field and metal rods (Scheme 1c).[25,26] Especially, the cutting of the magnetic induction line in a magnetic field could generate a polarized metal, resulting in the electron-transfer process. Compared to photoredox[27−29] or mechanoredox reaction,[30,31] such a magnetoredox approach introduces new reaction design

parameters, such as magnetic intensity, rotating frequency, and rod size, enabling the highly selective formation of chemical bonds through multifaceted regulation. Based on our previous report for magnetoredox-driven radical trifluoromethylation,[25,26] we envisioned that such a principle could open the door to transition-metal-catalyzed cross-electrophile coupling reactions, where the electron transfer through electromagnetic induction[32] could promote the reduction process. Herein, we report the first magnetoredox/nickel-catalyzed cross-electrophile coupling of aryl chlorides with alkyl chlorides using a rotating magnetic field and metal rods (Scheme 1d).

■ RESULTS AND DISCUSSION

As illustrated in Scheme 1D, the experimental setup consists of steel rods in a glass tube, two permanent magnets (Nd$_2$Fe$_{14}$B), a spacing sleeve, and a frequency conversion motor (Figure S1, Supporting Information). The two square magnets (50 mm × 20 mm × 25 mm) rotate around the sleeve to form a rotating magnetic field, which drives the standing steel rods in the glass tube to move. We initially examined the cross-coupling reaction of 4-chlorobiphenyl **1a** with 3-phenylpropyl chloride **2a** in the presence of steel rods (Φ = 1.0 mm) using a rotating magnetic field (Table 1). After extensive optimization of the reaction
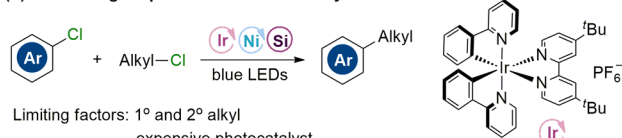
Scheme 1. Nickel-Catalyzed Cross-Electrophile Coupling of Organic Chlorides

**(a) Zinc reductant/nickel catalysis**
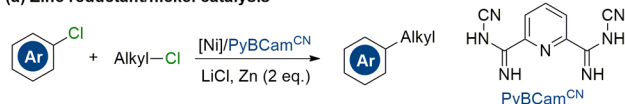
Limiting factors: 1° and 2° alkyl (one example with low efficiency)
poor reactivity for sterically hindered aryl chlorides
uncommon ligand; long reaction time (18-24 h)

(b) Silane reagent-photoredox/nickel catalysis

Limiting factors: 1° and 2° alkyl
expensive photocatalyst
silane reagent; long reaction time (18 h)

(c) Magnetoredox system
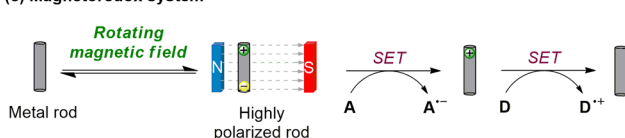
(d) Magnetoredox/nickel catalysis (this work)

- 1°, 2°, 3° alkyl, and benzyl chlorides
- novel reductive process via electromagnetic induction
- broad substrate scope (>50 examples); short reaction time (3-6 h)

Table 1. Control Reactions of Optimized Conditions[a]

Ni(acac)$_2$ (10 mol%)
L3 (10 mol%)
0.26 T, 40 Hz
40 mm steel rod × 40
TBAB (2 eq.), NMP, 3 h

L1: R = H
L2: R = OMe
L3: R = NH$_2$
L4: R = ^{t}Bu

L5

entry	variation of standard conditions	yield[b] (%)
1	none	85
2	NiBr$_2$ instead of Ni(acac)$_2$	65
3	NiI$_2$ instead of Ni(acac)$_2$	70
4	**L1** instead of **L3**	46
5	**L2** instead of **L3**	54
6	**L4** instead of **L3**	63
7	**L5** instead of **L3**	49
8	DMA instead of NMP	73
9	DMF instead of NMP	61
10	NaBr instead of TBAB	54
11	TBAI instead of TBAB	71
12	without TBAB	36
13	without Ni(acac)$_2$	trace
14	without **L3**	0
15	without rotating magnetic field	0
16	Zn powder, 100 °C instead of rotating magnetic field	23,58[c]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), Ni(acac)$_2$ (10 mol %), **L3** (10 mol %), TBAB (2.0 equiv), and 40 steel rods (Φ = 1.0 mm, L = 40 mm) in NMP (1 mL) using a rotating magnetic field (0.26 T, 40 Hz) under air for 3 h. [b]Isolated yield. [c]Under an argon atmosphere. L, rod length; B, magnetic intensity; and V, rotating frequency. TBAB, tetrabutylammonium bromide and TBAI, tetrabutylammonium iodide.

parameters (for details, see Table S2, Supporting Information), the desired product **3a** could be obtained in 85% yield in a rotating magnetic field (B = 0.26 T and V = 40 Hz) by employing steel rods (L = 40 mm), Ni(acac)$_2$ as the catalyst, and 4,4′-diamino-2,2′-bipyridyl (**L3**) as the ligand (entry 1). Other nickel catalysts, such as NiBr$_2$ and NiI$_2$, were examined with low efficiency (entries 2 and 3). The use of other bidentate ligands instead of **L3** resulted in low yields (entries 4−7). Decreased yields were observed when DMA and DMF were used in lieu of NMP (entries 8 and 9). We also investigated different additives and found that the use of TBAB provided the best result (entries 10−12). Control experiments established that the nickel catalyst, ligand, and rotating magnetic field were all necessary for product formation (entries 13−15). In addition, the comparative experiments were performed at 100 °C using zinc as a reductant, and the desired product was obtained in 23% and 58% yield under an air and argon atmosphere, respectively (entry 16). The result indicates the superiority of our magnetoredox system over the existing methods. For further insight into the effect of electromagnetic induction on the cross-coupling reaction, we conducted a series of experiments. To a certain extent, the results indicate that the increase in magnetic intensity, rotating frequency, rod length, or rod amount could enhance the yields (Figure 1).

