

Birch reductive arylation by mechanochemical anionic activation of polycyclic aromatic compounds

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Birch reduction is a well-known process for transforming aromatic compounds. The reduction of aromatic rings using alkali metals produces anionic species that react with protons or electrophiles. Generally, this reaction is accompanied by significant limitations in the available nucleophiles, since in most cases only alkyl halides and silyl chlorides are available. In particular, the arylation of unfunctionalized polycyclic aromatic hydrocarbons (PAHs), so-called Birch reductive arylation, has not yet been investigated. Herein, we report a Birch reductive arylation by mechanochemical anionic activation using a lithium(0) wire, followed by addition of various fluoroarenes. Specifically, not only Birch reductive arylation products but also formal C–H arylation products can be obtained from unfunctionalized PAHs, achieving one-pot annulative π -extension to give nanographenes. This process is a unique reaction that is rarely achieved in solution, and shows the interesting reactivity of lithium metal and fluoroarenes in the solid state.

The transformation of readily available aromatic compounds is considered one of the main methods of organic synthesis. In particular, connecting aromatics and extending π -systems have been extensively performed for synthesizing polyarylenes and polycyclic aromatic hydrocarbons (PAH) with intriguing properties^{1,2}. Except for cross-coupling reactions using halogenated and metalated arenes, Birch reductive functionalization is a classical representative transforming method for preparing arene-derived compounds via dearomative functionalization³. In the Birch reductive alkylation, the reduction of the aromatic ring using alkali metals initially produces anionic species^{4–7}, which are further reacted with electrophiles such as alkyl halides (Fig. 1a). This protocol is widely used in natural product synthesis and other fields but has almost only been applied to small aromatics such as benzenes and biphenyls^{8–10}. As recent examples, reductive alkylation biphenyls and PAHs with fluoroalkanes was reported by Albert and Miguel in 2007¹¹. Birch reductive silylation of anthracene with chlorotrimethylsilane was also reported by Kanno in 2013¹². Furthermore, in 2021, Yorimitsu and co-workers reported the reductive borylation of anthracene using highly reactive

sodium dispersion and methoxyboronic acid pinacol ester (MeOBpin)¹³. They also developed the multi-methylation of corannulene in a similar reaction system¹⁴. The generated anionic arene species are unstable under air and thus require immediate trapping with electrophiles such as co-existing proton (Birch reduction) or post-adding alkyl halides (Birch reductive alkylation)^{15–18}. However, no example of trapping the anionic arene species with aryl halides, i.e., ‘Birch reductive arylation’ have been reported so far, whereas inter-/intramolecular dearomative hydroarylations of arenes are achieved by radical and photocatalytic reactions¹⁹. One of simple potential pathways to afford Birch arylation products from simple aromatics would be nucleophilic aromatic substitution (S_NAr) of fluoroarenes with reduced arene nucleophiles. However, even S_NAr using inert fluoroarenes and carbon nucleophiles is expected to pose considerable challenges, and had not been achieved until the recent demonstration by Shigeno et al. using organic superbases²⁰. Such untapped “Birch reductive arylation” is challenging but has been regarded as an important missing piece in fundamental organic chemistry and polyaromatics synthesis.

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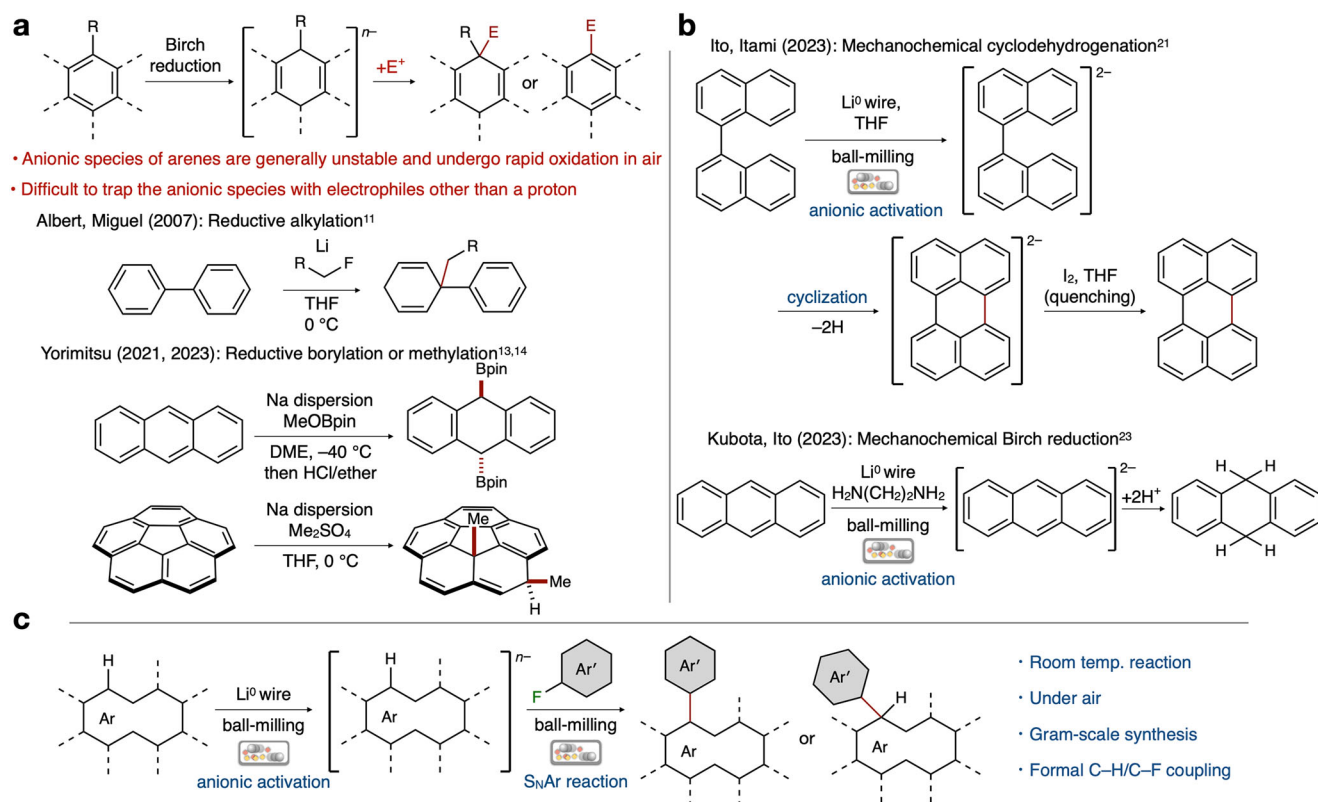


Fig. 1 | Li-mediated Birch reductive transformations and related reactions. a Birch reductive transformations of arenes. **b** Lithium-mediated mechanochemical reactions. **c** This work.

