

Birch Reductive Arylation by Mechanochemical Anionic Activation of Polycyclic Aromatic Compounds

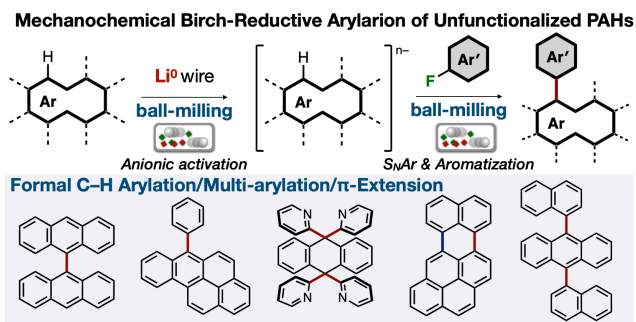
Yoshifumi Toyama,[†] Akiko Yagi,^{†,‡} Kenichiro Itami,^{*,†,‡,#} and Hideto Ito^{†,*}

[†]Department of Chemistry, Graduate School of Science, Nagoya University, Nagoya 464-8602, Japan.

[‡]Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Nagoya 464-8602, Japan.

[#]Molecule Creation Laboratory, Cluster for Pioneering Research, RIKEN, Wako, Saitama 351-0198, Japan.

ABSTRACT: Birch reduction is a well-known process for producing aromatic compounds. The reduction of aromatic rings using alkali metals produces anionic species that react with protons or electrophiles. However, this reaction is generally accompanied by significant restrictions on the available substrates because only alkyl halides are available in most cases. For example, most Birch reduction/transformation reactions are related to the alkylation of aromatic compounds, whereas reactions with other electrophiles are rare and have not yet been completely established. 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 for the first time by mechanochemical anionic activation using a lithium(0) wire followed by addition of various fluoroarenes. Specifically, we found that the not only Birch reductive arylation products but also formal C–H arylation products were obtained from unfunctionalized PAHs, achieving one-pot *fissure*-region annulative π -extension to give nanographenes. This newly found process is a unique reaction that is rarely achieved in solution, and showed the interesting reactivity of metal lithium and organofluorine compounds in the solid state.



Introduction

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 vigorously performed for synthesizing polyarylenes and polycyclic aromatic hydrocarbons (PAH) with intriguing properties.¹ 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 functionalization.² In the Birch reductive alkylation, the reduction of the aromatic ring using alkali metals initially produces anionic species,^{3,4} which are further reacted with electrophiles such as alkyl halides (Figure 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.⁵ As recent examples, reductive alkylation biphenyls and PAHs with fluoroalkanes was reported by Albert and Miguel in 2007.⁶ In 2021, Yorimitsu and co-workers reported the reductive borylation of anthracene using highly reactive Na dispersion and methoxyboronic acid pinacol ester (MeOBpin).⁷ They also developed the multi-methylation of corannulene in a similar reaction system.⁸ The generated anionic arene species are extremely

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).⁹ However, no example of trapping the anionic species with aryl halides via nucleophilic aromatic substitution (S_NAr) has been reported. Such untapped “Birch reductive arylation” is challenging but essential in fundamental synthetic organic chemistry and the simplest efficient synthesis of polyaromatics.

We recently developed Li(0)-mediated mechanochemical cyclodehydrogenation using a ball-milling machine for the efficient and rapid synthesis of PAHs (Figure 1B).¹⁰ 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 Li(0) was also reported by Kubota and Ito.¹¹ This process 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-dihydroanthracene. 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.¹² 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.

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 step-wise 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 employed 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 cyclodehydrogenation.¹⁰ Although related cross-coupling reactions using fluoroarenes and aryl metals via transition metal catalysis¹³ and the Birch reductive alkylation 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 and was enabled for the first time via mechanochemical anionic activation.