With these optimized conditions in hand, we explored the scope of nickel-catalyzed cross-coupling of organic chlorides using a rotating magnetic field (B = 0.26 T and V = 40 Hz) and steel rods (L = 40 mm). As summarized in Scheme 2, we were delighted to find that this magnetoredox/nickel catalysis approach served as a broadly applicable platform for coupling a variety of aryl chlorides and alkyl chlorides. With respect to the

Ni(acac)$_2$ (10 mol%)
L3 (10 mol%)
TBAB (2 eq.), NMP
steel rods (L, amount)
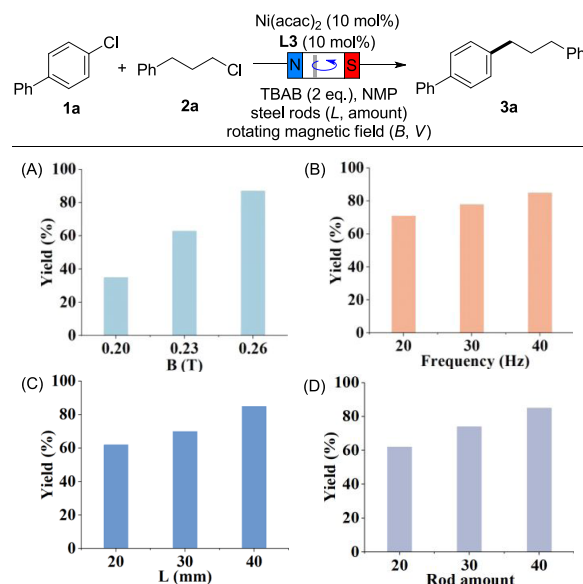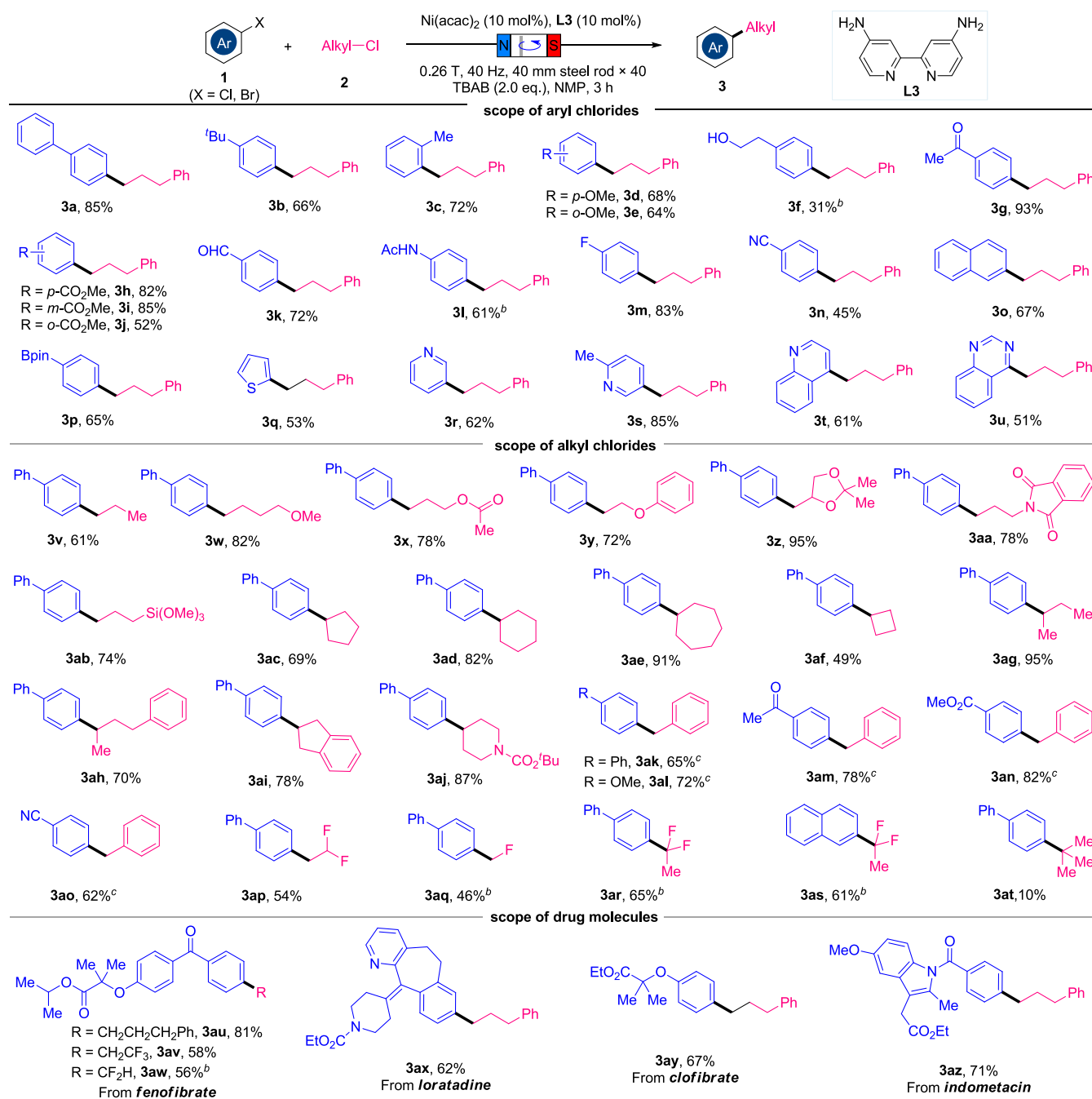rotating magnetic field (B, V)