We recently developed Li(O)-mediated mechanochemical cyclodehydrogenation using a ball-milling machine for the efficient and rapid synthesis of PAHs (Fig. 1b)²¹. Although bulk Li commonly exhibits low reactivity in the solution state, the mechanochemical direct grinding with pieces of lithium(0) wire and 1,1'-binaphthyl results in the efficient formation of aromatic anion followed by cyclization and dehydrogenation, realizing the efficient and rapid synthesis of rylene-type nanographenes. Mechanochemical Birch reduction using $K^+(LiHMDS)\cdot e^-$ (HMDS: 1,1,1,3,3,3-hexamethyldisilazide), Li(O) and Mg/Ca²² were also reported by Lu²³, Kubota/Ito²² and Aav/Kanovich²⁴ groups. The process developed by Kubota/Ito was realized via the mechanochemical grinding of aromatic compounds using a lithium(0) wire and an ethylene diamine additive afforded hydrogenated arenes such as 1,4-cyclohexadienes and 9,10-dihydroanthracene²³. A key feature in both reactions is the efficient and rapid generation of aromatic anion species using less reactive bulk lithium even under air at ambient temperature, without the use of a solvent or ammonia via “mechanochemical anionic activation,” which has been hardly achieved in the solution state^{25,26}. This type of mechanochemical reaction shows great potential for achieving efficient and practically known reactions and unknown challenging transformations specific to solid-state, thus significantly contributing to the further development of organic synthesis^{25,27–38}.

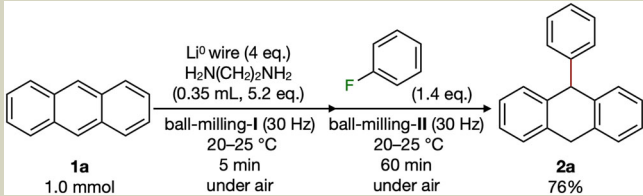
Herein, we report the C–C bond-forming S_NAr type Birch reductive arylation via the mechanochemical anionic activation of unfunctionalized PAHs using lithium(0) and fluoroarenes. By directly mixing pieces of easy-to-handle lithium(0) wire, PAHs, and stoichiometric amine additives using a ball-milling machine, the formation of aromatic anions, followed by the stepwise addition of fluoroarenes, enabled S_NAr -type reactions to afford arylated and hydroarylated PAHs. Depending on the reaction conditions and substrates, diverse unprecedented arylation processes have been achieved to produce mono-, di-, tetra-arylated PAHs and dihydro PAHs. Furthermore, the

synthesis of large PAHs using commercially available unfunctionalized aromatic compounds has been conducted via sequentially mechanochemical S_NAr reaction and mechanochemical cyclodehydrogenation¹⁹. Although related cross-coupling reactions using fluoroarenes and aryl metals via transition metal catalysis³⁹ and the Birch reductive arylation of arenes with alkyl halides have been reported, C–C bond forming reaction using unfunctionalized (less reactive) aromatic hydrocarbons with fluoroarenes is highly challenging and have not been achieved yet. Regardless of the reaction type and mechanism, the direct use of easily available unfunctionalized aromatics is highly desirable in organic synthesis. Such a long-awaited process is achieved via mechanochemical anionic activation.

Results and discussion

Modification of reaction conditions

We began our investigation with the Birch reductive arylation of anthracene **1a** (Table 1). Following previous work on mechanochemical Birch reduction, ethylenediamine was selected as the additive for stabilizing anion species²². By investigating the reaction conditions, we observed the unprecedented Birch reductive arylation of **1a** with fluorobenzene (PhF), yielding 9-phenyl-9,10-dihydroanthracene (**2a**), which can also be obtained by Birch reduction of 9-phenylanthracene⁴⁰. The protocol is as follows: (1) 1.0 mmol of **1a** (1 eq.), a piece of lithium wire (4.0 eq.), ethylenediamine (0.35 mL, 5.2 eq.) were weighed in air and added to a 5.0 mL stainless-steel jar along with two 7 mm stainless-steel balls, which were closed in air and then subjected to ball-milling at a rate of 30 Hz for 5 min (ball-milling-I); (2) after opening the jar, fluorobenzene (PhF, 1.4 eq.) was rapidly added to the dark black reaction mixture in air, and additional ball-milling was performed for 60 min at room temperature (20–25 °C) (ball-milling-II). Then, lithium and the anionic species were quenched by water, yielding the arylated product **2a** in 76% NMR yield and 73% isolated yield (Table 1, entry I). Based on the high magnetic field-shifted peaks in ¹H

Table 1 | Screening of conditions for Birch reductive arylation with fluorobenzene


Entry	Deviations from the standard conditions	Yield of 2a ^a
1	None	76% (73%) ^b
2	Ball-milling-II for 0 min and PhF was added dropwise to the jar over 5 min	Trace
3	Ball-milling-II for 5 min	18%
4	Li (2.0 eq.) instead of 4.0 eq.	48%
5	Na instead of Li	17%
6	PhCl instead of PhF	0%
7	PhBr instead of PhF	Trace
8	PhOSO ₂ CF ₃ or PhOSO ₂ Me instead of PhF	0%
9	<i>N,N</i> -Dimethylethylenediamine (0.35 mL, 3.3 eq.) instead of ethylenediamine	0%
10	TMEDA (0.35 mL, 2.3 eq.) instead of ethylenediamine	11%
11	THF (0.35 mL, 6.0 eq.) instead of ethylenediamine	75% (70%) ^b
12	2.5 mmol (0.45 g) scale with a 10-mL stainless-steel jar and two 10-mm balls	43% ^b (0.28 g)
13	6.0 mmol (1.1 g) scale with 50-mL stainless-steel jar and two 10-mm balls, 70 °C for ball-milling-II	41% ^b (0.63 g)
14	THF (0.35 mL, 6.0 eq.) instead of ethylenediamine in 6.0 mmol scale with 50-mL stainless-steel jar and two 10-mm balls, 70 °C for ball-milling-II	39% ^b (0.60 g)
15	2.5 mmol (0.45 g) scale with a 10-mL ZrO ₂ jar and two 10-mm ZrO ₂ balls	42% ^b (0.27 g)

Reactions were conducted in a 5.0-mL stainless-steel jar using two 7 mm stainless-steel balls. The reactions were quenched with H₂O after the indicated reaction times.

^a NMR yield using dibromomethane as an internal standard.

^b Isolated yield.

