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Mechanochemical synthesis of organosodium compounds through direct sodiation of organic halides

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Organometallic reagents are essential in organic synthesis, with organolithium compounds being most widely used. However, as lithium becomes less abundant and increasingly expensive, organosodium compounds have emerged as promising alternatives, but their use in organic synthesis is limited by their poor solubility in organic solvents, the need for pre-activated sodium sources and the necessity for highly anhydrous conditions. Here we report a mechanochemical protocol for the direct generation of organosodium compounds from cheap and shelf-stable sodium lumps and readily available organic halides under bulk, solvent-free conditions. These reactions generate an array of organosodium compounds in minutes, without special precautions against moisture or temperature control. These nucleophiles can be used directly for one-pot nucleophilic addition reactions with electrophiles and nickel-catalysed cross-coupling reactions. Furthermore, this mechanochemical approach enables the sodiation of inert C–F bonds in organic fluorides. This method is anticipated to drive progress in sodium-based synthetic chemistry.

Organolithium compounds have played a dominant role as carbon nucleophiles, Brønsted bases and precursors for a variety of other organometallic reagents in organic synthesis for over 100 years (Fig. 1a)[1–4]. Their widespread use is attributed to their relatively high stability in organic solvents, coupled with well-established methods for their preparation[5,6]. However, from a sustainability standpoint, there is an increasing demand for alternatives to lithium, which is becoming both less abundant and more expensive[7]. The growing demand for lithium-ion batteries is expected to further intensify competition for lithium resources[8–10].

Sodium, another *s*-block metal, is much more earth abundant than lithium (crustal abundance 22,700 ppm versus Li abundance 18 ppm)[11] and is therefore an attractive candidate for replacing lithium to explore sustainable organic synthesis (Fig. 1a)[12–23]. The first reports of organosodium chemistry emerged in the 1850s, pioneered by J. A. Wanklyn[24], but substantial challenges exist that have prevented the widespread adoption of organosodium reagents within the field of organic synthesis[25–29]. First, the highly reactive nature of organosodium reagents makes them incompatible with many solvents, including ethers, which can react via C–H and C–O activation, and even aromatic solvents such as toluene and benzene[29]. Only alkane solvents (for example hexanes) can be considered genuinely inert towards organosodiums, but the poor solubility of organosodium reagents in hydrocarbon solvents often causes substantial problems, limiting the potential for widespread application. Second, while direct metallation of organic halides with metallic sodium is an attractive and straightforward synthetic method, it has severe drawbacks: (1) traditional solution-based methods involving direct metallation of organic halides with metallic

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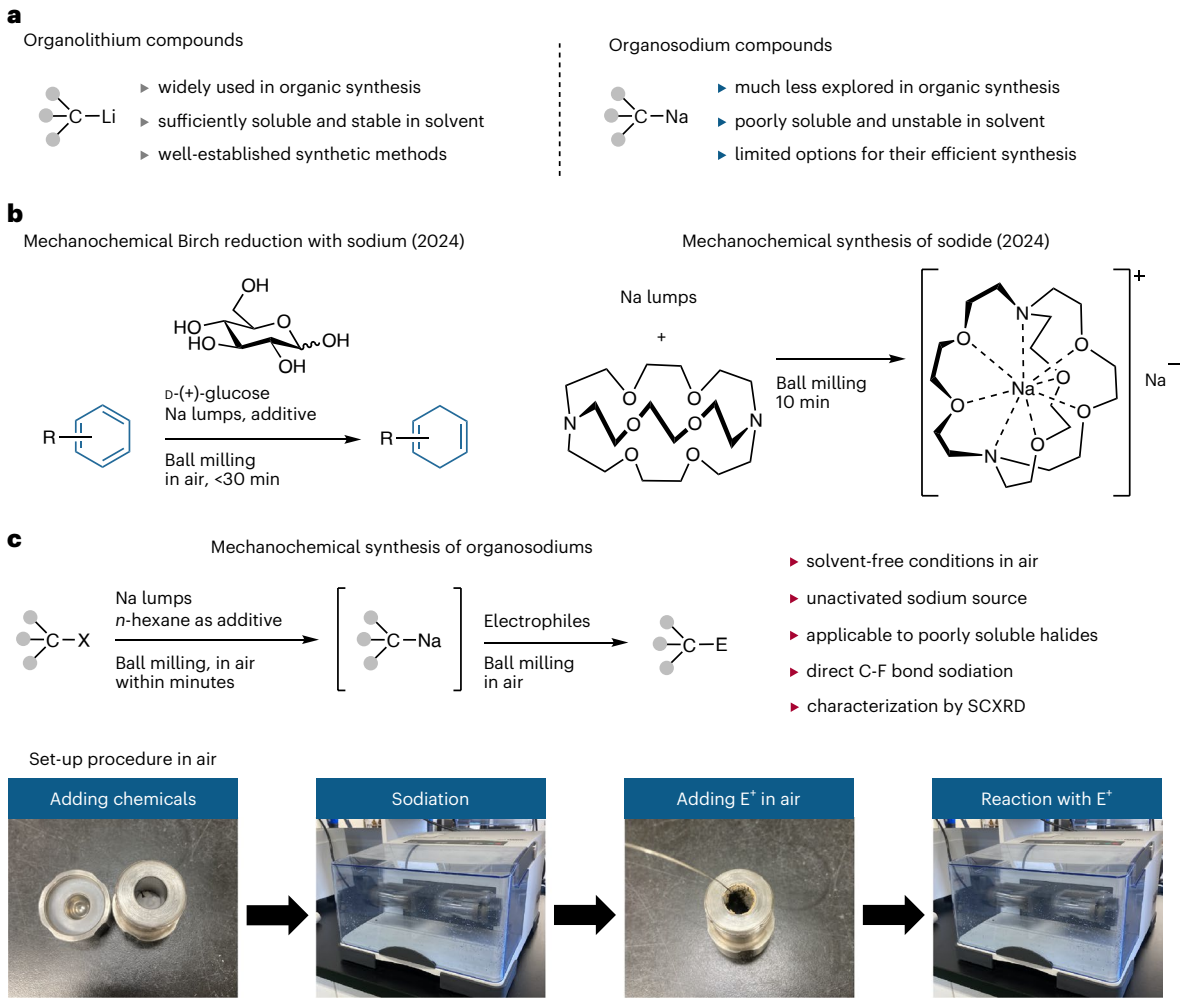

Fig. 1 | Mechanochemical synthesis of organosodium compounds. a, Comparison between organolithium compounds and organosodium compounds. **b**, Previous work involving mechanochemical activation of sodium metal. **c**, Direct mechanochemical synthesis of organosodium compounds through ball milling. E^+, electrophile; SCXRD, single-crystal X-ray diffraction.

sodium suffer from a severe side reaction, Wurtz coupling, where the newly formed organosodium (RNa) reacts with unreacted organohalide (RX) to form the homocoupling product R-R and sodium halide (NaX)[30]; (2) reactions often require a large excess of sodium lumps or unstable, expensive pre-activated sodium sources such as sodium dispersion[13,17]. To avoid Wurtz coupling, the mainstream method to prepare organosodiums is Li–Na exchange, by reacting organolithium (RLi) with sodium *tert*-butoxide (NaO^{t}Bu) to generate RNa and LiO^{t}Bu in a hydrocarbon solvent (usually hexanes), driven by the poor solubility of RNa in these solvents (see above)[31]. This Li–Na exchange still requires Li, which eliminates the sustainability merit of organosodiums. The need for rigorously dry and deoxygenated organic solvents and relatively complex setups involving inert-gas atmospheres presents additional practical drawbacks.