Figure 1. Effect of rotating magnetic field and steel rods on the reaction. (A) Effect of magnetic intensity on the reaction (L = 40 mm, V = 40 Hz). (B) Effect of rotating frequency on the reaction (B = 0.26 T, L = 40 mm) and (C) Effect of the length of steel rods on the reaction (B = 0.26 T, V = 40 Hz). (D) Effect of the amount of steel rods on the reaction (B = 0.26 T, V = 40 Hz, and L = 40 mm).

Scheme 2. Scope of Cross-Electrophile Coupling of Aryl Chlorides with Alkyl Chlorides[a]


scope of aryl chlorides

3a, 85%

3b, 66%

3c, 72%

R = *p*-OMe, **3d**, 68%
R = *o*-OMe, **3e**, 64%

3f, 31%[b]

3g, 93%

R = *p*-CO$_2$Me, **3h**, 82%
R = *m*-CO$_2$Me, **3i**, 85%
R = *o*-CO$_2$Me, **3j**, 52%

3k, 72%

3l, 61%[b]

3m, 83%

3n, 45%

3o, 67%

3p, 65%

3q, 53%

3r, 62%

3s, 85%

3t, 61%

3u, 51%

scope of alkyl chlorides

3v, 61%

3w, 82%

3x, 78%

3y, 72%

3z, 95%

3aa, 78%

3ab, 74%

3ac, 69%

3ad, 82%

3ae, 91%

3af, 49%

3ag, 95%

3ah, 70%

3ai, 78%

3aj, 87%

R = Ph, **3ak**, 65%[c]
R = OMe, **3al**, 72%[c]

3am, 78%[c]

3an, 82%[c]

3ao, 62%[c]

3ap, 54%

3aq, 46%[b]

3ar, 65%[b]

3as, 61%[b]

3at, 10%

scope of drug molecules

R = CH$_2$CH$_2$CH$_2$Ph, **3au**, 81%
R = CH$_2$CF$_3$, **3av**, 58%
R = CF$_2$H, **3aw**, 56%[b]
From *fenofibrate*

3ax, 62%
From *loratadine*

3ay, 67%
From *clofibrate*

3az, 71%
From *indometacin*

[a]Reaction conditions: aryl chlorides **1** (0.3 mmol), alkyl chlorides **2** (2.0 equiv), Ni(acac)$_2$ (10 mol %), **L3** (10 mol %), TBAB (2.0 equiv), and 40 steel rods (Φ = 1.0 mm, L = 40 mm) in NMP (1 mL) using a rotating magnetic field (B = 0.26 T, V = 40 Hz) under air for 3 h. Isolated yield. [b]The reaction was conducted for 6 h. [c]Aryl bromides were employed instead of aryl chlorides using a rotating magnetic field (B = 0.2 T, V = 40 Hz) in the lack of TBAB.

aryl chloride coupling partner, both electron-rich and -deficient chlorobenzene derivatives (**3b**−**3n**) performed well to afford the corresponding products in moderate to good yields. The reaction could tolerate a wide array of functional groups such as alkoxy, hydroxy, acetyl, ester, aldehyde, amide, fluorine, nitrile, Bpin, and silyl ether. We were pleased to find that heteroaryl fragments, such as thiophene, pyridine, quinoline, and quinazoline, could be readily alkylated with good efficiency (**3q**−**3u**). Notably, aryl chlorides bearing an *ortho*-Me, -OMe, or −CO$_2$Me group afforded the corresponding products (**3c**, **3e**, **3j**) in good

yields, indicating that this magnetoredox cross-coupling reaction was not sensitive to steric effects.