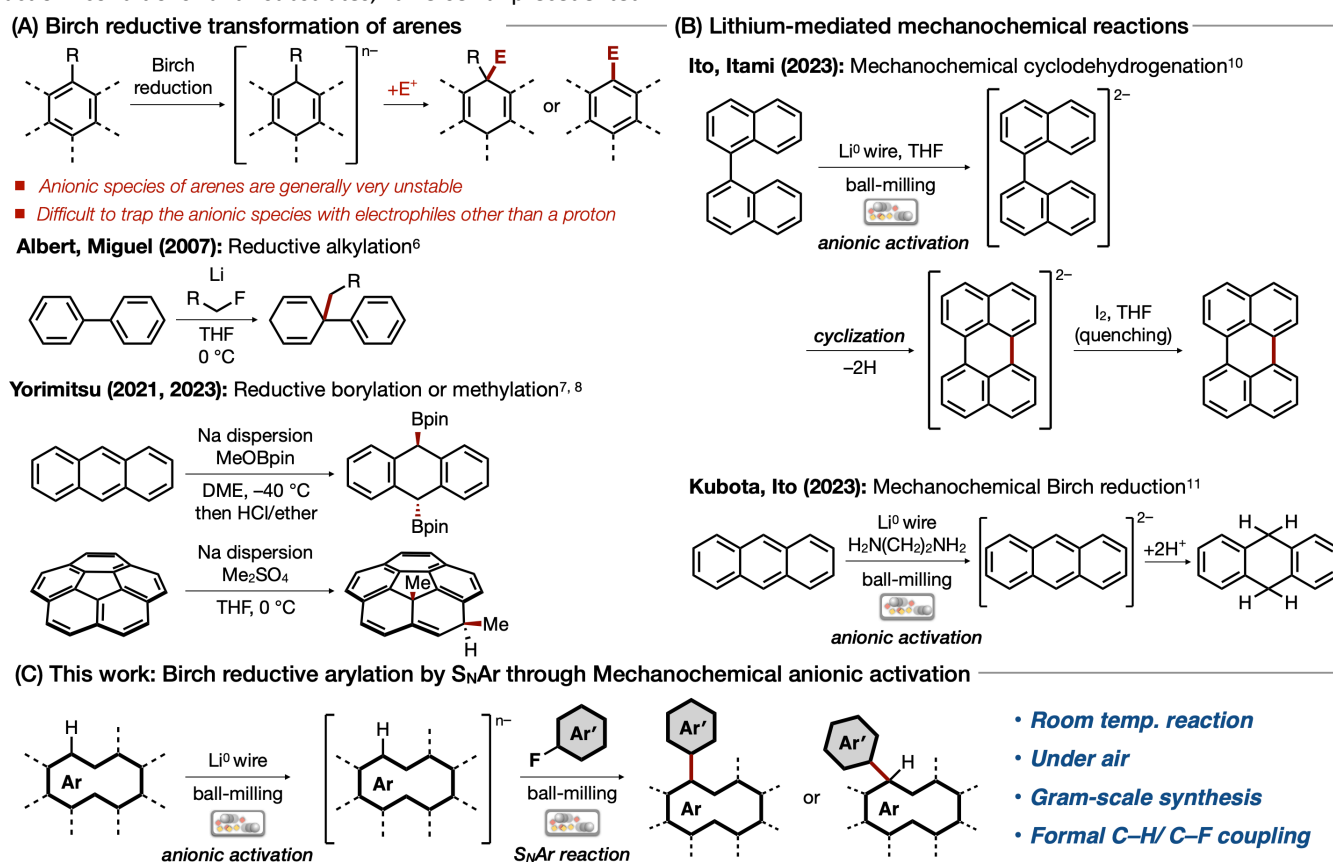


Figure 1. (A) Related Birch reductive transformations of arenes. (B) Lithium-mediated mechanochemical reactions. (C) This work.