Mechanochemical organic synthesis using ball-milling techniques has emerged as a new methodology to carry out organic synthesis under solvent-free conditions[32–43]. The advantages of this protocol include reduced solvent waste, fast reaction kinetics and operational simplicity under ambient conditions. Furthermore, recent studies have shown that vigorous mechanical agitation can activate zero-valent metals by removing the unreactive surface oxide layer and increasing the reactive surface area[44–53]. These mechanochemically activated, zero-valent metals readily undergo metal–surface reactions with organic halides to produce the corresponding organometallic species efficiently[51]. Surprisingly, by utilizing this strategy, organometallic compounds previously thought to be synthesizable only in solution have been successfully prepared under mechanochemical conditions, including Grignard reagents[54–57], organozinc[58–60], organocalcium[61–63], organomanganese[64,65], organobarium[66] and organolithium reagents[67]. However, the direct mechanochemical synthesis of organosodium compounds has yet to be explored. Recently, mechanochemical activation of sodium lumps has been utilized for highly efficient ammonia-free Birch reduction and the preparation of a sodium anion complex (Fig. 1b)[68,69]. Building on these successful results, we envisioned that a mechanochemical protocol could offer a practical and efficient solution to address the challenges associated with conventional solution-based methods for the preparation and application of organosodium compounds in synthetic chemistry.

In this Article, we report a mechanochemical generation of organosodium compounds from various organic halides and commercially available, cheap and stable sodium lumps and their application to organic synthesis (Fig. 1c). This protocol can be performed under ambient conditions without the need for pre-activated sodium metal, large amounts of anhydrous organic solvents or complex synthetic procedures that require precautions against moisture and strict temperature control. Furthermore, these rapid reactions complete within minutes. This is likely to be due to the mechanical activation of sodium metal in situ. The resulting organosodium species readily react with a

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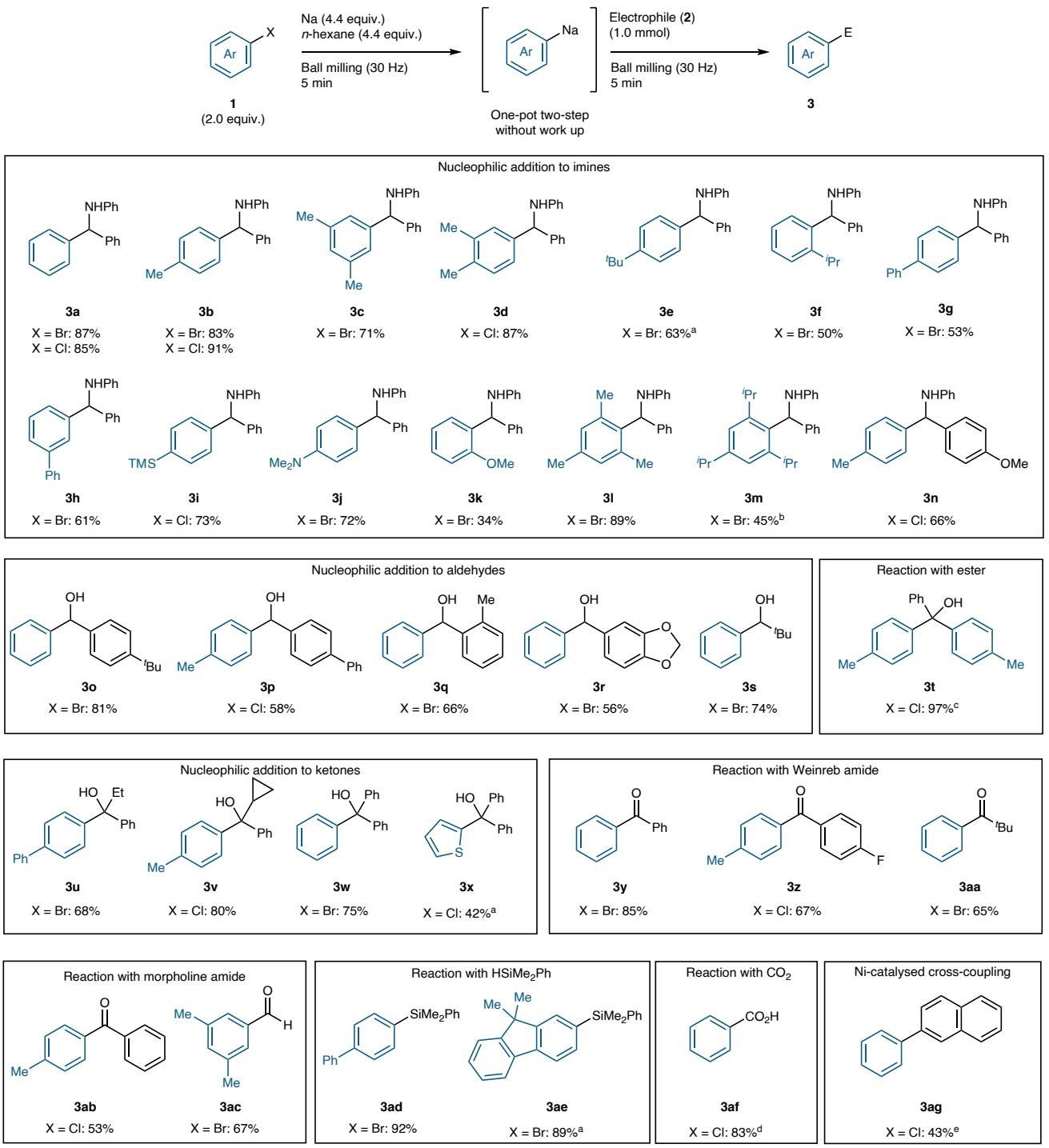