NMR, we showed that the dark black mixture after treatment with lithium(0) and ethylenediamine corresponded to the anthracene dianion (see Supplementary Information (SI) for details, Supplementary Fig. S1). In the controlled experiments, neither an addition and mixing of PhF for 5 min in the second step nor shortening ball-milling time (60 → 5 min) significantly reduced the yield (entries 2 and 3). A reduction in the amount of lithium(0) to 2 eq. and the use of sodium(0) pieces rather than lithium(0) reduced the yields of **2a** to 48% and 17% yields, respectively (entries 4 and 5). The use of other electrophiles such as chlorobenzene, bromobenzene, and benzenesulfonates in place of fluorobenzene did not afford the desired products (entries 6–8). Furthermore, the reactions using *N,N*-dimethylethylenediamine or *N,N,N,N*-tetramethylethylenediamine (TMEDA) significantly decreased the yields to 0% and 11% (entries 9 and 10). Although the Birch reduction to form anthracene dianion may proceed under both reaction conditions, the following arylation did not proceed. Finally, when 6 eq. of THF was added rather than ethylenediamine, the desired arylation reaction proceeded to afford **2a** in 75% NMR yield and 70% isolated yield (entry 11). Interestingly, regardless of the presence or absence of a proton source in the ball-milling-I step (e.g., entries 1 and 11), the use of lithium(0), ethylenediamine or THF, and PhF as nucleophiles was essential for this unprecedented arylation reaction. Finally, a gram-scale synthesis was performed using a large stainless-steel jar (10 mL or 50 mL volume), two or three 10-mm-diameter stainless-steel balls with 0.45 g (2.5 mmol) or 6.0 mmol (1.1 g) of **1a**, giving **2a** in a satisfactory yield of 43 or 41% (0.28 or 0.63 g) (entry 12 and 13). The yield in the 6.0 mmol scale (1.1 g) reaction of **2a** with THF

was comparable to the yield achieved using EDA (entry 14). In these large-scale reactions, significant amount of **1a** remained unreacted, and side-products such as **1b**, aromatized product **2a'**, 9,10-diarylanthracene (**5a'**), and other over-reduced anthracenes were observed in ¹H NMR and GC-MS analysis. As differences in the reaction profile in the different scale reaction are often observed in mechanochemical reactions, further investigation is needed on the reaction scale, size of vessel/balls, number of balls, vibration frequency, and amount of additive. To determine whether this reaction was influenced by trace metal contaminants, such as Ni and Cr, from the stainless-steel jar and balls, we also conducted the reaction using a ZrO₂ jar and ZrO₂ balls (entry 15). Compared to the comparable reaction conducted in the stainless-steel setup (entry 13), no significant difference in yield was observed (yield of **2a**: 42%).

Control experiments

Control experiments were conducted to verify the synthesis benefits of the solid-state ball-milling reaction over the solution-state reaction. When the solution-state reaction was performed using **1a** (1.0 mmol, 1.0 eq.) and Li (4.0 eq.) in THF (5.0 mL, 62 eq.) in a Schlenk tube under an argon atmosphere at 70 °C for 60 min followed by the addition of PhF, almost anthracene and lithium metal remained unreacted, and **2a** was not detected at all (Fig. 2a). However, the use of ethylenediamine (5.0 mL, 75 eq.) as a solvent, at room temperature and the same reaction time as entry 1 in Table 1, afforded a trace amount of **2a**. Moreover, the reaction time for the anionic activation step was extended to 60 min in ethylenediamine at 70 °C, and **2a** was

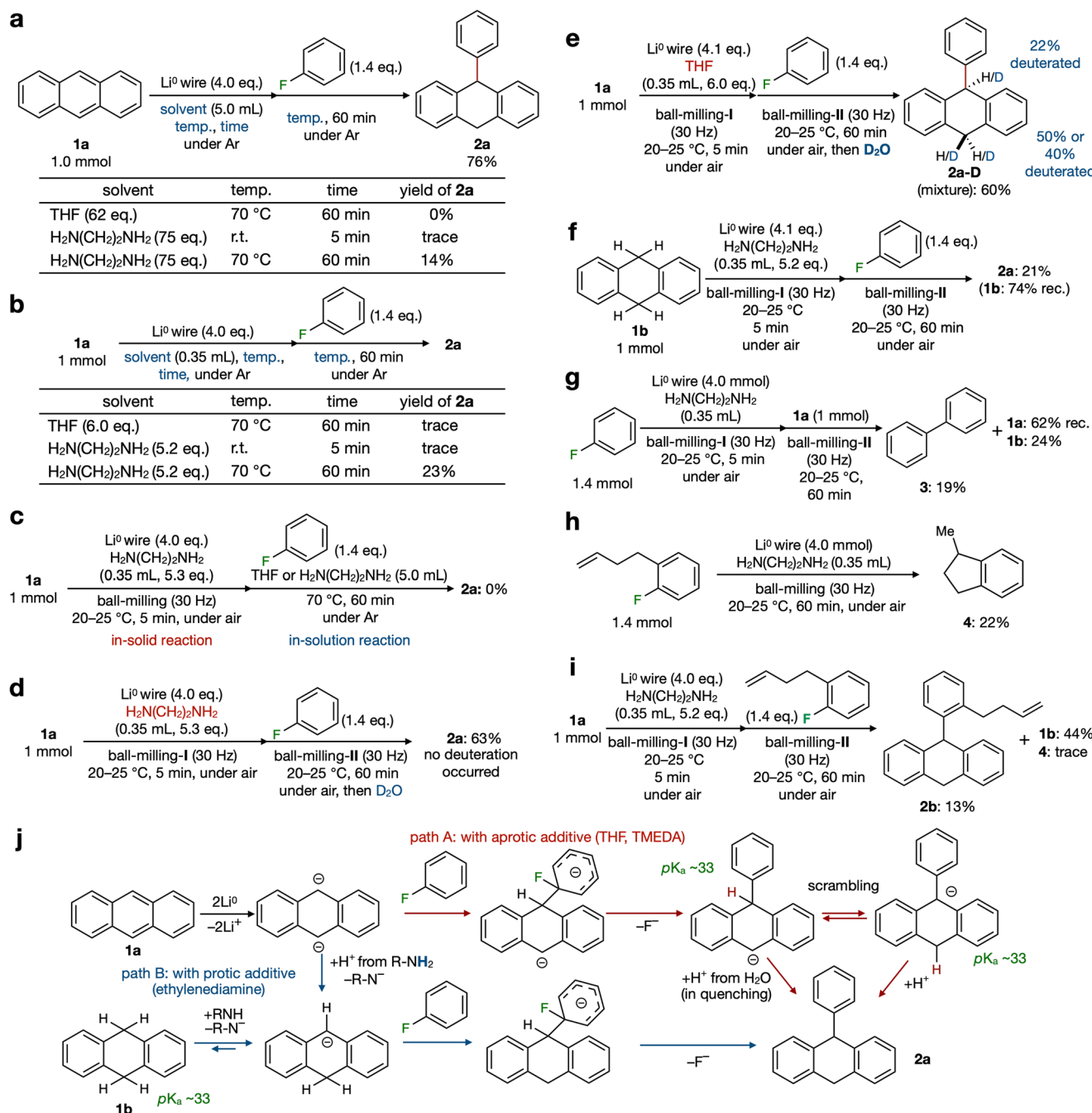


Fig. 2 | Control experiments for mechanistic study. a Comparison with the solution-state reactions. **b** High-concentrated reactions in the solution-state. **c** Stepwise in-solution and in-solid state reaction. **d** Deuteration experiment in the reaction with ethylenediamine by quenching D₂O. **e** Deuteration experiment in the

reaction with THF by quenching D₂O. **f** Reaction from dihydroanthracene **1b**. **g** Side reaction from fluorobenzene. **h** Cyclization of 1-(3-buten-1-yl)-2-fluorobenzene suggesting generation of anion radical. **i** Control reaction of anthracene with 1-(3-buten-1-yl)-2-fluorobenzene. **j** Plausible pathways of Birch reductive arylation.