RESULTS AND DISCUSSION

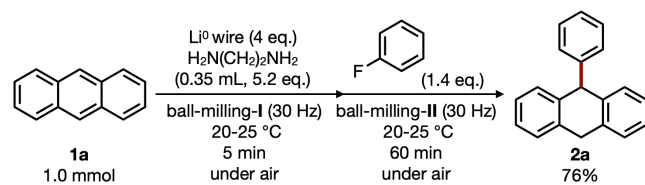
Modification of reaction condition

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 species.¹² By investigating the reaction conditions, we observed the unprecedented Birch reductive arylation of **1a** with fluorobenzene (PhF), yielding 9-

phenyl-9,10-dihydroanthracene (**2a**). 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 5-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-1); (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 (entry 1). Based on the high magnetic field-shifted protons in ¹H NMR, we showed that the dark black mixture after treatment with lithium(0) and ethylenediamine corresponded to the anthracene dianion (see Supporting Information (SI) for details). 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, benzenesulfonates rather than fluorobenzene significantly decreased the yields (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. Interestingly, regardless of the presence of a proton source in the ball-milling-I step (e.g., entries 1 and 11), the use of lithium(0), ethylenediamine, 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 (50-mL volume), three 10-mm-diameter stainless steel balls with 6.0 mmol (1.1 g) of **1a**, giving **2a** in a satisfactory yield of 41% (0.63 g).

Table 1. Screening of conditions for anionic activation of anthracene and S_NAr reaction with fluorobenzene.



Entry	Deviations from the standard conditions	Yield of 2a ^b
1	None	76% (73%) ^c
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%) ^c
12	6.0 mmol (1.1 g) scale ^d	41% ^c (0.63 g)

^a Reactions were conducted in a 5.0-mL stainless steel jar using two 3-mm stainless steel balls. The reactions were quenched with H₂O after the indicated reaction times. ^b NMR yield using dibromomethane as an internal standard. ^c Isolated yield. ^d The reaction was conducted in a 50-mL stainless steel jar using two 10-mm stainless steel balls. The reaction time and temperature of ball-milling-II were 180 min and 70 °C (heat-gun preset temperature), respectively.

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 (Figure 2A). However, the use of ethylenediamine (5.0 mL, 75 eq.) as a solvent, at the same reaction temperature and 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 obtained in 14% isolated yield. Under these solution-state conditions, unreacted lithium wire was observed before quenching the reaction. Furthermore, we conducted the first step of anionic activation by ball milling, followed by the second step of arylation in the solution state (Figure 2B). 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 in the solid and solution states. However, the present solid/slurry-state mechanochemical reaction was advantageous in terms of handleability in air, high reactivity at room temperature, yield, and scalability and reduced the 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 **2a-D** were not observed (Figure 2C). 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 **2a-D** as a mixture in 60% yield with 22%, and 40/50% deuteration of three benzylic protons were confirmed by ¹H NMR analysis (Figure 2D). Most benzylic anion species remained intact before the addition of D₂O. The other control experiment using 9,10-dihydroanthracene as the starting material provided the arylated product **2a** in a low yield of 21%, proving that the deprotonation of **1b** by an in-situ-generated strong base such as amide ion is an alternative minor pathway to affording **2a** (Figure 2E). Overall, these observations, and the results presented in Table 1, highlight two possible pathways: One is a 2-electron reduction by 2.0 eq. of Li(0), 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(0) in the present mechanochemical reaction is rationalized by the following: (1) the highest reduction potential of Li (-3.04 V)¹⁴ in the metals, (2) effective formation of reactive fine dispersion and rapid reduction by mechanochemical grinding,¹⁵ (3) enthalpically favorable

formation of LiF (a high lattice energy (ΔH_0)¹⁶ 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 expectations 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.