Fig. 2 | Mechanochemical generation of organosodium species and subsequent reactions with various electrophiles. Conditions: **1** (2.0 mmol), Na (4.4 mmol), *n*-hexane (4.4 mmol) and electrophile (1.0 mmol) in a stainless-steel ball-milling jar (5 ml) with a stainless-steel ball (10 mm). Ball milling (30 Hz) was carried out. Isolated yields are reported as percentages. [a]15 min for first step. [b]15 min for first step and 30 min for second step. [c]**1** (3.0 mmol), Na (6.0 mmol) and *n*-hexane (6.0 mmol). [d]First step: **1** (1.0 mmol), Na (2.2 mmol) and *n*-hexane (2.2 mmol) for 5 min. Second step: dry ice (excess) for 30 min. [e]First step: **1** (2.5 mmol), Na (5.0 mmol) and *n*-hexane (5.0 mmol) for 5 min. Second step: Ar–Cl (1.0 mmol), $NiCl_2$(dppe) (0.10 mmol). [*i*]Pr, isopropyl; [*t*]Bu, *tert*-butyl; TMS, trimethylsilyl; pin, pinacol.

wide range of electrophiles in a one-pot mechanochemical process. Nickel-catalysed direct cross-coupling of organosodium compounds with aryl halides also proceeded under mechanochemical conditions. Additionally, this mechanochemical strategy was applicable to the direct sodiation of poorly soluble aromatic halides as well as organic fluorides, which are unreactive towards sodiation under conventional solution-based conditions. Single-crystal X-ray diffraction (SCXRD) analysis and NMR spectroscopy studies were successfully performed to confirm the identity of the key mechanochemically generated organosodium intermediates. Overall, the present study provides a synthetic platform centred on organosodium compounds, which has the potential to replace conventional organolithium-based synthesis with a more sustainable, cost-effective and environmentally friendly approach.

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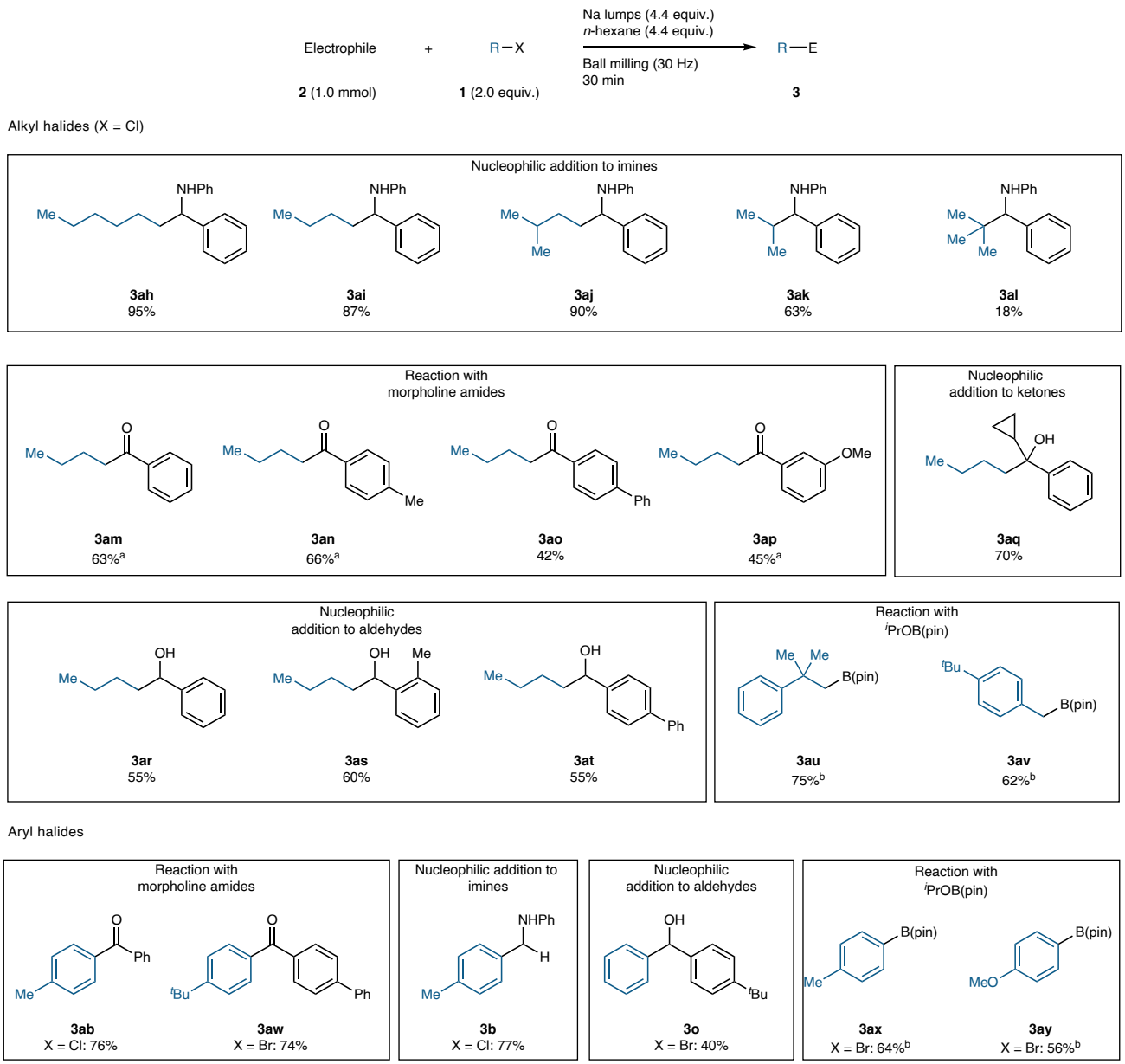

Fig. 3 | Mechanochemical Barbier-type reactions. Conditions: **1** (2.0 mmol), Na (4.4 mmol), *n*-hexane (4.4 mmol) and electrophile (1.0 mmol) in a stainless-steel ball-milling jar (5 ml) with a stainless-steel ball (10 mm). Ball milling (30 Hz) was carried out. Isolated yields are reported as percentages. [a]Addition of *n*-hexane (4.4 mmol). [b]**1** (1.0 mmol), Na (2.2–4.0 equiv.) and ^{i}PrO–B(pin) (2.0 mmol). ^{i}Pr, isopropyl; ^{t}Bu, *tert*-butyl; pin, pinacol.