obtained in 14% isolated yield. Under these solution-state conditions, unreacted lithium wire was observed before quenching the reaction. The solution-state, concentrated reactions were carried out using a minimal amount of THF (0.35 mL, 6.0 eq.) or ethylenediamine (0.35 mL, 5.2 eq.) in a Schlenk tube with a magnetic stirring bar under an argon atmosphere (Fig. 2b). While the reaction with THF at 70 °C and ethylene diamine at room temperature afforded trace amount of **2a**, the reaction with ethylene diamine at elevated temperature (70 °C) resulted in the formation of **2a** in 23% yield. These results indicate that the Birch arylation is also promoted by the concentration effects in the conventional Schlenk tube solution-state reaction, but the reaction efficiency of these solution-state reactions was even

lower than that in the ball-milling reaction in terms of yield, temperature, and reaction time. Furthermore, we conducted the first step of anionic activation by ball-milling, followed by the second step of arylation in the solution state (Fig. 2c). However, only a trace amount of **2a** was obtained under both conditions. In these reactions, the Birch reduction product (9,10-dihydroanthracene) was the main product. These results showed that the newly discovered arylation reaction proceeded not only in the solid state but also in the solution state. However, the present solid/slurry-state mechanicochemical reaction was advantageous in terms of handleability in air, high reactivity at room temperature, yield, and reduced use of solvents.

Further, we conducted control experiments to elucidate the arylation reaction mechanism. In deuteration experiments involving the addition of D₂O rather than H₂O in the quenching step of the reaction with ethylenediamine additives, deuterated products were not observed (Fig. 2d). This indicated that protonation occurred by ethylenediamine before the addition of H₂O/D₂O. However, D₂O-quenching in the reaction with THF as an additive resulted in the formation of deuterated products **2a–D** as a mixture in 60% yield with 22%, and 40/50% deuteration of three benzylic hydrogen atoms, which were confirmed by ¹H NMR analysis (Fig. 2e). This fact indicated that most benzylic anion species remained intact before the addition of D₂O. Using 9,10-dihydroanthracene (**1b**) as the starting material with Li(O) and ethylene diamine provided the arylated product **2a** in a low yield of 21% along with 74% recovery of **1b**, proving that the deprotonation of **1b** by an in-situ-generated strong base such as amide ion is an alternative minor pathway affording **2a** (Fig. 2f). In addition, the ball-milling process with lithium and fluorobenzene followed by the addition of anthracene (**1a**) afforded biphenyl (**3**) in 19%, **1b** in 24%, and recovery of unreacted **1a** in 62% (Fig. 2g), suggesting the competitive formation of anion radical or phenyl anion species from Li(O) and fluorobenzene⁴¹. The reaction with simultaneous mixing all reagents resulted in a lower yield of **2a** along with considerable formation of by-products such as **3**, **1b** and other Birch reduction products (see Supplementary Fig. 5). To further investigate the active species, the ball-milling process was performed with lithium(O) and 1-(3-buten-1-yl)-2-fluorobenzene without anthracene, resulting in the formation of 1-methylindane (**4**) as the main product in 22% isolated yield (Fig. 2h). These results indicate the generation of the arenium radical anion by one-electron reduction, and the aryl radical species after elimination of fluoro ion followed by radical cyclization in a 5-*exo-trig* manner, to afford **4**^{42–45}. Finally, the Birch reductive arylation of anthracene with 1-(3-buten-1-yl)-2-fluorobenzene was performed, and we obtained **1b** and the arylated product **2b** in 44% and 13% yield, respectively (Fig. 2i). However, the formation of a trace amount of **4** was observed by GC-MS analysis. The radical cyclization of 1-(3-buten-1-yl)-2-fluorobenzene is considered to be much faster than the other intermolecular reactions, which suggests that the formation of arenium radical anion/aryl radical via one-electron reduction of fluoroarene by anthracene dianion or remaining Li(O) is a minor pathway in the present Birch reductive arylation. Overall, these observations and the results presented in Table 1, highlight two possible pathways (Fig. 2j): One is a 2e[−] reduction by 2.0 eq. of Li(O), followed by S_NAr with fluorobenzene and protonation by ethylenediamine or post-added H₂O (path A). Another minor pathway is initiated by Li(O)-promoted Birch reduction with ethylenediamine as the proton source, along with the formation of lithium amide (R–NLi). Following the reformation of the benzyl anion in equilibrium with R–NLi, S_NAr reaction with fluorobenzene can afford **2a** (path B). The use of lithium(O) in the present mechanochemical reaction is rationalized by the following: (1) the highest reduction potential of Li (−3.04 V)⁴⁶ in the metals, (2) effective formation of reactive fine dispersion and rapid reduction by mechanochemical grinding^{47,48}, (3) enthalpically favorable formation of LiF (a high lattice energy (ΔH₀)⁴⁹ of LiF (1041 kJ/mol) than those of NaF (858 kJ/mol) and KF (799 kJ/mol), and thus lowering both the relative Gibbs energy of formation and the activation energy in S_NAr step. Although these assumptions are unclear at this stage, they provide a new aspect of the mechanochemical (solid-state) reaction that cannot easily be achieved using typical solution-state reactions. Further theoretical and experimental investigations of the reaction mechanism are required to understand this reaction.

Substrate scope with various fluoroarenes

We explored the substrate scope using various fluoroarenes with a highly efficient and easy-to-handle mechanochemical arylation (Fig. 3). All the experiments were performed on a 1.0 mmol scale of anthracene (**1a**) unless otherwise stated. The reactions with 1,2- and 1,4-

difluorobenzenes afforded corresponding fluorophenyldihydroanthracenes **2c** and **2d** in 42% and 41% yields, respectively (Fig. 3). However, the reaction with 1,3-difluorobenzene yielded 9-(3-phenyl)anthracene (**2e'**), which is considered to form through spontaneous oxidation of 9-(3-fluorophenyl)-9,10-dihydroanthracene (**2e**) by air during a purification process. The use of 4-fluorobenzonitrile afforded cyanophenyldihydroanthracene **2f** in 26%. In contrast, other fluoroarenes bearing electron-withdrawing groups such as 4-ethoxycarbonyl, 4-nitro, 4-trifluoromethyl groups, and hexafluorobenzene were proved to be ineffective in this reaction (see SI for details). Fluoroarenes with electron-donating groups, such as methoxy, methyl-, and dimethyl groups, were also applicable to this reaction. When using 3- and 4-fluoroanisoles, methoxy groups were tolerated to some extent and the 9-arylanthracenes **2g'** and **2h'** (via oxidation) were obtained in 31% and 32% yields, respectively. The reactions of 1-fluoro-3-methylbenzene and 1-fluoro-3,5-dimethylbenzene proceeded well, affording the corresponding arylated dihydroanthracenes **2i** and **2j** in 69% and 50% yields, respectively. The use of 2-fluoropyridine afforded 9-(2-pyridyl)-9,10-dihydroanthracene (**2k**) in 64% yield, whereas the reaction using 3-fluoropyridine resulted in the formation of 9-(3-pyridyl)anthracene (**2l'**) in a 41% yield. When using 1-fluoronaphthalene or 9-fluoroanthracenes, 9-(naphthalen-1-yl)anthracene (**2m'**) and 9,9'-bianthryl (**2n'**) were obtained in 48% and 27% yields, respectively. In another demonstration, the diarylation of anthracene was performed using 2.5 eq. of fluoroarenes. The reactions with fluorobenzene, 1,4-difluorobenzene, and 1-fluoronaphthalene afforded the corresponding diarylated anthracenes **5a'**, **5b'** and **5c'** in 57%, 50%, and 43% yield, respectively. Fluoroarenes with electron-withdrawing groups such as 2-fluoropyridine or 1,3,5-trifluorobenzene were converted to 9,10-diaryl-9,10-dihydroanthracenes *syn*-**5d** and a separable mixture of *syn*-**5e** and *anti*-**5e** in 43%, 19%, and 22% yields, respectively. Single crystals of *syn*-**5e** and *anti*-**5e** were obtained by recrystallization from hexane (for *syn*-**5e**) and CHCl₃/MeOH (*anti*-**5e**), respectively, and their structures were elucidated by X-ray diffraction analysis. The reaction with 2-fluoropyridine afforded only *syn*-**5d**, probably because of the Li chelation effect between pyridine and the benzyl anion in the mono-arylated intermediate (see SI for details); thus, *syn*-face-selective second arylation would preferentially occur. This result contrasts with the use of 1,3,5-trifluorobenzene with almost no stereoselectivity for *syn*-**5e** and *anti*-**5e** because of the absence of the chelation effect.

