RSC Mechanochemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Mechanochem.*, 2026, 3, 27

Received 22nd July 2025
Accepted 4th September 2025

DOI: 10.1039/d5mr00094g

rsc.li/RSCMechanochem

Mechanoradical-driven C–H halogenation and nitration of arenes and vicinal dibromination of alkenes in the solid state

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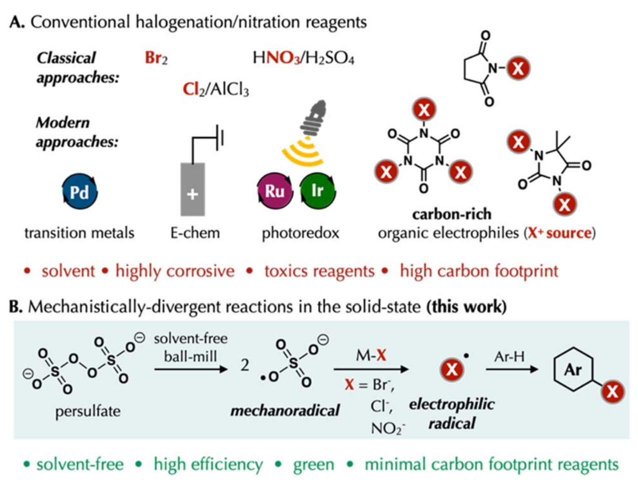
We report a solvent-free mechanochemical approach for the C–H halogenation and nitration of arenes. *In situ*-generated oxygen-centered mechanoradicals readily oxidize halide or nitrite salts, enabling C–H functionalization of arenes. Radical trapping experiments confirm the involvement of bromine radical species, distinct from conventional solution-phase processes that predominantly proceed *via* brominium intermediates. This operationally simple and carbon-free strategy is further extended to solid-state vicinal dibromination reactions of unactivated alkenes.

The direct C–H functionalization of arenes represents a powerful transformation in organic synthesis,[1–3] providing critical intermediates for pharmaceuticals, agrochemicals, and advanced materials.[4–7] However, conventional methods often rely on hazardous reagents (*e.g.*, molecular halogens, nitric acid, transition metals or strong Lewis acids) and harsh conditions, generating stoichiometric waste (*e.g.* increasing carbon footprints) and posing significant safety and environmental concerns (Scheme 1A).[8–15] These persistent challenges underscore the need for new strategies to bypass hazardous reagents, minimize waste, and operate under mild conditions.

Mechanochemistry, which exploits the mechanical force to drive chemical reactions, has emerged as an alternative for organic synthesis, offering unparalleled advantages over conventional solution-based approaches in terms of atom economy, reduced energy consumption, and elimination of solvent waste.[16–21] Among all the attributes of mechanochemistry, its ability to directly homolyze chemical bonds to generate radical species, known as mechanoradicals, is distinct from other known reaction driving forces. In theory, the mechanochemical formation of redox neutral radicals does not require external sacrificial reagents, photoredox or piezoelectric catalysts, or electrodes (Scheme 1A).[22–24] Although this idea represents the most straightforward and environmentally benign approach to produce radicals, literature examples employing this strategy in C–H bond activation reactions are scarce. Hong reported mechanochemical fluorination with unactivated C(sp^3)–H bonds, but control experiments revealed that the process was likely facilitated by trace metals (*e.g.* Fe and Ni) in the milling apparatus (*e.g.* stainless steel (SS) jars and balls).[25] Replacing them with non-metal ones completely quenches the reactivity. Mechanochemical halogenation of arenes, especially bromination,[26] definitively going through a halogen radical intermediate was reported by Mal,[26] which was supported by spin trapping experiments and EPR study.

Although cleavage of O–O bonds in persulfate ($S_2O_8^{2-}$) can be promoted by various sources of energy input (*e.g.*, heat or high-energy photons) in solution, our group recently showed that oxygen-centered mechanoradicals (*O*-mechanoradicals) can be generated *in situ* from persulfate salts directly by ball-milling treatments, even at low temperature (−50 °C) with



Scheme 1 (A) Overview of conventional solution-based strategies of arene C–H halogenation and nitration reactions; and (B) a mechanistically divergent mechanoradical strategy in the solid state (this work).