Results

Mechanochemical generation of aryl sodium compounds and subsequent reactions with electrophiles

We initially attempted the generation of organosodium species through the reaction of bromobenzene (**1a**) with sodium lumps using a Retsch MM400 mixer mill (5 ml stainless-steel milling jar with one stainless-steel ball; ball diameter: 10 mm). The mineral oil on the sodium lumps was removed by wiping them with a paper towel, before the lumps were cut into pieces approximately 4–5 mm in width and depth. Subsequently, the sodium-metal pieces were weighed and introduced into the jar, followed by addition of **1a** under atmospheric conditions. After optimization (see Supplementary Table 1 for details), we established the following mechanochemical protocol for generating organosodium compounds (Fig. 2): ball milling of **1a** (2.0 equiv.) and sodium lumps (4.4 equiv.) in the presence of *n*-hexane (4.4 equiv.) as a liquid additive for efficient grinding was conducted for 5 min. The jar was opened in air and *N*-benzylideneaniline **2a** (1.0 mmol) was added to the reaction mixture. The jar was then quickly closed (without any inert gas purging) and a second phase of ball milling was conducted for 5 min, yielding the desired amine **3a** in excellent yield (87%). The scope of the aromatic halides and electrophiles using this one-pot, two-step mechanochemical protocol is shown in Fig. 2. Phenylsodium could also be generated from chlorobenzene, and subsequent reaction with **2a** produced **3a** in 85% yield. Organosodium species were prepared from various alkylated aryl halides (**1b**–**1f**) and reacted with **2a** smoothly to produce the corresponding amines (**3b**–**3f**) in moderate to excellent yields (50–91%). Biphenyl bromides (**1g** and **1h**) were also readily metallated, and subsequent reaction with **2a** afforded **3g** and **3h** in 53 and 61% yields, respectively. Aryl halides bearing trimethylsilyl, dimethylamino and methoxy groups were compatible with this reaction, and the corresponding amines (**3i**–**3k**) were obtained in moderate to high yields (34–73%). We tested the generation of organosodium compounds from sterically hindered aryl bromides such as mesityl bromide (**1l**) and 2-bromo-1,3,5-triisopropylbenzene (**1m**). Mesityl sodium was efficiently

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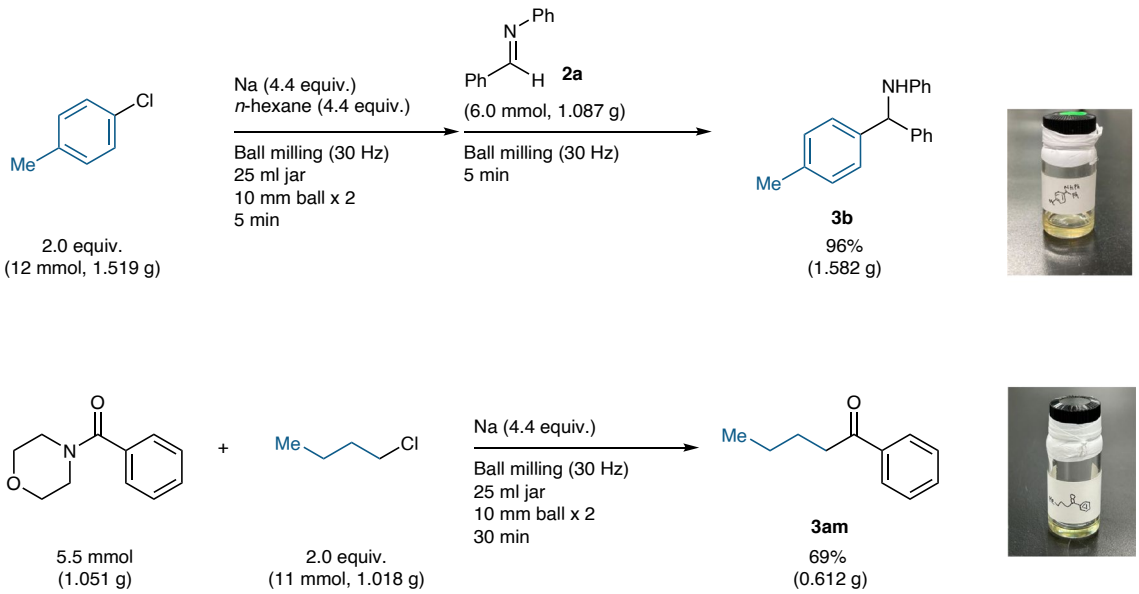

Fig. 4 | Scale-up reactions. Isolated yields are reported as percentages. See Supplementary Section 4 for full details.

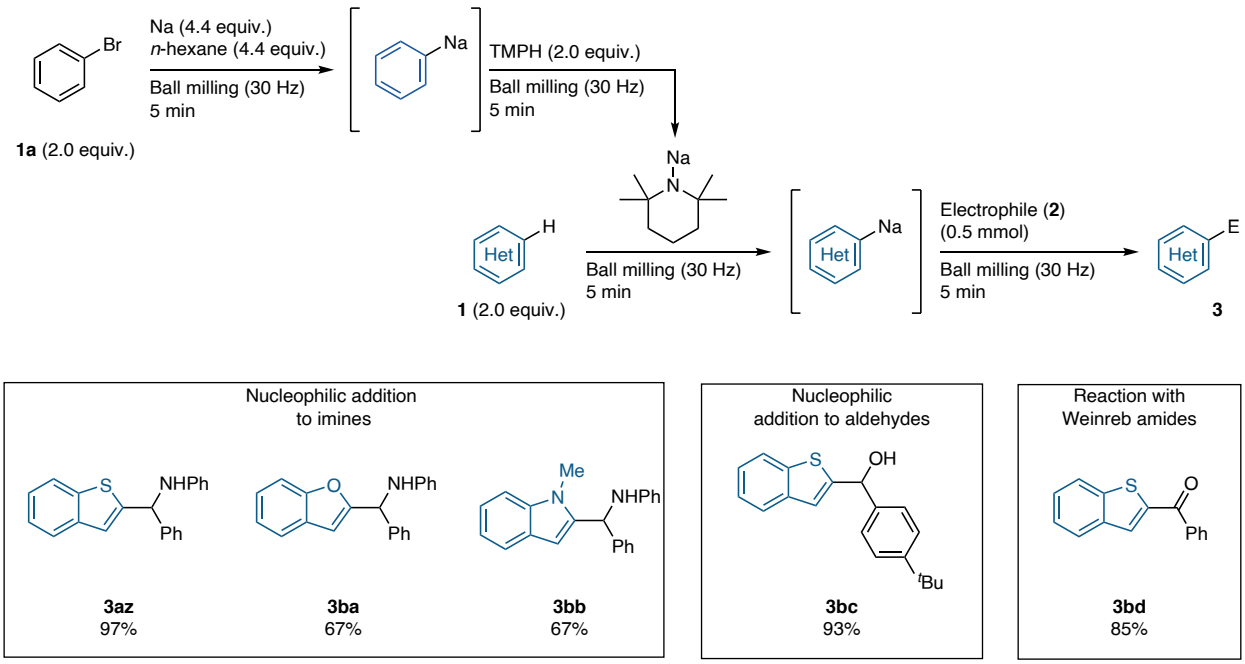

Fig. 5 | Mechanochemical preparation of sodium 2,2,6,6-tetramethylpiperidide (NaTMP). Isolated yields are reported as percentages. Conditions: **1a** (1.0 mmol), Na (2.2 mmol), *n*-hexane (2.2 mmol), TMPH (1.0 mmol), **1** (1.0 mmol) and electrophile (0.5 mmol) in a stainless-steel ball-milling jar (5 ml) with a stainless-steel ball (10 mm). Ball milling (30 Hz) was carried out. See Supplementary Section 3F for full details.

generated, and subsequent nucleophilic addition to **2a** proceeded to give **3l** in 90% yield. A more sterically hindered aryl halide **1m** also underwent direct sodiation under mechanochemical conditions to afford the desired product **3m** in 45% yield. *N*-(4-Methoxybenzylidene) aniline (**2b**) also reacted with the mechanochemically generated aryl sodium compound, 4-tolyl sodium, to give **3n** in 66% yield.