Substrate scope with various PAHs and applied for nanographene synthesis

Following the established mechanochemical arylations of anthracene, we investigated the arylation of other PAHs for the synthesis of largely π-extended structures and nanographenes (Fig. 4). Based on the results that aryldihydroanthracenes **2/5** and arylanthracenes **2'/5'** were obtained depending on the types of electronically different fluoroarenes, we conducted standard mono-arylation reactions using various PAHs (step-A) followed by oxidation of arylated dihydro-PAHs **7** to fully aromatized aryl PAHs **7'** (step-B) if the reaction gave mixtures of **7** and **7'**. Interestingly, the use of TMEDA as an additive was also effective in the arylation of other PAHs. First, the oxidation of dihydroanthracene **2a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was examined to afford 9-arylanthracene (**2a'**) in a good isolated yield (94%). The application of mono-arylation (step-A) to fluoranthene (**6a**) yielded complex mixtures, including dihydroarylated product **7a**, arylated 3-phenylfluoranthene (**7a'**), and other Birch reduction side-products, in the crude mixture. Therefore, oxidation (step-B) with *o*-chloranil was conducted to obtain **7a'** in 20% yield. The reaction of pyrene (**6b**) and benzo[*a*]pyrene (**6c**) afforded the corresponding spontaneously oxidized arylated-PAH **7b'** and **7c'** as single products without step-B. The arylation reaction with benzo[*a*]anthracene (**6d**) afforded 7-phenyl-7,12-dihydrotetraphene (**7d**), whose structure was elucidated by X-ray crystallographic analysis, in a 42% yield. **7d** could

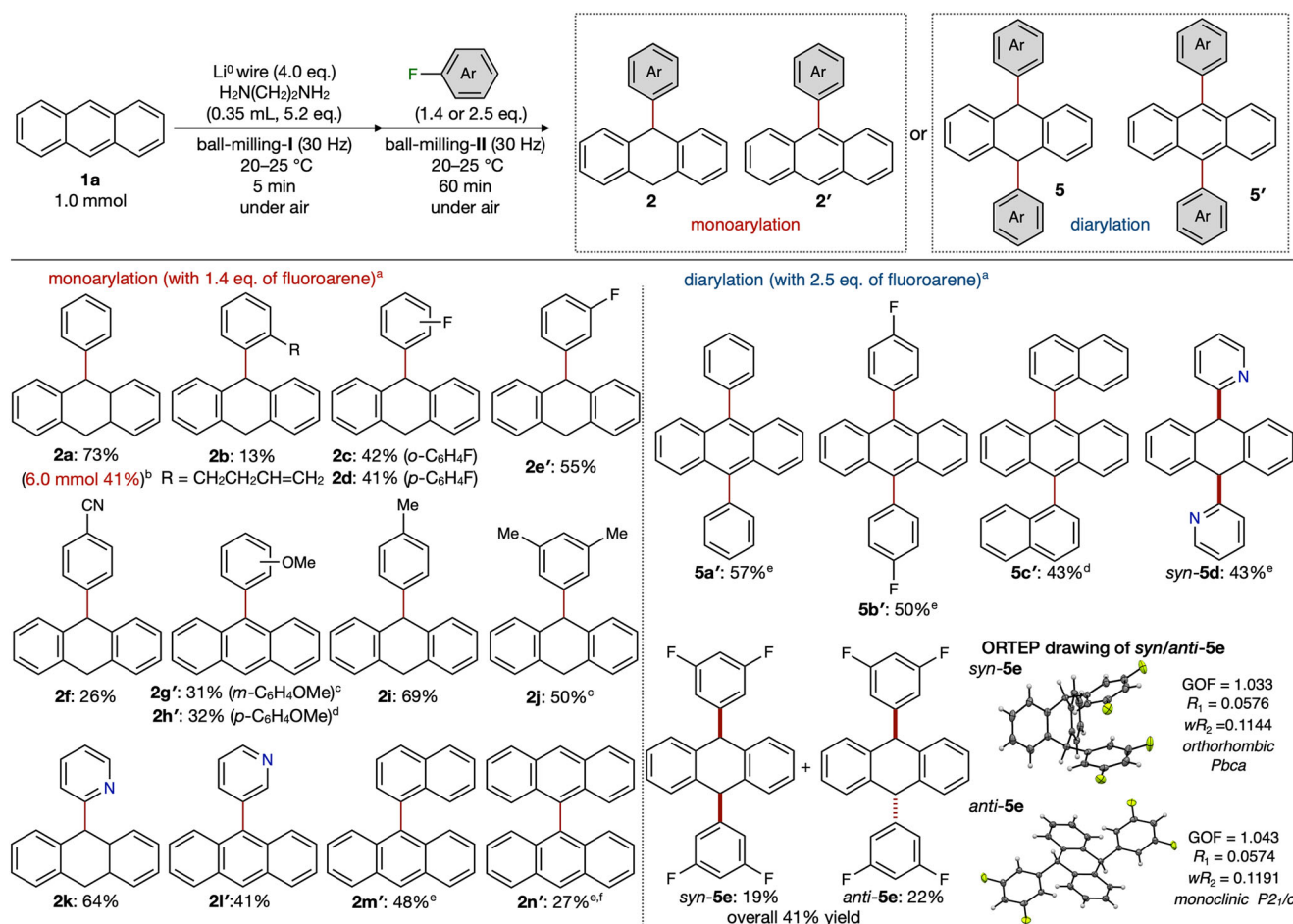


Fig. 3 | Monoarylation and diarylation of anthracene with various fluoroarenes.