Next, we turned our attention to the scope of the alkyl chloride coupling partner. We were pleased to find that a number of functionalized primary alkyl chlorides could be successfully engaged in our coupling methodology (**3v**−**3ab**, 61−95% yield). In particular, alkyl chlorides containing acyclic and cyclic ethers could be employed to access the desired products (**3w**, **3y**, and **3z**) in good yields. Our investigation revealed that secondary alkyl chlorides, such as five-, six-, seven-,
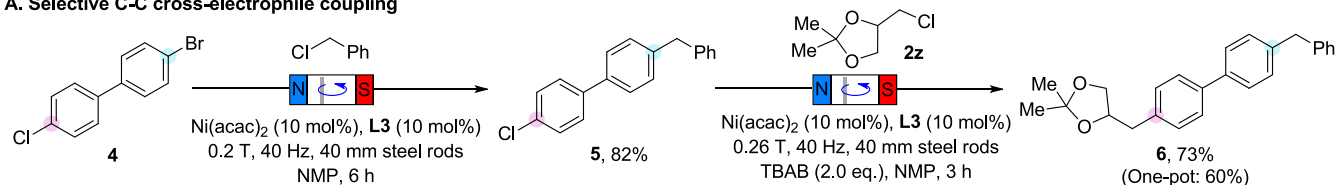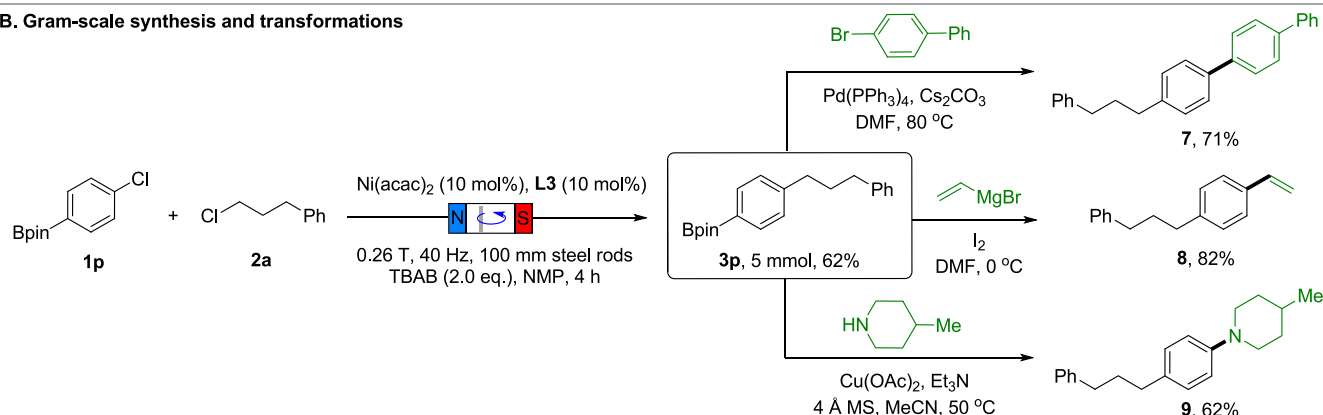
Figure 2. Synthetic application. Isolated yield: (A) Chemoselective sequential C−C coupling. (B) Gram-scale synthesis and transformations of product **3p**.

and four-membered cyclic systems (**3ac−3af**, **3ai**, **3aj**) also underwent this transformation smoothly, affording the desired products in moderate to good yields. While benzyl chlorides were unsuitable for Fe-catalyzed cross-electrophile coupling reactions,[18] we were delighted to find that a variety of aryl bromides could be readily coupled with benzyl chlorides (**2ak−2ao**) in the lack of TBAB using a rotating magnetic field ($B = 0.2$ T and $V = 40$ Hz). Given the importance of fluoroalkyl-substituted skeletons in pharmaceuticals,[33−35] various fluoroalkyl chlorides were employed to provide the fluoroalkylated products (**3ap−3as**) in moderate to good yields. Notably, we were pleased to find that a tertiary alkyl chloride (CH_3CF_2Cl) could be coupled smoothly with aryl chlorides, affording the desired products (**3ar**, **3as**) in good yields. Regrettably, tertiary butyl chloride has proven more challenging in cross-coupling with aryl chlorides,[36,37] exhibiting low efficiency (**3at**, 10% yield detected by GC-MS) in the current study. Finally, to demonstrate the applicability of our method to the late-stage diversification of bioactive molecules, we examined several drug molecules containing aryl chlorides under the optimized conditions. We were delighted to find that the desired $C(sp^2)−C(sp^3)$ adducts (**3au−3az**) could be obtained in good yields. These results highlight the efficacy of this protocol in the elaboration of complex pharmaceuticals.

We further investigated a series of reactions to demonstrate the advantage of the magnetoredox approach to selectively couple highly functionalized substrates in a chemoselective manner (Figure 2A). We carried out the sequential alkylation of 4-bromo-4′-chlorobiphenyl (**4**) with benzyl chloride using a rotating magnetic field ($B = 0.2$ T) to afford **5** in 82% yield and then with alkyl chloride **2z** using a rotating magnetic field ($B = 0.26$ T), resulting in the formation of the bis-alkylated aryl **6** in 73% yield. To further demonstrate the synthetic utility of this protocol, we performed the reaction on a gram scale with **1p**, and the desired product can be obtained in 62% yield (Figure 2B). With compound **3p** in hand, various transformations have been performed. The Suzuki−Miyaura reaction of **3p** with bromobiphenyl afforded product **7** in 71% yield. Treatment of

3p with vinylmagnesium bromide could provide vinylated product **8** in 82% yield. The Cu-catalyzed C−N coupling reaction of **3p** with the piperidine derivative also performed well, affording the coupled product **9** in 62% yield.