In addition to imines as trapping reagents, aromatic and aliphatic aldehydes also smoothly reacted with mechanochemically generated organosodium compounds to afford the corresponding alcohols (**3o**–**3s**) in moderate to excellent yields (56–81%). Methyl benzoate could also be used as an electrophile and the desired tertiary alcohol **3t** was obtained in 97% yield. Nucleophilic additions to aromatic ketones also proceeded rapidly, providing the corresponding alcohols (**3u**–**3x**) in moderate to excellent yields (42–80%). Additionally, various aromatic ketones (**3y**–**3aa**) were successfully prepared by reactions between organosodium compounds and Weinreb amides in good to excellent yields (65–85%). Morpholine amides were also reactive with the organosodium compounds, and the desired ketone **3ab** and aldehyde **3ac** were obtained in 53 and 67% yields, respectively. Reactions of dimethylphenyl silane ($HSiMe_2Ph$) with the organosodium compounds bearing biphenyl and fluorene moieties provided the corresponding silylated products **3ad** and **3ae** in 92 and 89% yields, respectively. Mechanochemically generated phenylsodium could be trapped by dry ice, and benzoic acid **3af** was obtained in 83% yield. The feasibility

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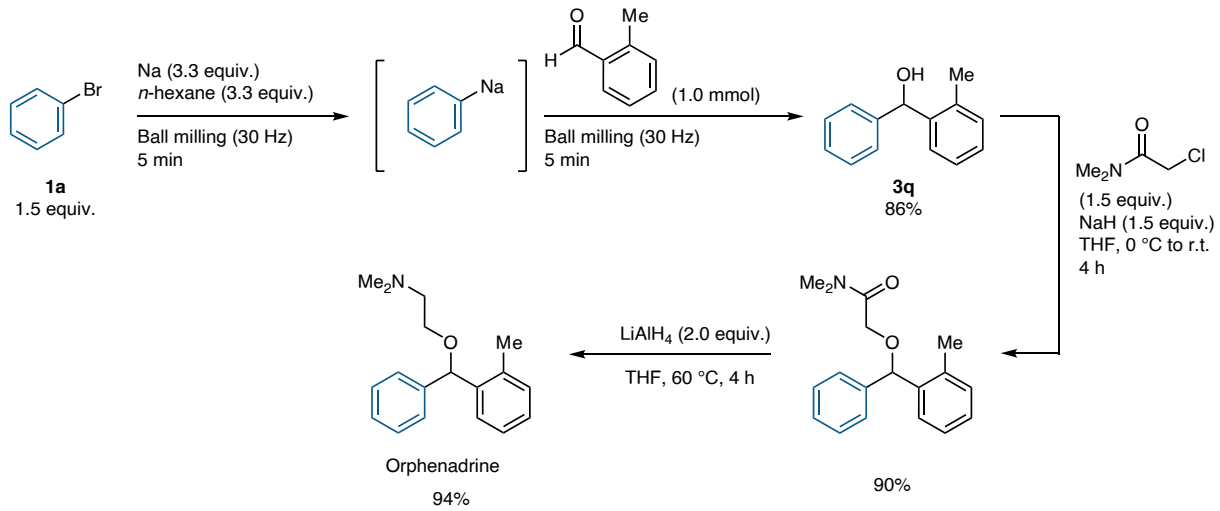

Fig. 6 | Synthesis of orphenadrine using mechanochemically generated phenylsodium. Isolated yields are reported as percentages. TMPH, 2,2,6,6-tetramethylpiperidine; THF, tetrahydrofuran; r.t., room temperature. See Supplementary Section 6 for full details.

of mechanochemical nickel-catalysed cross-coupling reaction with organosodium compounds was also investigated[70]. Following catalyst optimization (see Supplementary Table 2 for details), we found that $NiCl_2$(dppe) (dppe, 1,2-bis(diphenylphosphino)ethane) was an ideal catalyst for this reaction, and the cross-coupling between phenylsodium and 2-chlorolonapthalene gave the corresponding coupled product **3ag** in 43% yield. In our substrate scope studies, side products such as homocoupled products of organic halides were not detected.

One-pot, one-step reactions for various organosodium compounds

Unfortunately, unlike aryl halides, alkyl halides proved difficult to use in one-pot, two-step reactions, and the desired products were not obtained. This was probably due to rapid decomposition of the reactive alkyl sodium intermediates formed during the metallation step. To address this limitation, we explored one-pot, one-step transformations in which the electrophile was introduced at the start of the reaction, enabling trapping of the reactive organosodium intermediate as soon as it was formed (Fig. 3). Pleasingly, we found that employing this Barbier-type approach, a reaction between 1-chlorohexane, sodium lumps and imine **2a** proceeded smoothly to provide the corresponding amine **3ah** in 95% yield. Shorter and branched primary alkyl chlorides could also be used for this reaction, and the desired products **3ai** and **3aj** were obtained in 87 and 90% yields, respectively. Reactions using secondary and tertiary alkyl chlorides produced the corresponding amines **3ak** and **3al** in 63 and 18% yields, respectively. Fortunately, morpholine amides were also compatible under these strongly reducing conditions, enabling nucleophilic acyl substitution with *n*-butyl sodium to deliver the corresponding ketones (**3am**–**3ap**) in 42–66% yield. Nucleophilic addition to cyclopropyl phenyl ketone also readily proceeded and alcohol **3aq** was obtained in 70% yield. Aldehyde electrophiles were also compatible, enabling access to secondary alcohol products (**3ar**–**3at**) in moderate to good yields (55–60%). Additionally, mechanochemical borylation of in situ-generated primary alkyl sodium species provided the corresponding boronic esters **3au** and **3av** in yields of 75 and 62%, respectively (in the latter case, 5% of Wurtz-type homocoupled product was detected as a minor side product).