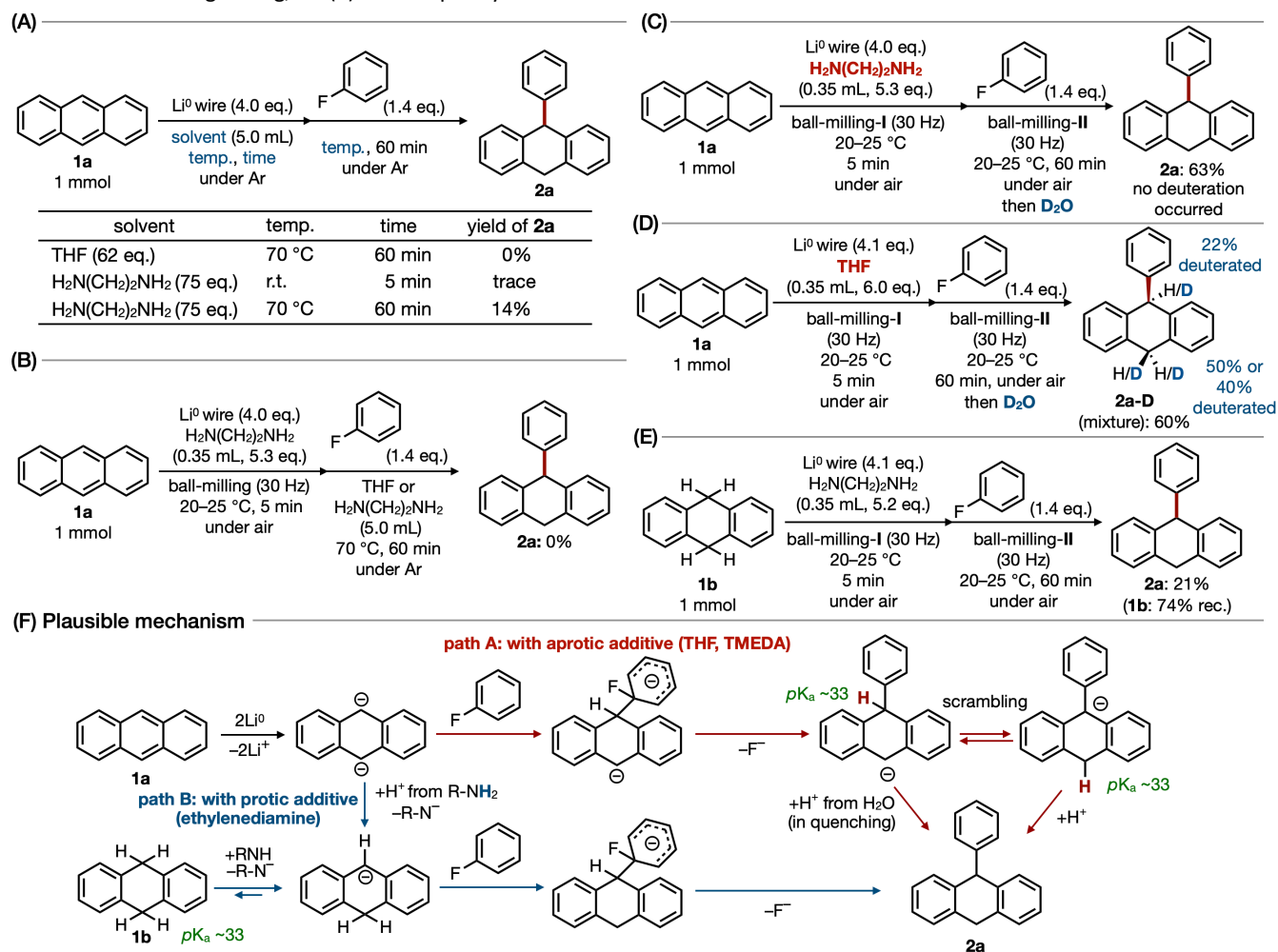


Figure 2. (A)(B)(C)(D)(E) Control experiments for mechanistic study and (F) plausible pathways in Birch reductive arylation.