To gain insights into the reaction mechanism, we conducted experiments to probe possible intermediates (Figure 3). When butylated hydroxytoluene (BHT) was treated with **1a** and **2a**, the reaction was significantly suppressed (Figure 3A). Furthermore, when 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was added to the reaction mixture, the adduct of TEMPO with the phenylpropyl radical was detected by GC-MS (Figure 3B). It is notable that the grinding of steel rods generates heat, so we explored the thermal effect on the current reaction. The temperature inside the tube during the reaction was measured by using an infrared thermograph, and the image showed that the temperature was around 100 °C (Figure 3C). In view of this, when the temperature was kept at 70 and 20 °C, the reaction performed in a rotating magnetic field gave the product in 51% yield and no product, respectively. In addition, when the reaction was performed at 100 °C for 3 h without a rotating magnetic field, no product was observed (Figure 3D). These results suggest that the heat generated by the grinding of rods is also essential, as well as the electron reduction for the reaction. It was found that some powder was isolated after the reaction, which is probably due to the grinding of steel rods (for details, see the Supporting Information). The energy-dispersive spectrum (EDS) indicated that the component of the powder is almost the same as that of the steel rod (Figure S5, Supporting Information). To rule out the powder as a reductant in the reaction, we performed the reaction using the powder together with insulated rods for good mixing of the reaction system in a rotating magnetic field. No product was observed under those conditions, and very little product (2% yield) was detected by GC-MS even when heating to 100 °C (Figure 3E). Furthermore, we conducted the reaction using iron, chromium, or nickel dust at 100 °C under an argon atmosphere, and it was found that no reaction occurred (Figure 3F). Although manganese dust gave the product in 36% yield, the content of manganese in the steel
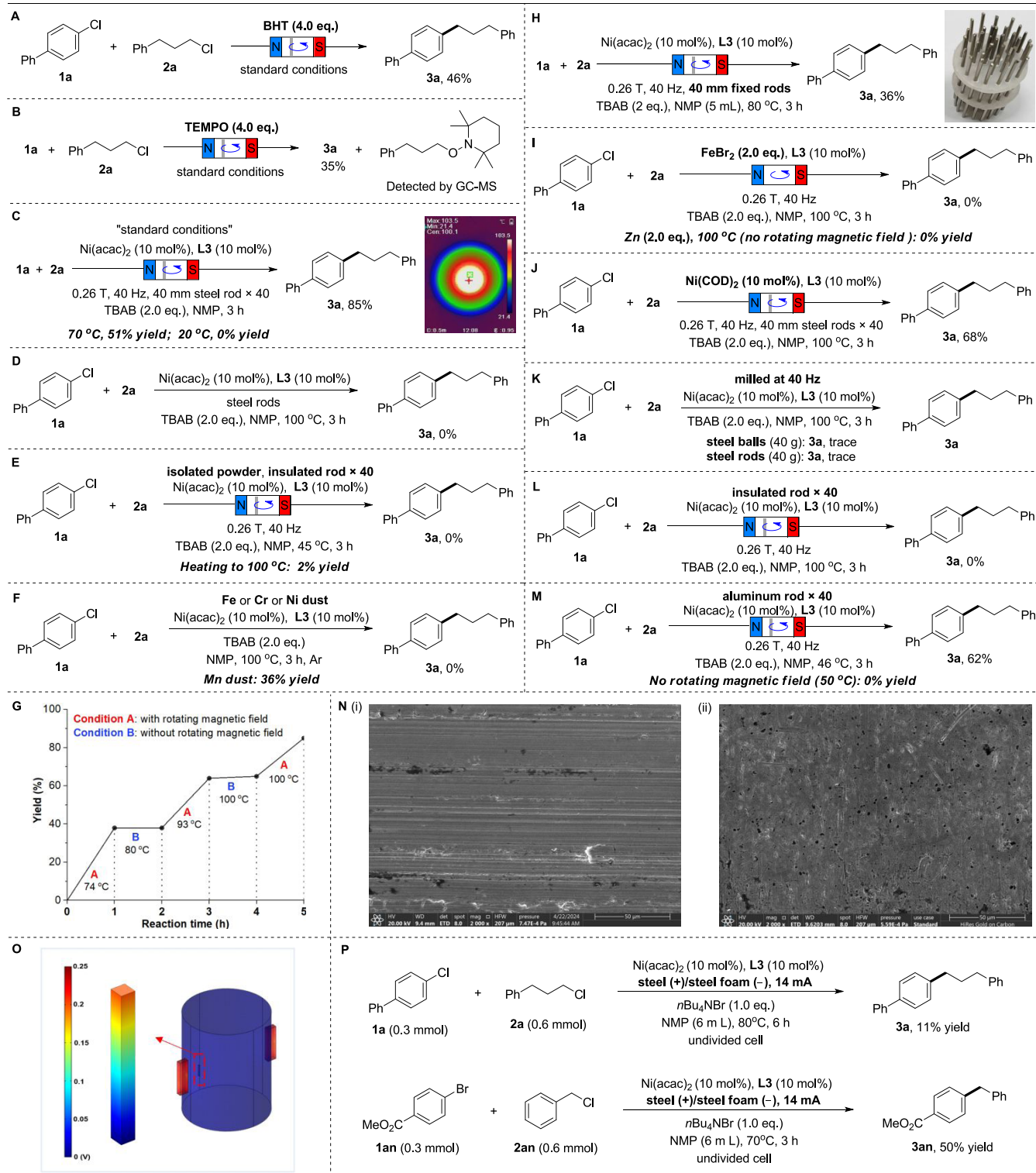
Figure 3. Mechanistic investigations. (A, B) Radical inhibition experiments. (C, D) Comparative experiments. (E−J) Control experiments. (K, L, M) Mechanical impact experiments. (N) SEM images of steel rod (i) before reaction and (ii) after reaction. (O) Simulation of the electromotive force of a steel rod (1.5 mm × 1.5 mm × 30 mm) using COMSOL Multiphysics. (P) Electrochemical reactions.