We also applied this operationally simple one-pot, one-step protocol to reactions using aryl sodium compounds (Fig. 3). Under our optimized conditions, both 4-chlorotoluene and 4-*tert*-butylbromobenzene reacted with morpholine amides to furnish the corresponding ketones **3ab** and **3aw** in 76 and 74% yields, respectively. Nucleophilic additions of aryl sodium compounds to aldimine **2a** and 4-*tert*-butylbenzaldehyde were also investigated, and the desired products **3b** and **3o** were successfully obtained in 77 and 40% yields, respectively. One-pot, one-step borylations were applied to 4-bromotoluene and 4-bromoanisole to deliver boronic esters **3ax** and **3ay** in 64 and 56% yields, respectively. These results are comparable to the corresponding one-pot, two-step reactions (Fig. 2).

Gram-scale reactions and applications to prepare sodium 2,2,6,6-tetramethylpiperidide

To underline the practical utility of our developed mechanochemical protocol, we investigated its use in preparative-scale reactions (Fig. 4). 4-Tolyl sodium was successfully prepared on a 12-mmol scale under mechanochemical conditions, and its nucleophilic addition to aldimine **2a** gave **3b** without any decrease in efficiency (96%, 1.582 g) compared to small-scale synthesis. Likewise, a one-pot, one-step reaction between 1-chlorobutane and 4-benzoylmorpholine was also carried out on a gram scale to furnish **3am** in 69% yield. These results underscore the practical utility of this protocol.

To further expand the range of synthetically accessible organosodium compounds, we explored C–H sodiation of heteroaromatic arenes using a mechanochemically generated sodium amide (Fig. 5)[71]. We were delighted to find that sodium 2,2,6,6-tetramethylpiperidide (NaTMP) could be generated by the reaction between phenylsodium and 2,2,6,6-tetramethylpiperidine (TMPH), and employed to deprotonate benzothiophene. Subsequent addition to aldimine **2a** proceeded smoothly to afford **3az** in 97% yield. Benzofuran and 1-methylindole were also deprotonated by mechanochemically generated NaTMP and the resulting organosodium compounds reacted with aldimine **2a** to produce **3ba** and **3bb** in good yields. Aldehyde and Weinreb amide electrophiles could also be employed as electrophiles, delivering the corresponding alcohol (**3bc**) and ketone (**3bd**) products in yields of 93 and 85%, respectively.

To highlight the synthetic utility of our developed mechanochemical protocol, we applied it to synthesize the drug molecule orphenadrine, an anticholinergic agent used to treat painful muscle spasms (Fig. 6). After minor optimization, the generation of phenylsodium, followed by nucleophilic addition to 2-methylbenzaldehyde under mechanochemical conditions, afforded the intermediate **3q** in 86% yield. Subsequent alkylation and reduction with $LiAlH_4$ yielded orphenadrine in 85% yield over two steps.

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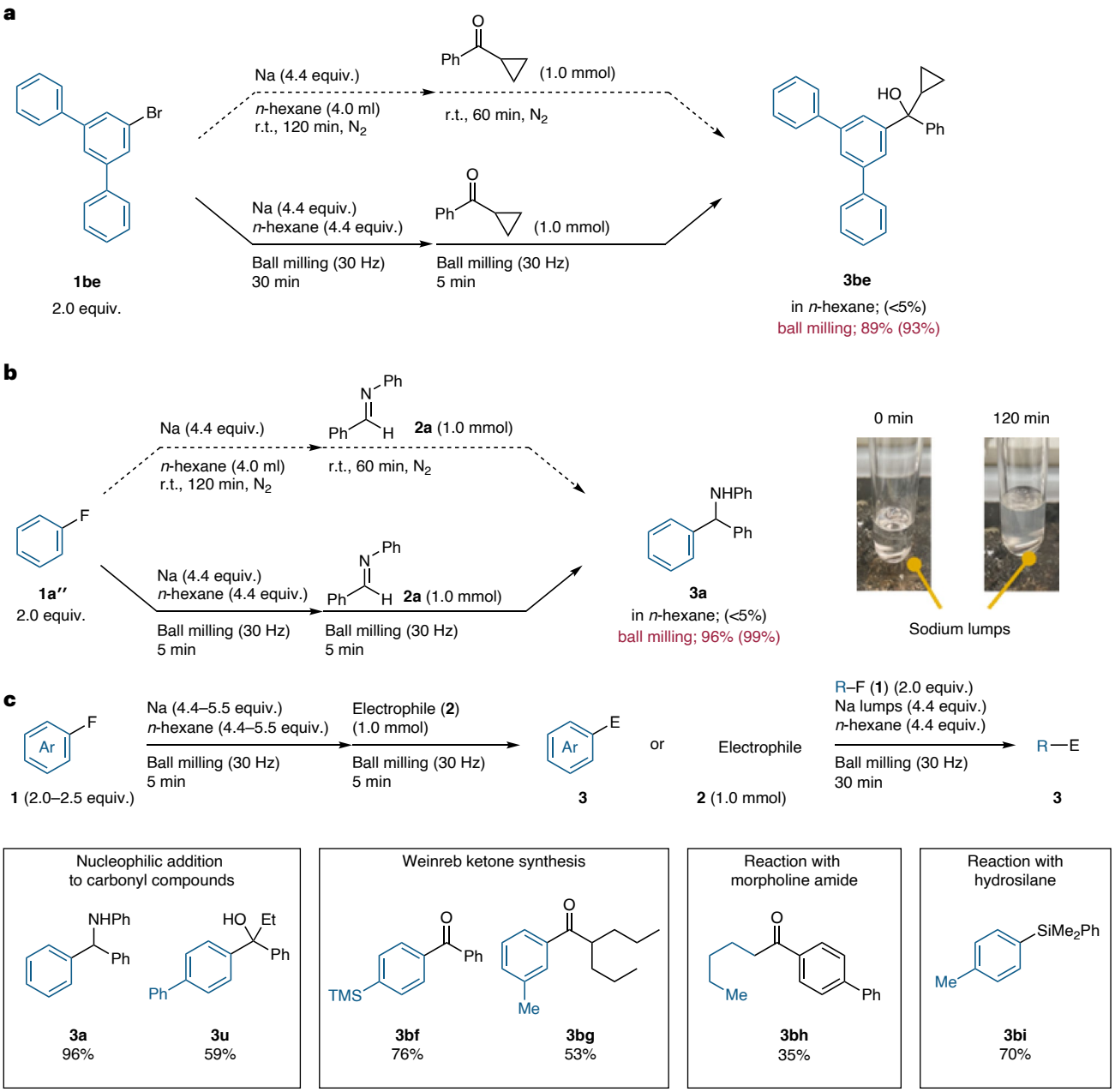

Fig. 7 | Direct sodiation of a poorly soluble halide and organofluorides. **a**, Generation of organosodium compounds from a poorly soluble halide and nucleophilic addition to ketone. **b**, Generation of organosodium compounds from an organofluoride and nucleophilic addition to **2a**. **c**, Various Na-meditated transformations of C–F bonds. Isolated yields are reported as percentages. Integrated ^{1}H NMR spectroscopy yields are shown in parentheses. TMS, trimethylsilyl. See Supplementary Section 5 for details.