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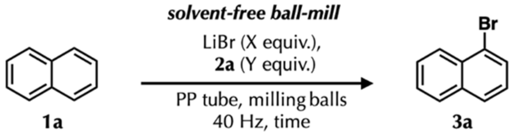
a non-stainless steel milling apparatus (*e.g.* ZrO_2 balls and polypropylene (PP) tubes).[27] These reactive radical species would subsequently oxidize carbon-based nucleophiles to engage in Minisci-type coupling reactions. Building on this foundation, we herein report that *O*-mechanoradicals could be further employed with simple metal salts (MBr) for bromination of arenes (Scheme 1B). More significantly, although oxidative halogenation reactions employing a combination of halide salts (*e.g.* NaBr, LiCl, *etc.*) and oxidants (*e.g.* H_2O_2, persulfate, *etc.*) under solution-based conditions were investigated,[28,29] most of these studies suggested the involvement of halonium ion intermediates. This work highlights that an unusual radical-based reaction pathway is operative under ball-milling conditions, divergent from solution-based reactions. The mechanochemical oxidative functionalization is further extended to arene nitration and alkene dibromination reactions, demonstrating the broad applicability of our strategy.

At the outset, bromination of naphthalene (**1a**) was chosen as a model reaction to test the feasibility of our idea. When a mixture of **1a**, $(NH_4)_2S_2O_8$ (**2a**), and LiBr in a 1 : 2 : 2 molar ratio was charged in a 5 mL polypropylene (PP) milling vial with stainless steel (SS) balls (15 balls, diameter: 3.0 mm), and subjected to ball-milling treatment in a mixer mill machine for 2 h at 40 Hz, 1-bromonaphthalene (**3a**) was obtained in 66% NMR yield (Table 1, entry 1). The use of other halides such as NaBr, KBr or NH_4Br afforded lower yields (entry 2). Switching to a smaller vial (2 mL) and utilizing fewer milling balls slightly improved the yield (entries 3–4), apparently providing better filling capacity for more efficient milling. Replacing SS balls with ZrO_2 ones didn't affect the reaction performance (entry 5). This rules out that bromination is promoted by trace metal residues from SS balls. When the reaction time was shortened to 1 h, **3a** was obtained in the best yield of 90% (entry 6), but further reduction of reaction time decreased the yield (entry 7). Exchanging **2a** with either $K_2S_2O_8$ (**2b**) or $Na_2S_2O_8$ (**2c**), or using a different **2a**/LiBr ratio resulted in a lower yield of **3a** (entries 8–12). Meanwhile, a corresponding solution-based (CH_3CN/H_2O = 1 : 1) reaction at 50 °C for 6 h yielded **3i** in 15% yield (entry 13).

With the optimum reaction conditions in hand, we turned our attention to explore the scope of other arene substrates. The results are summarized in Scheme 2. In short, the mechanochemical method is applicable to a wide range of naphthalene derivatives with different electronic properties, including electron-neutral (**3b–e**), electron-donating (**3f–h**), and electron-withdrawing groups (**3i**) in up to 92% yield of the mono-brominated product. Other arenes such as anthracene derivatives (**3j–k**), phenanthroline (**3l**), and fluorene (**3m**) can also be well tolerated. In addition, to demonstrate the practicality of the mechanochemical reaction, a gram-scale reaction using a 15 mL SS milling vessel and one SS ball (diameter: 16 mm) was conducted and it provided **3i** in 72% isolated yield.