^a Isolated yield. ^b Reactions are conducted in a 50-mL stainless-steel jar using two 10-mm stainless-steel balls. The reaction time and temperature of ball-milling-II are

180 min and heated 70 °C (heat-gun preset temperature). ^c The reaction time of ball-milling-II is 6 h. ^d The reaction time of ball-milling-II is 8 h. ^e The reaction time of ball-milling-II is 120 min. ^f 1.6 equivalent of 9-fluoroanthracene is used.

be converted to 7-phenyltetraphene (**7d'**) using DDQ in 54% isolated yield. The use of benzo[*f*]tetraphene (**6e**), tetracene (**6f**), and pentacene (**6g**) provided arylated dihydro-PAHs **7e–7g**, and **7g-py** were obtained in 27% to 56% yields.

Inspired by these regioselective arylations of PAHs, we performed natural bond orbital (NBO) analysis using density functional theory calculations to understand high regioselectivities. As shown in Fig. 2j, we hypothesized that this reaction mainly proceeds via the dianion species of PAHs and that each reactive site can be formed by disproportional HOMO coefficients and NBO charges^{50,51} in each peripheral carbon atom of the PAH dianions (Fig. 5). Notably, the carbon atoms with the maximum absolute value of the HOMO coefficient and the largest negative value of the NBO charge are identical to each arylated position in the case of dianions of **1a**, **6a**, **6b**, and **6d–6g**. In the case of the dianions of **6c**, the experimental reaction positions did not match the positions with the largest positive or negative values. However, arylations occurred at the carbon atoms where the negative charges tended to be localized. The analysis of the electrostatic potential⁵² of the same dianionic PAHs also supported this regioselectivity (see SI for details).

Multi-fold arylation of acenes

Next, we attempted multi-fold arylation at the C9 and C10 positions of anthracene. When using 8.2 eq. of lithium(0), TMEDA, and an excess amount of 2-fluoropyridine, 9,9,10,10-tetra(pyridin-2-yl)-9,10-dihydroanthracene (**8**) was obtained in 27% isolated yield (Fig. 6a). This multi-fold arylation can be also applied to pentacene, affording

6,6,13,13-tetra(pyridin-2-yl)-6,13-dihydropentacene (**9**) in a 24% isolated yield (Fig. 5b). At this stage, we confirmed that only 2-fluoropyridine was effective for the four-fold arylation of acenes, whereas reactions with excess amounts of other fluoroarenes resulted in the formation of diarylated products as major products, along with small quantities of four-fold arylation products. One reason for this is the increased acidity of pyridylated intermediates. For example, when the reaction of **1a** with Li and TMEDA was conducted, anthracene dianion **A** was formed in the first step (Fig. 5c), followed by diarylation to afford **5d**, as shown in Fig. 3. Compound **5d** was considered to possess more acidic benzylic hydrogen atoms (blue-colored protons) than simple hydrocarbon compounds such as **2a**. This implied that further deprotonation occurred easily in the presence of co-existing strong anions, such as dianion **A** and monoanion **B**. Finally, repeating the S_NAr reaction with 2-fluoropyridine affords the multi-fold arylation product **9**. Single crystals of **8** and **9** were also obtained by recrystallization from CHCl₃/hexane (for **8**) and MeOH/Et₂O (for **9**), respectively, and X-ray diffraction analyses revealed that the original flat acene structures were retained even after the central carbon atoms changed to sp³ carbons.

Annulative π-extension by the sequence of mechanochemical arylation and cyclodehydrogenation

Finally, to apply current mechanochemical arylation for nanographene synthesis, we attempted *fissure-region*^{53,54} annulative π-extension^{2,54–61} (*fissure-APEX*) reaction by combining previously developed lithium(0)-mediated mechanochemical cyclodehydrogenation²¹. Grinding

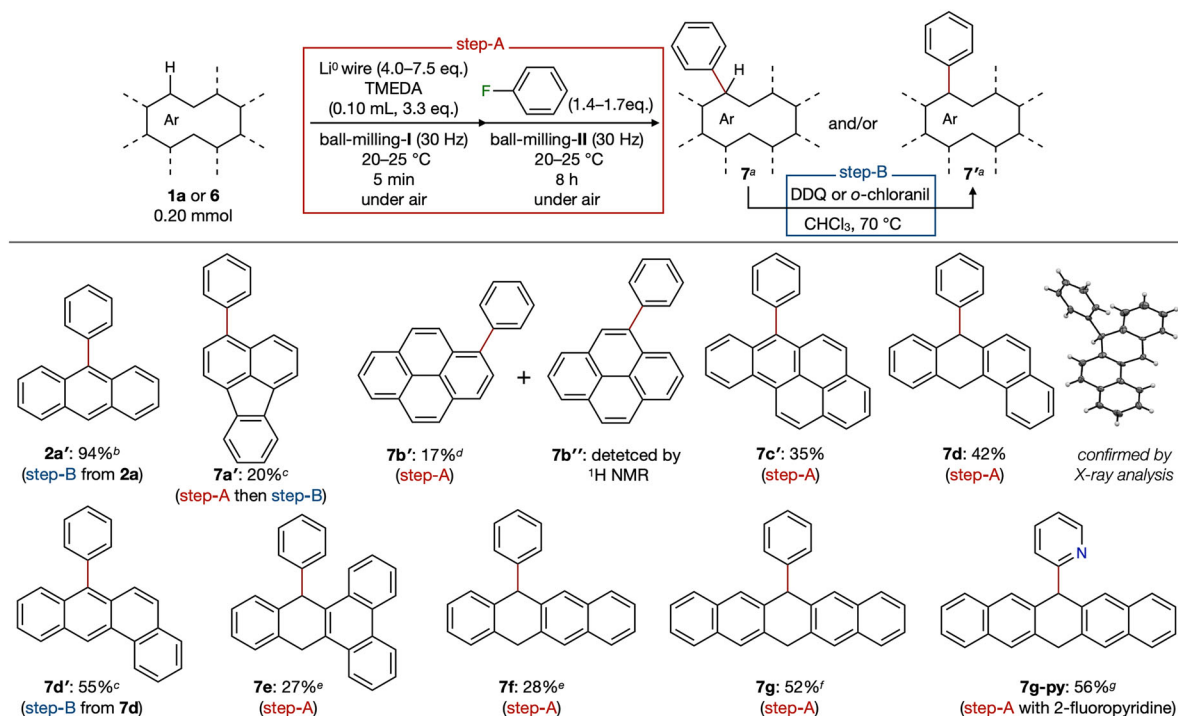


Fig. 4 | Substrate scope in arylation of PAHs and oxidation of dihydroanthracene to anthracene derivatives. ^a Indicated yields are isolated ones. ^b Step-B is conducted with *o*-chloranil (2.0 eq.) in benzene (10 mL). ^c Step-B is conducted with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (4 eq.) after the ball-milling-II. ^d The reaction is conducted in a 5.0-mL stainless-steel jar using two 7-mm stainless-

steel balls at a 1.0-mmol scale. ^e The reaction time of ball-milling-II is 6 h. ^f The reactions are conducted on a 0.12 mmol scale. ^g The reactions are conducted on a 0.15 mmol scale, and 2-fluoropyridine is used rather than fluorobenzene. Anthracene (**1a**), fluoranthene (**6a**), pyrene (**6b**), benzo[*a*]pyrene (**6c**), benzo[*f*]tetraphene (**6e**), tetracene (**6f**), and pentacene (**6g**) were used as starting materials.