Substrate scope with various fluoroarenes

We explored the substrate scope using various fluoroarenes with a highly efficient and easy-to-handle mechanochemical arylation (Figure 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 **2b** and **2c** in 42% and 41% yields, respectively (Figure 3A). However, the reaction with 3-difluorobenzene yielded 9-(3-phenyl)anthracene (**2d'**), which is considered to form through spontaneous oxidation

of 9-(3-fluorophenyl)-9,10-dihydroanthracene (**2d**) by air during a purification process. Fluoroarenes with electron-donating groups, such as methoxy, methyl-, and dimethyl groups, were also applicable to this reaction. When using 3- and 4-fluoroanisoles, methoxyl groups were tolerated to some extent and the 9-arylanthracenes **2e'** and **2f'** were obtained in 31% and 32% yields via oxidation, respectively. The reactions of 1-fluoro-3-methylbenzene and 1-fluoro-3,5-dimethylbenzene proceeded well, affording corresponding arylated dihydroanthracenes **2g** and **2h** in 69% and 50% yields, respectively. The use of 2-

fluoropyridine afforded 9-(2-pyridyl)-9,10-dihydroanthracene (**2i**) in 64% yield, whereas the reaction using 3-fluoropyridine resulted in the formation of 9-(3-pyridyl)anthracene (**2j'**) in a 41% yield. When using 1-fluoronaphthalene or 9-fluoroanthracenes, 9-(naphthalen-1-yl)anthracene (**2k'**) and 9,9'-bianthryl (**2l'**) were obtained in 48% and 27% yields, respectively. In another demonstration, the diarylation of anthracene was performed using 2.5 eq. of fluoroarenes (Figure 3B). The reactions with fluorobenzene, 1,4-difluorobenzene and 1-fluoronaphthalene afforded corresponding diarylated anthracenes **3a'**, **3b'** and **3c'** in 57%, 50%, and 43% yield, respectively. Fluoroarenes with electron-withdrawing groups such as 2-fluoropyridine or 1,3,5-trifluorobenzene afforded 9,10-diaryl-9,10-

dihydroanthracenes *syn*-**3d** and a separable mixture of *syn*-**3e** and *anti*-**3e** in 43%, 19%, and 22% yields, respectively. Single crystals of *syn*-**3e** and *anti*-**3e** were obtained by recrystallization from hexane (for *syn*-**3e**) and CHCl₃/MeOH (*anti*-**3e**), respectively, and their structures were elucidated by X-ray diffraction analysis (Figure 3C and SI). The reaction with 2-fluoropyridine afforded only *syn*-**3d**, probably because of the Li chelation effect between pyridine and the benzyl anion in the monoarylated 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*-**3e** and *anti*-**3e** because of the absence of the chelation effect.