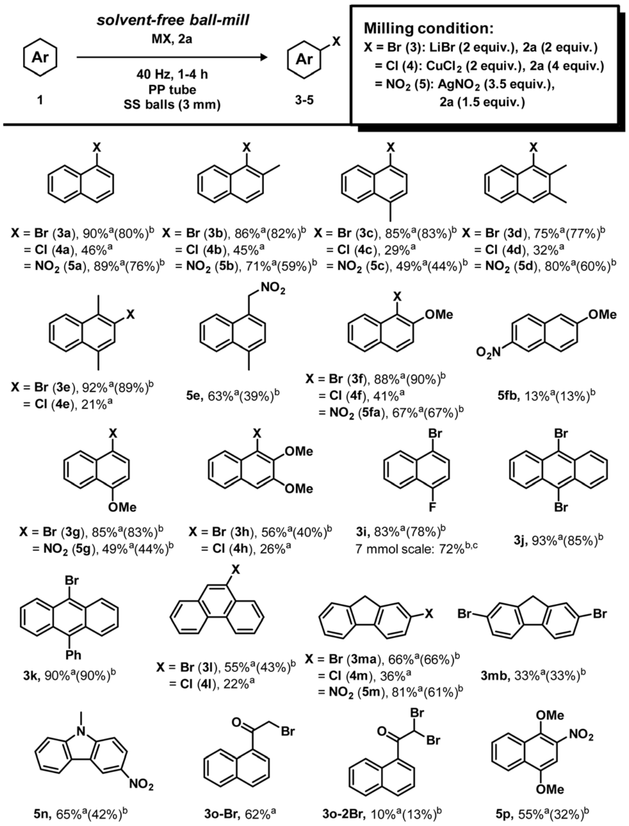
The advantage of this mechanochemical method with persulfate and inorganic halide salts is that it can be easily extended to other C–H functionalization processes with arenes. By employing different inorganic chlorides (MCl) and nitro sources (MNO_n; $n = 2$ or 3), the method can be extended to arene C–H chlorination and nitration (Scheme 2). For chlorination, $CuCl_2$ stood out as the most suitable chlorine source (Table S5). Ball-milling of **2a** with $CuCl_2$ and **1a** afforded 1-chloroanthracene (**4a**) in 46% yield. For nitration, among various inorganic nitro sources tested, $AgNO_2$ performed the best (Tables S7 and S8). Together, these solvent-free methods

Table 1 Reaction condition screening in mechanochemical reactions between **1a**, LiBr, and **2a**.[a]



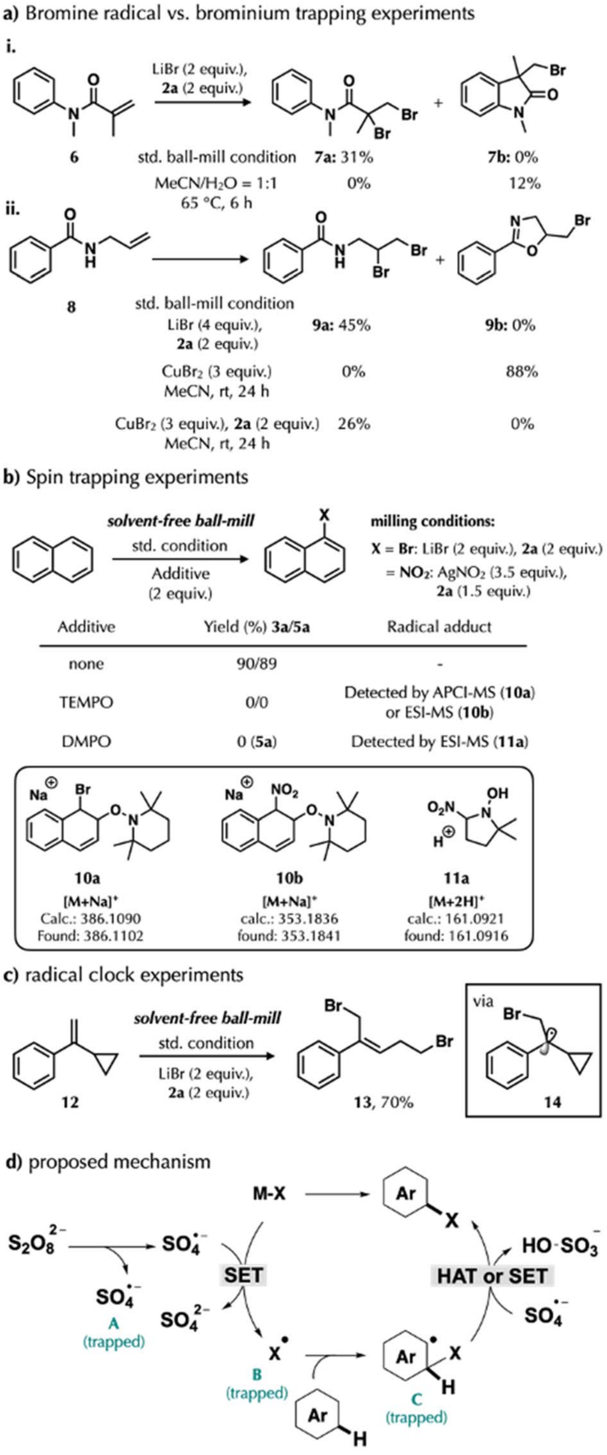
Entry	Tube vol. (mL)	Ball size	*X*	*Y*	Time (h)	Yield **3a**[a] (%)
1	5	SS 15 × 3 mm	2.0	2.0	2	66
2	5	SS 15 × 3 mm	2.0	2.0	2	53[b]/58[c]/7[d]
3	2	SS 15 × 3 mm	2.0	2.0	2	72
4	2	SS 3 × 3 mm	2.0	2.0	2	74
5	2	ZrO_2 3 × 3 mm	2.0	2.0	2	71
6	**2**	**SS 3 × 3.0 mm**	**2.0**	**2.0**	**1**	**90/60**[e]
7	2	SS 3 × 3.0 mm	2.0	2.0	0.5	72
8	2	SS 3 × 3.0 mm	2.0	2.0	1	76[f]/79[g]
9	2	SS 3 × 3.0 mm	2.0	1.5	1	75
10	2	SS 3 × 3.0 mm	2.0	2.5	1	83
11	2	SS 3 × 3.0 mm	1.5	2.0	1	55
12	2	SS 3 × 3.0 mm	2.5	2.0	1	79
13	—	—	2.0	2.0	6	15[h]