rods is very low (1.1%). In addition, we performed the reaction using steel rods with or without a rotating magnetic field, and it was found that the reaction hardly occurred in the absence of a rotating magnetic field (Figure 3G). Moreover, we conducted the reaction using the fixed steel rods with PP (polypropylene) sheets in a rotating magnetic field, and no formation of metal

powder was found, while the product was obtained in 36% yield (Figure 3H, for details, see the Supporting Information). These results demonstrate that the steal powder or rods hardly serve as the reductant even at a high temperature (100 °C) for the cross-electrophile coupling reaction. The reaction solution, after removal of the powder, was detected by KSCN and KMnO$_4$ in

sequence, and the result indicates that there is Fe^{2+} in the reaction mixture (for details, see the Supporting Information). In order to rule out the possibility of a Fe-catalyzed coupling reaction, we conducted the reaction in the presence of $FeBr_2$, resulting in no formation of product **3a** (Figure 3I). When $Ni(COD)_2$ in lieu of $Ni(acac)_2$ was employed in the reaction, the desired product was obtained in 68% yield under the optimized conditions (Figure 3J).

To investigate the mechanical impact on the reaction, we carried out the reaction using steel balls and steel rods in a stainless-steel milling jar, and very little product **3a** was observed (Figure 3K). In addition, the reaction was conducted using steel rods insulated by ZrO_2 in a rotating magnetic field, resulting in no formation of product (Figure 3L, for details, see the Supporting Information). Furthermore, we performed the reaction using nonmagnetic aluminum rods with a magnetic stirrer insulated by Teflon for good mixing of the reaction mixture. It is noted that the reaction could afford product **3a** in 62% yield in a rotating magnetic field, while no product was detected in the absence of a rotating magnetic field (Figure 3M). These results better support the role of the field-driven reduction process via electromagnetic induction and thus discount the possibility of the triboelectric effect[38,39] on the reaction. We also investigated the surface of steel rods before and after the reaction. The SEM image of steel rods shows a regular texture before reaction (Figure 3N-i) and a rough surface after reaction (Figure 3N-ii), indicating that the electron-transfer process through electromagnetic induction most likely occurs on the surface of steel rods. Moreover, we simulated the distribution of the surface-induced electromotive force of a steel rod (1.5 mm × 1.5 mm × 30 mm) using COMSOL Multiphysics, and the maximum electromotive force is 0.2 V (Figure 3O, for details, see the Supporting Information). The result demonstrates that the electromotive force of a steel rod simulated as an absolute value is not equivalent to the reduction potential of the catalyst, although there is positive relativity between electromotive force and reduction potential.[25,26] To demonstrate whether the steel could be polarized under electrochemical conditions, we conducted electrochemical reactions with a steel anode and a steel cathode. The electrochemical reaction gave product **3a** in 11% yield and product **3an** in 50% yield (Figure 3P).

Based on these results and previous reports,[8,20,37a,40] we suggest two competing mechanistic pathways for cross-electrophile coupling reaction with nickel catalyst using a rotating magnetic field and steel rods: a radical chain path along with a sequential reduction process (Scheme 3). In a radical chain mechanism, the aryl chloride undergoes oxidative addition to Ni(0) complex **10**. The resulting Ni(II) intermediate **11** then combines with the alkyl radical to give Ni(III) complex **12**, which proceeds via reductive elimination to afford the coupled product **3** and Ni(I) complex **13**. The resulting intermediate **13** could abstract a bromide prior to a chloride from alkyl halides to generate the alkyl radical.[41] Finally, Ni(II) species **14** can be reduced through electromagnetic induction along with the formation of Fe(II) from Fe(0) in steel rods, regenerating Ni(0) complex **10** to close the catalytic cycle. The second proposed mechanism involves a sequential reduction process. The aryl chloride undergoes oxidative addition to Ni(0) complex **10** to give Ni(II) intermediate **11**, which is then reduced through electromagnetic induction to form **15**, along with the formation of Fe(II) from steel rods. The Ni(I)−aryl complex **15** then affect halide abstraction to form intermediate **16**. Subsequent

Scheme 3. Proposed Mechanism
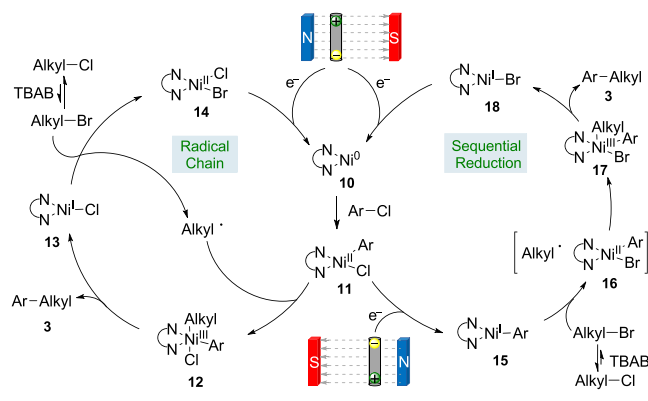
reductive elimination affords product **3** and Ni(I) complex **18**, which could be reduced to regenerate Ni(0) complex **10** through electromagnetic induction.