Preparation of organosodium compounds from poorly soluble aromatic halides and organic fluorides via C–F bond cleavage

Due to the high basicity of organosodium species, the scope of available solvents is limited to simple hydrocarbon solvents. Therefore, aryl halides containing a large π-conjugated system, which are often sparingly soluble in such solvents, are difficult to directly sodiate under conventional solution-based conditions. For example, 1-bromo-3,5-diphenylbenzene (**1be**) is poorly soluble in *n*-hexane, and an attempted solution-state sodiation followed by addition to cyclopropyl phenyl ketone did not afford the desired product **3be** (Fig. 7a). By contrast, we were delighted to find that our mechanochemical protocol was successfully able to deliver alcohol **3be** in excellent yield (89%), highlighting the potential of this approach to access organosodium compounds that cannot be accessed via conventional solution-based reactions.

In a similar vein, we also explored the generation of organosodium species from organic fluorides via inert C–F bond cleavage (Fig. 7b)[72]. Direct metallation of organofluorine compounds is challenging because it involves breaking a strong C–F bond, and reports on the direct sodiation of fluoroarenes with unactivated sodium lumps are lacking[73]. Indeed, an attempted solution-phase (*n*-hexane) sodiation of fluorobenzene followed by addition of aldimine (**2a**) resulted in no product formation. On the other hand, we discovered that phenylsodium was rapidly generated from fluorobenzene in 5 min under mechanochemical conditions, and subsequent nucleophilic addition to aldimine **2a** furnished **3a** in 96% yield. We found that other sodium-meditated transformations via C–F bond activation were feasible under mechanochemical conditions (Fig. 7c). For example, sodiation of 4-fluorobiphenyl also proceeded smoothly, and nucleophilic

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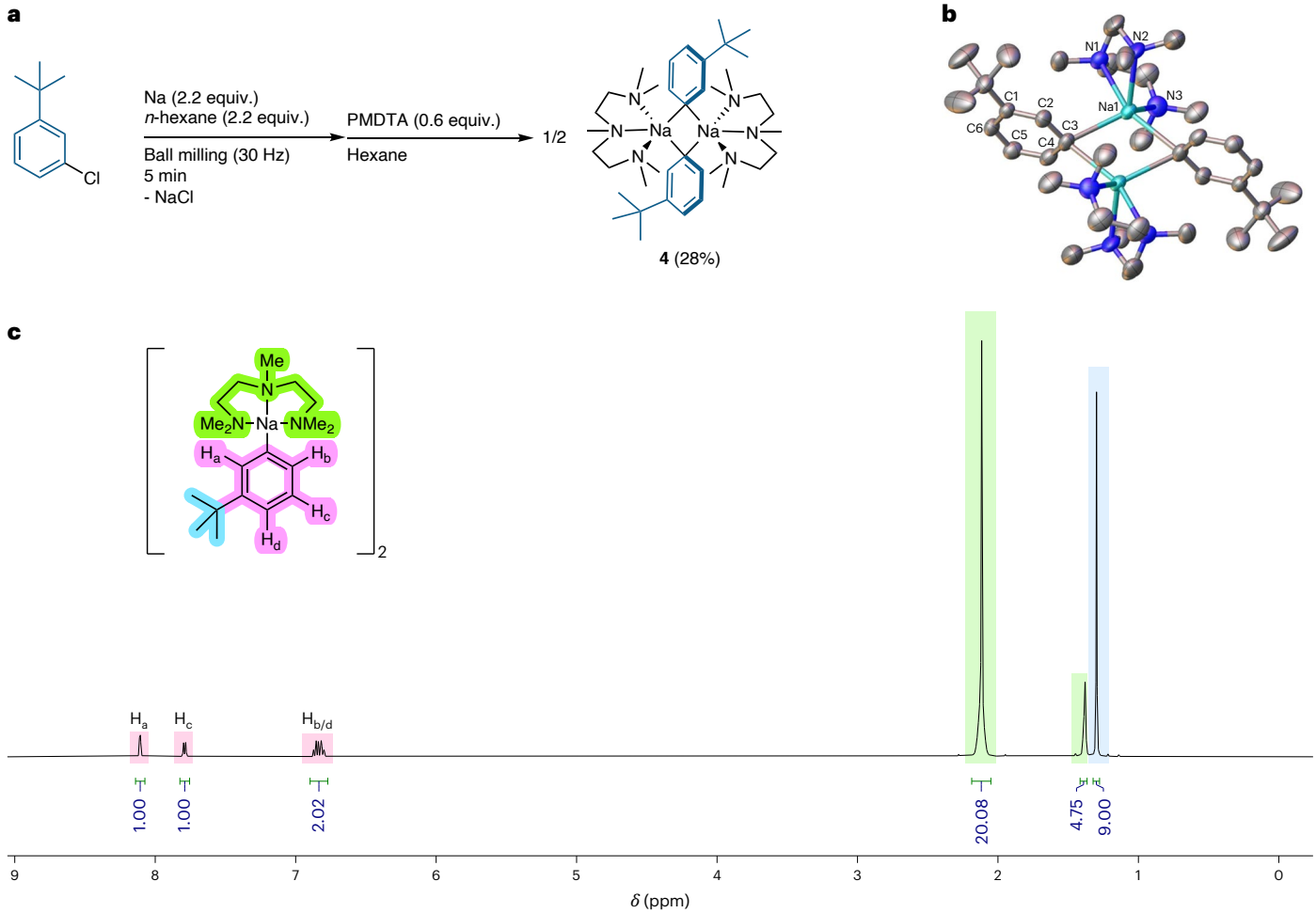

Fig. 8 | Isolation of a mechanochemically generated organosodium complex and single-crystal X-ray diffraction studies. a, Mechanochemical synthesis of [3-(*tert*-butyl)phenyl]sodium followed by ligation with PMDTA and crystallization to afford [Na(μ^C-3-^{t}Bu-C_6H_4)(κ^3-*N,N',N''*-PMDTA)]$_2$ (**4**). **b**, Single-crystal X-ray structure of **4**. For clarity only the disordered components with the highest occupancy are depicted and hydrogen atoms are omitted. Key bond lengths (Å): Na1–C3 2.616(2), Na1–C3A 2.643(2), Na1–N1 2.663(9), Na1–N2 2.565(5), Na1–N3 2.547(9). **c**, ^{1}H NMR spectrum of **4** (d_{12}-cyclohexane, 298 K). The colours in the ^{1}H NMR spectrum indicate which signals correspond to the protons of compound 4. PMDTA, *N,N,N′,N′,N′*-pentamethyldiethylenetriamine.

addition to phenyl ethyl ketone produced **3u** in 59% yield. Likewise, fluoroarenes bearing trimethylsilyl (TMS) and methyl groups could also be successfully sodiated, and nucleophilic substitutions with Weinreb amides afforded the corresponding ketones **3bf** and **3bg** in 76 and 53% yields, respectively. A Barbier-type reaction between [1,1′-biphenyl]-4-yl(morpholino)methanone and 1-fluoropentane afforded **3bh** in 35% yield. 4-Tolyl sodium could be generated from 4-fluorotoluene and reacted with $HSiMe_2Ph$ to give the silylation product **3bi** in 70% yield.