[a] Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. LiBr replaced with. [b] NaBr, [c] KBr, or [d] NH_4Br. [e] Milling conducted at a jar temperature of −10 °C. **2a** replaced with [f] $K_2S_2O_8$ or [g] $Na_2S_2O_8$. [h] Solution reactions conducted in CH_3CN/H_2O = 1 : 1 at 50 °C (**1i** as the starting material).



Scheme 2 Substrate scope of mechanochemical C–H bromination, chlorination, and nitration reaction between **1**, X group precursor (LiBr, $CuCl_2$ or $AgNO_2$) and **2a**. ^{a}Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. ^{b}Isolated yield. ^{c}7 mmol scale reaction with a 15 mL SS milling vessel and one SS ball (diameter: 16 mm) for 1 h.

can be applied to numerous arene substrates, achieving chlorination and nitration products in yields up to 45% and 89%, respectively.



Additive	Yield (%) **3a/5a**	Radical adduct
none	90/89	-
TEMPO	0/0	Detected by APCI-MS (**10a**) or ESI-MS (**10b**)
DMPO	0 (**5a**)	Detected by ESI-MS (**11a**)

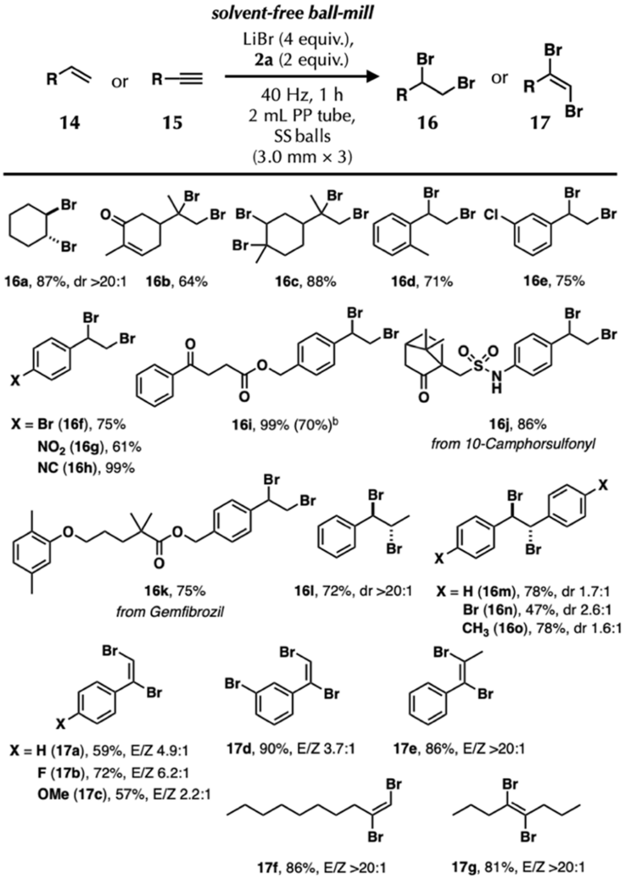
Scheme 3 Mechanistic studies: (a) radical-ionic pathway studies; (b) spin trapping experiments; (c) radical clock experiments; and (d) proposed mechanism.