CONCLUSIONS

In summary, we have developed the cross-electrophile coupling of aryl chlorides with alkyl chlorides via the merger of magnetoredox and nickel catalysis by using a rotating magnetic field and steel rods. This magnetoredox-based methodology, with a broader scope than current protocols, allows access to highly functionalized $C(sp^2)−C(sp^3)$ coupled products under mild conditions. Mechanistic studies demonstrate that electron transfer via electromagnetic induction could promote the reduction process to accomplish the catalytic cycle. The novel approach enables chemoselective C−C couplings through the multifaceted regulation of magnetic intensity, rod size, and rotating frequency.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c00381.

AUTHOR INFORMATION

Corresponding Author

Xinjin Li − School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China; ⊙ orcid.org/0000-0002-8406-4372; Email: lixj@sdut.edu.cn

Authors

Xiaomei Feng − School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China

Xiangye Li − School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China; ⊙ orcid.org/0000-0002-3103-345X

Ning Zhang − School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China

Lizhi Zhang − *School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China*

Fenggang Sun − *School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China;* ⊙ orcid.org/0000-0001-9366-6087

Hui Liu − *School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China*

Zengdian Zhao − *School of Chemistry and Chemical Engineering, Shandong University of Technology, Zibo, Shandong 255000, China*

Complete contact information is available at:
https://pubs.acs.org/10.1021/jacs.5c00381

Author Contributions

[†]X.F. and X.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793−4798.

(2) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C. Jacobi von Wangelin, A. Reductive Cross- Coupling Reactions between Two Electrophiles. *Chem. - Eur. J.* **2014**, *20*, 6828−6842.

(3) Wang, X.; Dai, Y.; Gong, H. Nickel-Catalyzed Reductive Couplings. *Top. Curr. Chem.* **2016**, *374*, No. 43.

(4) Yi, L.; Ji, T.; Chen, K.-Q.; Chen, X.-Y.; Rueping, M. Nickel-Catalyzed Reductive Cross-Couplings: New Opportunities for Carbon-Carbon Bond Formations through Photochemistry and Electrochemistry. *CCS Chem.* **2022**, *4*, 9−30.

(5) Goldfogel, M. J.; Huang, L.; Weix, D. J. Cross-Electrophile Coupling. In *Nickel Catalysis in Organic Synthesis: Methods and Reactions*; Ogoshi, S., Ed.; Wiley-VCH: Weinheim, 2020.

(6) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417−1492.

(7) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C−C Bonds. *Chem. Rev.* **2015**, *115*, 9587−9652.

(8) (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.

(9) Gu, J.; Wang, X.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Other Electrophiles: Concept and Mechanistic Considerations. *Org. Chem. Front.* **2015**, *2*, 1411−1421.

(10) Liu, J.; Ye, Y.; Sessler, J. L.; Gong, H. Cross-Electrophile Couplings of Activated and Sterically Hindered Halides and Alcohol Derivatives. *Acc. Chem. Res.* **2020**, *53*, 1833−1845.

(11) (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. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146−6159.

(12) (a) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. Nickel-Catalyzed Reductive Cross-Coupling of Unactivated Alkyl Halides. *Org. Lett.* **2011**, *13*, 2138−2214. (b) Liu, J.; Ren, Q.; Zhang, X.; Gong, H. Preparation of Vinyl Arenes by Nickel-Catalyzed Reductive Coupling of Aryl Halides with Vinyl Bromides. *Angew. Chem., Int. Ed.* **2016**, *55*, 15544−15548.

(13) 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.

(14) Ackerman, L. K. G.; Lovell, M. W.; Weix, D. J. Multimetallic Catalysed Cross-Coupling of Aryl Bromides with Aryl Triflates. *Nature* **2015**, *524*, 454−457.

(15) Zhang, P.; Le, C. C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 8084−8087.

(16) (a) Perkins, R. J.; Pedro, D. J.; Hansen, E. C. Electrochemical Nickel Catalysis for Sp^2-Sp^3 Cross-Electrophile Coupling Reactions of Unactivated Alkyl Halides. *Org. Lett.* **2017**, *19*, 3755−3758. (b) Jiao, K.-J.; Liu, D.; Ma, H.-X.; Qiu, H.; Fang, P.; Mei, T.-S. Nickel-Catalyzed Electrochemical Reductive Relay Cross-Coupling of Alkyl Halides to Aryl Halides. *Angew. Chem., Int. Ed.* **2020**, *59*, 6520−6524. (c) Su, Z.-M.; Deng, R.; Stahl, S. S. Zinc and Manganese Redox Potentials in Organic Solvents and Their Influence on Nickel-Catalysed Cross-Electrophile Coupling. *Nat. Chem.* **2024**, *16*, 2036−2043.

(17) Zhang, W.; Lu, L.; Zhang, W.; Wang, Y.; Ware, S. D.; Mondragon, J.; Rein, J.; Strotman, N.; Lehnherr, D.; See, K. A.; Lin, S. Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides. *Nature* **2022**, *604*, 292−297.

(18) Zhang, Y.; Du, P.; Ji, Y.; Wang, S.; Zhu, Y.; Liu, Z.; He, Y.; Peng, Q.; Feng, Z. Catalytic Cross-Electrophile Coupling of Aryl Chlorides with Unactivated Alkyl Chlorides: The Synergy of Iron and Li. *Chem* **2023**, *9*, 3623−3636.