Structural evidence for the generation of organosodium species through isolation of a mechanochemically generated organosodium compound and structural studies

Finally, to offer unambiguous evidence for the mechanochemical generation of the Na–C bond during our reactions, we attempted to isolate and characterize a mechanochemically generated organosodium compound. For these structural studies, we selected a model aromatic organosodium bearing a lipophilic *tert*-butyl substituent, which we hoped would ensure sufficient hydrocarbon solubility to enable crystallization. Given that organosodium compounds are well known to form poorly soluble aggregates[74] that could hamper their study by SCXRD, we also introduced a neutral amine ligand, namely *N,N,N′,N′,N′*-pentamethyldiethylenetriamine (PMDTA), to break up these aggregates and form a soluble compound, allowing for crystallization.

Accordingly, under an argon atmosphere, 3-chloro-*tert*-butylbenzene and 2.2 equiv. of Na metal were ball milled with 2.2 equiv. of *n*-hexane according to our standard optimized conditions (Fig. 8). The crude product was treated with 0.6 equiv. of PMDTA solution in *n*-hexane followed by filtration to remove NaCl. Concentration followed by crystallization from *n*-hexane solution at −35 °C afforded a dimeric PMDTA-coordinated organosodium compound [Na(μ^C-3-^{t}Bu-C_6H_4)(κ^3-*N,N′,N′*-PMDTA)]$_2$ (**4**) (28% yield based on 1-(*tert*-butyl)-3-chlorobenzene). The single-crystal X-ray diffraction structure of **4** is shown in Fig. 8b, featuring two bridging phenyl groups, with Na–C bond lengths within the range 2.61–2.65 Å. Solution state characterization of **4** was also performed by ^{1}H, ^{13}C and ^{23}Na NMR spectroscopy in d_{12}-cyclohexane. The ^{23}Na NMR spectrum of **4** features a broad signal at −14.90 ppm (line width at half height $LW_{1/2}$ approximately 10 ppm), which matches reported Na^+ cation signals[69]. The ^{1}H NMR spectrum of **4** clearly exhibits a characteristic pattern of four protons consistent with a 1,3-disubstituted phenyl group, and the PMDTA remains coordinated (Fig. 8c). The ^{13}C NMR spectrum (d_{12}-cyclohexane) of **4** features a Na–C^{sp2} quaternary carbon signal at 195.1 ppm similar to other PMDTA-ligated aryl sodium complexes described in the literature[75]. The NMR spectra indicate that the SCXRD structure of **4** persists in solution in cyclohexane—this is particularly important in organo-alkali metal chemistry, where fast equilibria are often prevalent, such as ligand coordination–dissociation and

deprotonation–reprotonation. The isolation and characterization of **4** unambiguously supports the formation of a Na–C bond during the mechanochemical sodiation reactions in our methodology.

Discussion

Organosodium compounds have garnered substantial attention as promising, sustainable alternatives to organolithium reagents. However, their practical and widespread application in organic synthesis has been hindered by the lack of efficient generation methods using easy-to-handle sodium sources and their limited solubility in organic solvents. This study demonstrates that a mechanochemical protocol can overcome these challenges, enabling rapid synthesis of a wide range of organosodium compounds, including aryl, primary, secondary alkyl and benzylic examples from inexpensive, abundant sodium lumps and organic halides within minutes, without the need for large volumes of solvents or complex inert-gas techniques. The resulting mechanochemically generated organosodium compounds react smoothly with various electrophiles in a one-pot manner (either stepwise or Barbier-type conditions), negating any requirement to isolate the organosodium intermediates. The operational simplicity of the procedure, in particular the ability to proceed without exclusion of air is especially noteworthy, substantially lowering the barrier for synthetic chemists to make and apply these reagents. Notably, this method facilitated the direct sodiation of poorly soluble halides, which are typically unreactive to sodiation under solution-based conditions. Furthermore, the study revealed that the sodiation of organofluorides, which are generally inert in solution, could be achieved via C–F bond cleavage under mechanochemical conditions. These findings highlight the effectiveness of this mechanochemical approach in expanding the accessible scope of organosodium chemistry. Finally, the isolation and characterization of mechanochemically generated organosodium compounds by single-crystal X-ray analysis and NMR spectroscopy was performed, providing unambiguous support for the key organosodium species proposed in this methodology. Given the increasing demand for organosodium compounds, this efficient and straightforward mechanical strategy is expected to advance the development of sodium-based synthetic chemistry, contributing to more sustainable syntheses of value-added molecules.

Methods

Representative procedure for the virtually solvent-less synthesis of sodium-based carbon nucleophiles and their reactions with electrophiles

Sodium lumps (4.4 equiv.) were cut into small pieces (approximately 4–5 mm in width and depth) and weighed in air after wiping off the mineral oil on them with paper. These were then added into a milling jar (5 ml) with a ball (10 mm diameter). An organic halide (2.0 equiv.) and *n*-hexane (4.4 equiv.) were added to the jar. After the jar was closed without purging with inert gas, it was placed in the ball mill (Retsch MM400, 30 Hz). After grinding for 5 min, the jar was opened in air and charged with an electrophile (1.0 mmol, 1.0 equiv.) as quickly as possible. The jar was then closed without purging with inert gas, and was placed in the ball mill (Retsch MM400, 30 Hz). After grinding for 5 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (30 ml × 3). The solution was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The crude material was purified by flash chromatography (SiO_2, typically EtOAc/*n*-hexane, typically 0–10:90) to give the corresponding product.

Data availability

The data that support the findings of this study are available in the Article and its Supplementary Information. For full characterization data, including NMR spectra of the new compounds and experimental details, see the Supplementary Information. The X-ray crystallographic coordinates for the structure reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 2423000 (**4**). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

R.J.A., E.L., K.K. and H.I. conceived and designed the study. All authors co-wrote the paper. K.K. and M.L. performed chemical experiments and analysed the data. N.D. performed preliminary piloting experiments at an early stage of this project. P.G.W. collected and refined the single crystal structure of **4**. All authors discussed the results and the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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