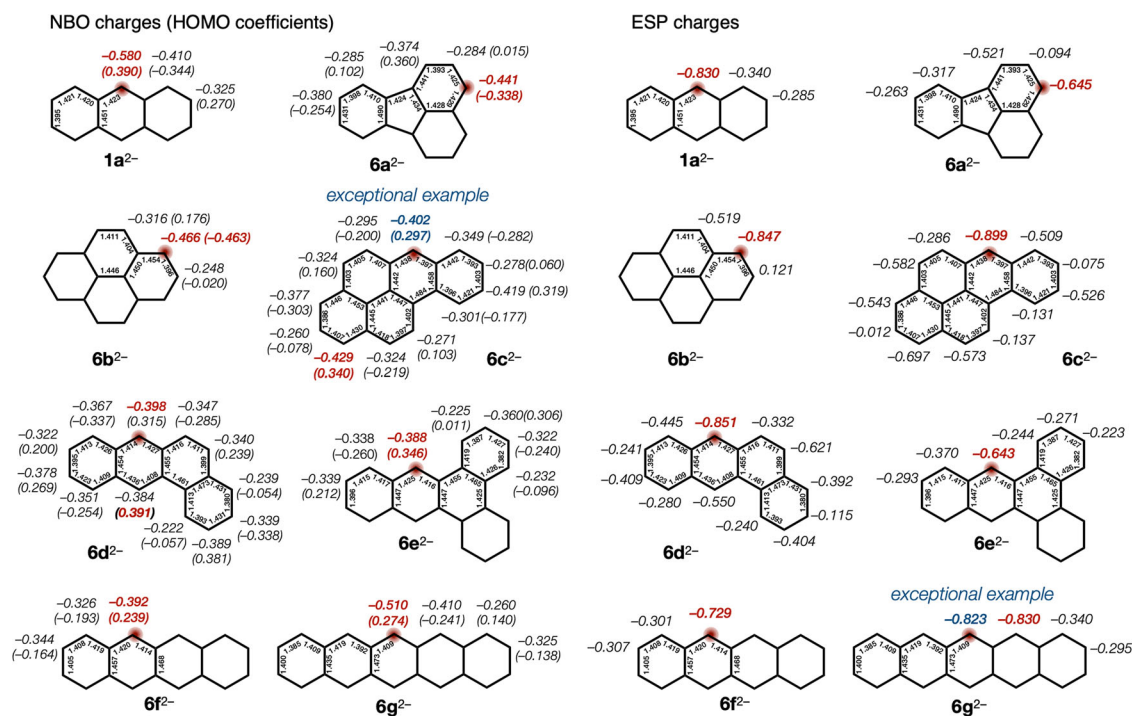


Fig. 5 | NBO, ESP charges and HOMO coefficients (in brackets) of PAH dianions. Red-colored values represent the positive or negative largest values of the HOMO coefficient and negative largest NBO charge. Red-colored circles represent the

experimental arylation positions. The bond lengths (Å) are shown inside structures. All values were calculated at B3LYP/6-31 + G(d,p) level of theory.

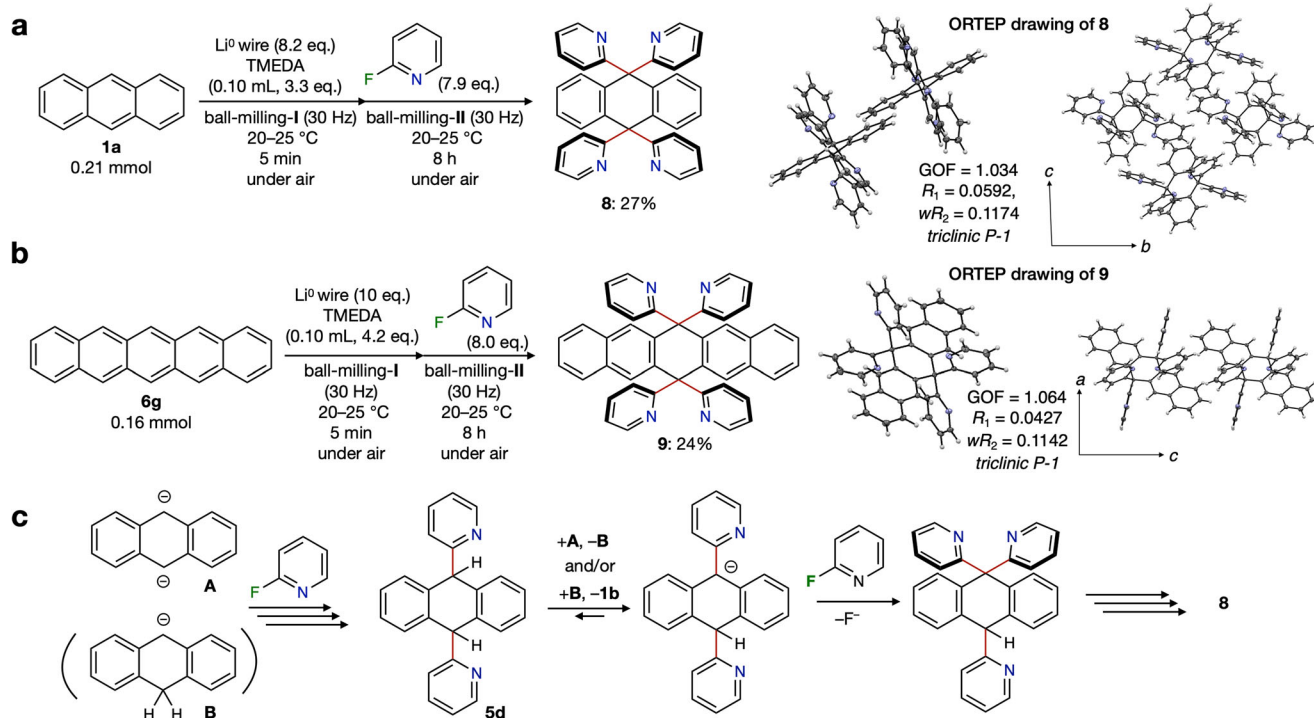


Fig. 6 | Four-fold arylation of acenes. a Four-fold arylation of anthracene for synthesis of tetrapyrindinyldihydroanthracene **8**. **b** Four-fold arylation of pentacene for synthesis of tetrapyrindinyldihydropentacene **9**. **c** Proposed reaction mechanism.

fluoranthene (**6a**) with lithium(0) wire and 1-fluoronaphthalene afforded 3-(1-naphthalenyl)fluoranthene (**10**) in an 18% yield (Fig. 7a). **10** was converted to a perylene derivative **11** using the mechanochemical cyclodehydrogenation method that we previously reported²¹. The one-pot C–H arylation and cyclodehydrogenation was attempted with pyrene (**6b**) and afforded **12** as an orange solid in a 6% yield (Fig. 7b). While the yield was not unsatisfactory, this reaction represents the first example of one-pot *fissure-region* APEX. Further investigations on the conditions of *fissure-region* APEX reaction are ongoing in our laboratory.