(19) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255−263.

(20) Xu, C.; Guo, W.-H.; He, X.; Guo, Y.-L.; Zhang, X.-Y.; Zhang, X. Difluoromethylation of (Hetero)Aryl Chlorides with Chlorodifluoromethane Catalyzed by Nickel. *Nat. Commun.* **2018**, *9*, No. 1170.

(21) Mirabi, B.; Marchese, A. D.; Lautens, M. Nickel-Catalyzed Reductive Cross-Coupling of Heteroaryl Chlorides and Aryl Chlorides. *ACS Catal.* **2021**, *11*, 12785−12793.

(22) (a) Liu, J.; Zhang, J.; Li, X.; Wu, C.; Liu, H.; Liu, H.; Sun, F.; Li, Y.; Liu, Y.; Li, X. Nickel-Catalyzed 1,1-Difluoroethylation of (Hetero)aryl Halides with 1,1-Difluoroethyl Chloride (CH$_3$CF$_2$Cl). *Asian J. Org. Chem.* **2020**, *9*, 391−394. (b) Diao, Z.; Feng, Y.; Zhang, J.; Wang, X.; Li, H.; Ding, C.; Zhou, Z.; Li, X. Nickel-Catalyzed Reductive Cross-Coupling of (Hetero)aryl Halides with 2-Chloro-1,1-difluoroethane: Facile Access to 2,2-Difluoroethylated Aromatics. *Asian J. Org. Chem.* **2022**, *11*, No. e202200169.

(23) (a) 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. (b) Akana, M. E.; Tcyrulnikov, S.; Akana-Schneider, B. D.; Reyes, G. P.; Monfette, S.; Sigman, M. S.; Hansen, E. C.; Weix, D. J. *J. Am. Chem. Soc.* **2024**, *146*, 3043−3051.

(24) Sakai, H. A.; Liu, W.; Le, C. C.; MacMillan, D. W. C. Cross-Electrophile Coupling of Unactivated Alkyl Chlorides. *J. Am. Chem. Soc.* **2020**, *142*, 11691−11697.

(25) Liu, H.; Han, X.; Feng, X.; Zhang, L.; Sun, F.; Jia, F.; Zhao, Z.; Liu, H.; Li, X. Redox Reactions of Organic Molecules Using Rotating Magnetic Field and Metal Rods. *J. Am. Chem. Soc.* **2024**, *146*, 18143−18150.

(26) Han, X.; Liu, H.; Feng, X.; Jia, F.; Zhao, Z.; Li, X. Catalyst-Free, Radical Tri- and Difluoromethylation of Isocyanidesand N-Arylacrylamides Using Rotating Magnetic Field and Metal Rods. *Chin. J. Chem.* **2025**, *43*, 155−160.

(27) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102−113.

(28) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363.

(29) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166.

(30) Leitch, J. A.; Browne, D. L. Mechanoredox Chemistry as an Emerging Strategy in Synthesis. *Chem. - Eur. J.* **2021**, *27*, 9721−9726.

(31) Ren, Z.; Peng, Y.; He, H.; Ding, C.; Wang, J.; Wang, Z.; Zhang, Z. Piezoelectrically Mediated Reactions: From Catalytic Reactions to Organic Transformations. *Chin. J. Chem.* **2023**, *41*, 111−128.

(32) Galili, I.; Kaplan, D.; Lehavi, Y. Teaching Faraday's Law of Electromagnetic Induction in an Introductory Physics Course. *Am. J. Phys.* **2006**, *74*, 337−343.

(33) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2013.

(34) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.

(35) Johnson, B. M.; Shu, Y.-Z.; Zhuo, X.; Meanwell, N. A. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem.* **2020**, *63*, 6315−6386.

(36) For Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides, see: (a) Wang, X.; Wang, S.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 11562−11565. (b) Lin, Q.; Gong, H.; Wu, F. Ni-Catalyzed Reductive Coupling of Heteroaryl Bromides with Tertiary Alkyl Halides. *Org. Lett.* **2022**, *24*, 8996−9000.

(37) For Reductive Coupling of Aryl Iodides with Tertiary Alkyl Halides, see: (a) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H. Ni-Catalyzed Reductive Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2018**, *140*, 14490−14497. (b) Ying, X.; Li, Y.; Li, L.; Li, C. Nickel-Catalyzed C−I-Selective $C(sp^2)$−$C(sp^3)$ Cross-Electrophile Coupling of Bromo(iodo)arenes with Alkyl Bromides. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202304177.

(38) Zhang, J.; Coote, M. L.; Ciampi, S. Electrostatics and Electrochemistry: Mechanism and Scope of Charge-Transfer Reactions on the Surface of Tribocharged Insulators. *J. Am. Chem. Soc.* **2021**, *143*, 3019−3032.

(39) Yoo, D.; Jang, S.; Cho, S.; Choi, D.; Kim, D. S. A Liquid Triboelectric Series. *Adv. Mater.* **2023**, *35*, No. 2300699.

(40) Wu, H.; Zhang, S.-Q.; Hong, X. Mechanisms of Nickel-Catalyzed Reductive Cross Coupling Reactions. *Chem. Synth.* **2023**, *3*, No. 39.

(41) Control experiments indicate that the alkyl radical probably could not be generated by the reduction of alkyl chlorides through electromagnetic induction (for details, see Supporting Information).