From a synthetic perspective, the use of persulfate and bromide salts was previously shown to provide a similar C–H bromination outcome.[29] To identify a clear mechanistic difference (if any) between solution-based and solvent-free mechanochemical methods, acrylamide (**6**) was employed under the standard ball-mill conditions (Scheme 3a-i). The reaction provided an alkene dibromination product (**7a**) in 31% yield. Intriguingly, when an analogous reaction was carried out in CH_3CN/H_2O (v/v = 1 : 1) at 65 °C for 6 h, a completely different ring-closing product (**7b**) was obtained, albeit in low yield (12%). The conflicting outcomes strongly supported that the solvent-free method undergoes a radical-based process,[30] while the solution-based reaction follows a brominium (Br^+) pathway.[31] We also ruled out the idea that arene bromination is directed by *in situ* generated Br_2. When **6** was milled in the presence of Br_2, only **7b** was obtained in 23% yield besides the arene bromination product (Fig. S6). **7a** was not detected in the reaction mixture. For additional experimental support, *N*-allylbenzamide (**8**) was also examined (Scheme 3a-ii). In a similar manner, the ball-milling reaction selectively afforded the alkene dibromination product (**9a**) in 45% yield, and the solution reaction with $CuBr_2$, which is known to go through the Br^+ intermediate,[32] gave a dihydrooxazole cyclization species (**9b**) in a decent 88% yield. Intriguingly, simply adding **2a** to the same reaction condition shifts the reaction product from **9b** to **9a**, suggesting the crucial role of **2a** in facilitating radical bromination. The formation of **5e** and **3o-Br**/**3o-2Br** is also indicative of radical-based processes (Scheme 2).

To further confirm the radical-based process, mechanochemical reactions in the presence of various kinds of spin-trapping agents were conducted (Scheme 3b). In the presence of TEMPO (2 equiv.), the reaction was completely suppressed, and **3a** was not observed. In the reaction mixture, **10a** was identified in APCI-MS data (calc. $[M + Na]^+$ 386.1090; found 386.1102). Analogously, the presence of TEMPO or DMPO would also shut down the nitration reaction. In addition to **10b**, nitrogen dioxide radical $NO_2^{\bullet}$ can also be trapped by DMPO, as detected by ESI-MS (**11a**: calc. $[M + 2H]^+$ 161.0921; found 161.0916). Moreover, a radical clock experiment was conducted (Scheme 3c). When a cyclopropyl substrate (**12**) was co-milled with LiBr and **2a**, the ring-opening dibromide product (**13**) was obtained in 70% yield. The formation of **13** provided strong evidence for the involvement of a carbon radical intermediate (**14**), which was generated *via* the addition of the bromine radical to the olefin.

Considering that bromination of **1a** takes place effectively even at low temperature (−10 °C) by ball-milling (Table 1, entry 6), the argument for mechanical force (not thermally driven) to induce persulfate O–O bond homolysis is validated. With these mechanistic insights, we tentatively proposed a mechanism where highly oxidizing $SO_4^{\bullet-}$ (**A**) is generated upon homolysis of persulfate salt **2**, followed by single electron transfer (SET) to generate either an electrophilic halogen or nitrogen dioxide radical (**B**) from the corresponding inorganic salts MX. The addition of **B** to arenes provides a dearomatized radical species (**C**), which could be trapped and detected with TEMPO as shown above. Finally, either a hydrogen atom transfer (HAT) or a SET process with $SO_4^{\bullet-}$ enables the formation of **3–5** (Scheme 3d).