In this study, we developed an arylation reaction of unfunctionalized PAHs by mechanochemical anionic activation with lithium(0) followed by adding various fluoroarenes. To the best of our knowledge, this is the first example of a Birch reductive arylation of polyaromatic compounds and a rare example of carbon–carbon bond formation reaction between carboanions and fluoroarenes via $\text{S}_{\text{N}}\text{Ar}$. Unlike previous solution-based Birch reductive functionalizations, the discovered method allows a rapid, in-air and at-room temperature reaction with least amount of liquid additives. Using this method, various arylated polyaromatic compounds including mono-, di-, tetraarylated ones could be rapidly synthesized from unfunctionalized PAHs. One of highlighting applications is the demonstration of *fissure-region* APEX reaction by mechanochemical Birch reductive arylation and cyclodehydrogenation providing nanographenes. Our methodology is useful not only as a formal direct arylation method for unfunctionalized aromatics, but also a complementary arylation method for conventional cross-coupling reaction. Further investigations into the reaction mechanism are ongoing in our laboratory.

Methods

General procedure A for a 1.0 mmol scale reaction at room temperature (20–25 °C)

The synthesis of 9-phenyl-9,10-dihydroanthracene (**2a**) is described as a representative example of the general procedure A for 1.0-mmol

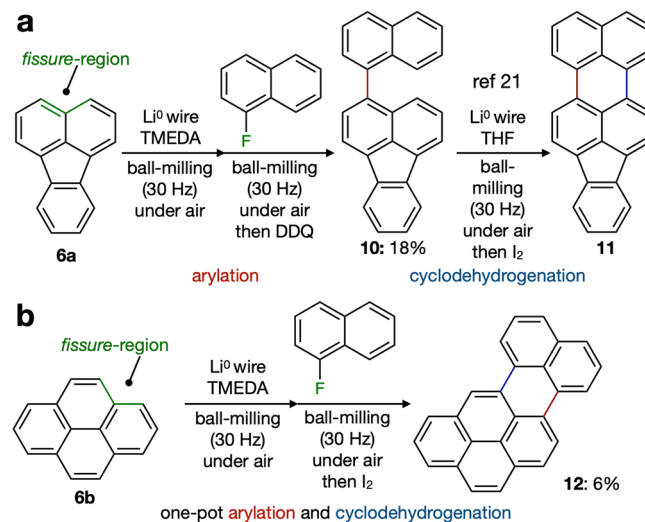


Fig. 7 | Application to APEX reaction. a Stepwise *fissure*-APEX reactions via lithium-mediated mechanochemical arylation and cyclodehydrogenation. **b** One-pot *fissure*-APEX reaction.

scale reaction. To a 5.0-mL stainless-steel jar containing two 7-mm-diameter stainless-steel balls was added anthracene (**1a**) (177.7 mg, 1.0 mmol, 1.0 eq.). Pieces of Li (27.4 mg, 4.0 mmol, 4.0 eq.) cut from Li wire (3.2 mm in diameter, 99.9% purity) were washed with hexane for removing mineral oil, weighed on an electronic balance, and added into the jar under air. Then, ethylenediamine (0.35 mL, 5.2 mmol, 5.2 eq.) was added to the jar by a syringe under air. The jar was capped with a stainless-steel cap equipped with a handmade O-shaped packing made of 1 mm width polyethylene sheet, and the jar was sealed tightly with a wrench and a vise. The reaction jar and a same-weight blank jar (or a same-weight reaction jar) were

fixed in a mixer mill (Retsch MM400 or MM500 Vario), and shaken at 30 Hz (1800 rpm) at room temperature (20–25 °C) for 5 min (ball-milling-I). The reaction jar was opened under air, and fluorobenzene (136.6 mg, 1.4 mmol, 1.4 eq.) was added by a glass syringe in one portion in ca. 2–3 s. Then, the jar was sealed tightly again, and shaken in a same manner at 30 Hz (1800 rpm) at room temperature (20–25 °C) for 60 min (ball-milling-II). Notably, the entire experimental manipulations including opening the jar, adding PhF, and closing the jar take 2–3 min in air, and no noticeable air-oxidation of anionic species was observed. After shaking, the reaction jar was opened, and the reaction was quenched by adding water. Then, the organic phase was extracted three times with chloroform (10 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to obtain a crude product which was further purified by silica gel column chromatography (eluent: hexane), affording **2a** as a white solid (186.6 mg, 0.73 mmol, 73% yield).

General procedure B for a 1.0-mmol scale reaction at 25 °C

The synthesis of 9,10-diphenylanthracene (**5a**) is described as a representative example of the general procedure B for 1.0-mmol scale reaction. To a 5.0-mL stainless-steel jar containing two 7-mm-diameter stainless-steel balls was added anthracene (**1a**) (178.2 mg, 1.0 mmol, 1.0 eq). Pieces of Li (28.1 mg, 4.0 mmol, 4.0 eq.) cut from Li wire (3.2 mm in diameter, 99.9% purity) was washed with hexane for removing mineral oil, weighed on an electronic balance, and added into the jar under air. Then, ethylenediamine (0.35 mL, 5.2 mmol, 5.2 eq.) was added to the jar by a syringe under air. The jar was capped with a stainless-steel cap equipped with a handmade O-shaped packing made of 1 mm width polyethylene sheet, and the jar was sealed tightly with a wrench and a vise. The reaction jar and a same-weight blank jar (or a same-weight reaction jar) were fixed in a mixer mill (Retsch MM400 or MM500 Vario), and shaken at 30 Hz (1800 rpm) at room temperature (20–25 °C) for 5 min (ball-milling-I). The reaction jar was opened under air, and fluorobenzene (241.2 mg, 2.5 mmol, 2.5 eq.) was added by a glass syringe in one portion in ca. 2–3 s. Then, the jar was sealed tightly again, and shaken in a same manner at 30 Hz (1800 rpm) at room temperature (20–25 °C) for 120 min (ball-milling-II). Notably, the entire experimental manipulations including opening the jar, adding PhF, and closing the jar take 2–3 min in air, and no noticeable air-oxidation of anionic species was observed. After shaking, the reaction jar was opened, and the reaction was quenched by adding water. Then, the organic phase was extracted three times with chloroform (10 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to obtain a crude product which was further purified by silica gel column chromatography (eluent: hexane/CHCl₃ = 100:0 → 90:10), afforded **5a** as a white yellow solid (186.7 mg, 0.57 mmol, 57% yield).

Data availability

CCDC numbers of *anti*-**5e** (2374003), *syn*-**5e** (2374004), **8** (2374002), and **9** (2379941) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. All other data supporting the findings of this manuscript are also available in the Supplementary Information, Supplementary Datasets, or from the corresponding author upon request.

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Author contributions

H.I. conceived the concept and directed the project. Y.T. conducted experiments, analyses, and calculations. H.I. and A.Y. acquired the funding. Y.T. and H.I. prepared the manuscript with feedback from A.Y. and K.I. All authors approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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