Notably, the mechanochemical radical bromination strategy can be extended to dibromination of alkenes, affording vicinal dibromides, a common structural motif in pharmaceuticals, agrochemicals, and bioactive natural products.[33–35] Conventional methods[36] for vicinal dibromide synthesis typically rely on highly hazardous elemental bromine, posing significant safety concerns. While alternative strategies employing organic bromine sources have been developed, these approaches often require metal catalysts, photosensitizers, or electrochemical setups, along with organic solvents and inert atmospheres.[37–41] More recently, solvent-free mechanochemical methods have emerged, as demonstrated by the pioneering work of Lian[42] and Katayev.[30]



Scheme 4 Substrate scope in mechanochemical vicinal dibromination of alkenes (**14**) or alkynes (**15**) with LiBr and **2a**.[a] [a] Yields and stereochemical ratios determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. [b] Reaction performed on a 3.4 mmol scale with a 15 mL SS milling vessel and one SS ball (diameter: 16 mm) for 1 h.

In our opinion, the combination of LiBr and **2a** was identified as a feasible approach for vicinal dibromination reactions (Scheme 4). Initial optimization of ball-milling conditions revealed that cyclohexene (**14a**), LiBr, and **2a** in a 1 : 4 : 2 ratio afforded *trans*-1,2-dibromohexane (**16a**) in 87% yield (dr > 20 : 1) after 1 h at 40 Hz. The protocol proved equally effective for terminal alkenes (**14b**), while substrates containing both internal and terminal alkenes underwent double dibromination to afford tetrabromide (**16c**) in 88% yield. A broad scope of styrene derivatives (**16d–16l**) was generated, encompassing diverse electronic properties (electron-donating and -withdrawing groups) and complex drug-like scaffolds (10-camphorsulfonyl (**16j**)) and gemfibrozil (**16k**), all of which were compatible with the standard mechanochemical conditions. The solvent-free mechanochemical dibromination can also be conveniently scaled-up (**16i**, Scheme 4). Internal aryl olefins such as **14k** yielded exclusively the *anti*-dibromide product (**16k**), whereas 1,2-diphenylethene (**14l**) provided dibromide **16l** with moderate diastereoselectivity (dr 1.7 : 1). Finally, the methodology was successfully extended to alkynes (**15**), including both aliphatic and aryl-substituted derivatives to produce dibromoolefins (**17**) (Scheme 4). For example, aryl alkynes with different electronic properties work well, affording the corresponding 1,2-dibromoethene species in good yield and decent diastereoselectivity (up to $E : Z$ ratio: 20 : 1).

Conclusions

In summary, we have developed a mechanochemical strategy for C–H bromination, chlorination, and nitration of arenes, mediated by in situ-generated sulfate mechanoradicals ($SO_4^{\bullet-}$). This method was further extended to vicinal dibromination of unactivated alkenes. Mechanistic studies reveal fundamental divergence between mechanochemical and solution-phase pathways. Specifically, ball milling promotes bromine radical formation, whereas solution conditions favor bromonium intermediates (Scheme 3a-i). This dichotomy underscores how mechanochemistry unlocks distinct reaction manifolds that are inaccessible by conventional solution-based methods. The combined advantages of solvent-free conditions and halide/nitrite salts render this approach both environmentally benign and synthetically versatile, with minimal environmental impact (zero carbon content in MX/**2a**). As such, the methodology outlined here offers a different approach distinct from that of prior mechanochemical halogenation reports.[43–45] We anticipate that this work will stimulate broader exploration of mechanical-force-driven radical transformations in organic synthesis.

Author contributions

The work was conceptualized by Y. J., X. G. and K. Y. All experiments were conducted by Y. J., X. G. and T. W. The manuscript was written by K. Y. with input from all the authors. Y. J. and X. G. contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures, reaction optimizations, analytical and spectroscopic information of the products, detailed mechanistic information and green chemistry metrics. See DOI: https://doi.org/10.1039/d5mr00094g.

Acknowledgements

Financial support for this work was generously provided by the ShanghaiTech University start-up funding. We also thank other staff members at the Analytical Instrumentation Center of SPST, and ShanghaiTech University (contract no. SPST-AIC10112914) for characterization support.

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