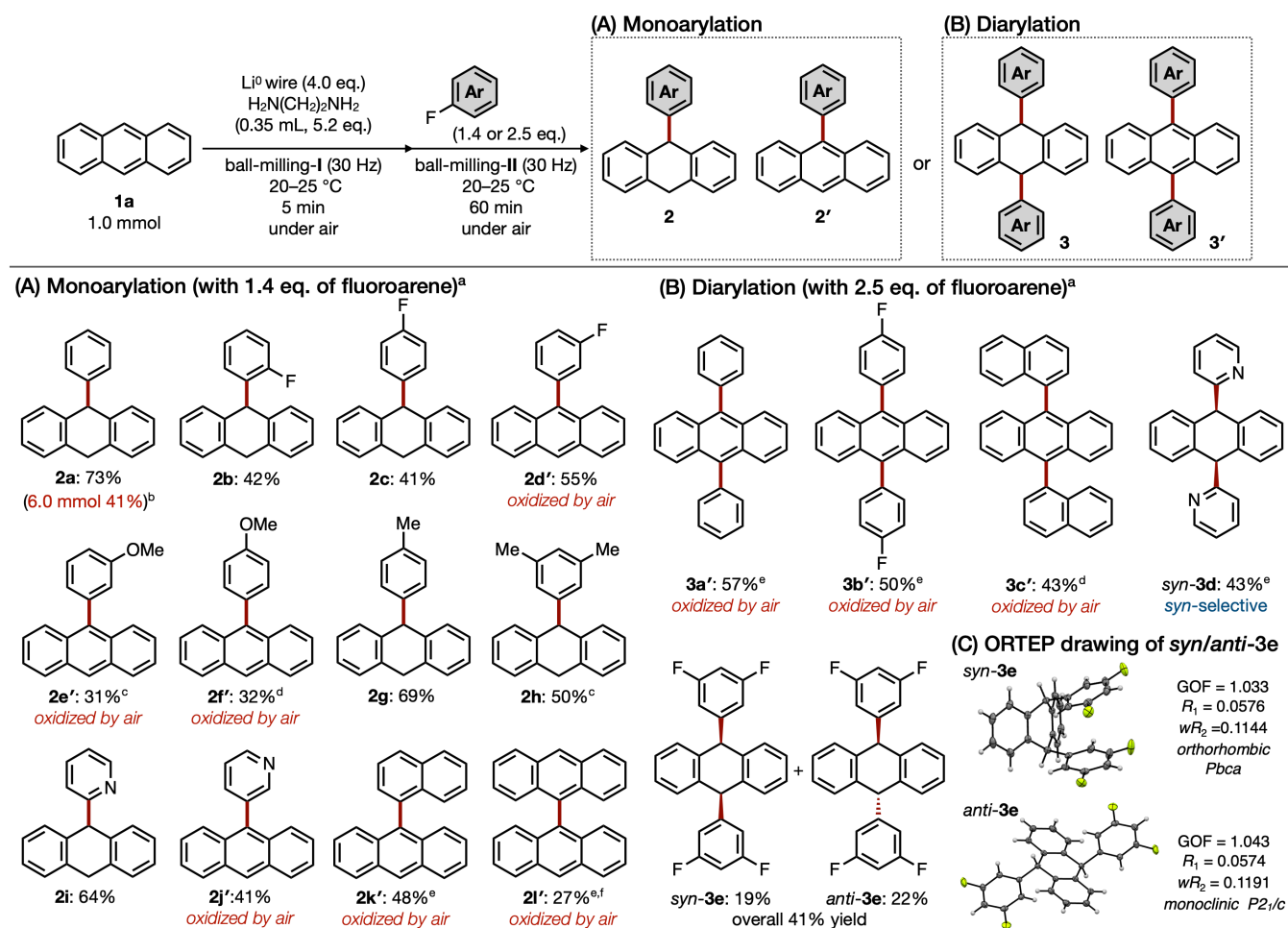


Figure 3. (A) Monoarylation of anthracene with 1.4 eq. of fluoroarenes. (B) Diarylation of anthracene with 2.5 eq. of fluoroarenes. (C) ORTEP drawing of compounds *syn*-**3e** and *anti*-**3e**. ^a Isolated yield. ^b Reactions are conducted in a 50-mL stainless steel jar using two 10-mm stainless steel 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.

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 (Figure 4). Based on the results that arylidihydroanthracenes **2/3** and arylanthracenes **2'/3'** 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 **5** to fully aromatized aryl PAHs **5'** (step-B) if the reaction gave mixtures of **5** and **5'**. 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 (**4a**) yielded complex mixtures, including dihydroarylated product **5a**, arylated 3-phenylfluoranthene (**5a'**), and other Birch reduction side-products, in the crude mixture. Therefore, oxidation (step-B) with *o*-

chloranil was conducted to obtain **5a'** in 20% yield. The reaction of pyrene (**4b**) and benzo[*a*]pyrene (**4c**) afforded corresponding spontaneously oxidized arylated-PAH **5b'** and **5c'** as single products without step-B in 17% and 35% isolated yields, respectively. The arylation reaction with benzo[*a*]anthracene (**4d**) afforded 7-phenyl-7,12-dihydrotetraphene (**5d**), whose structure was elucidated by X-ray crystallographic analysis, in a 42% yield. **5d** could be converted to 7-phenyltetraphene (**5d'**) using DDQ in 54% isolated yield. The use of benzo[*f*]tetraphene (**4e**), tetracene (**4f**), and pentacene (**4g**) provided arylated dihydro-PAHs **5e–5g**, and **5g-py** were obtained in 27% to 56% yields.

Application to other polycyclic aromatic hydrocarbons ^a

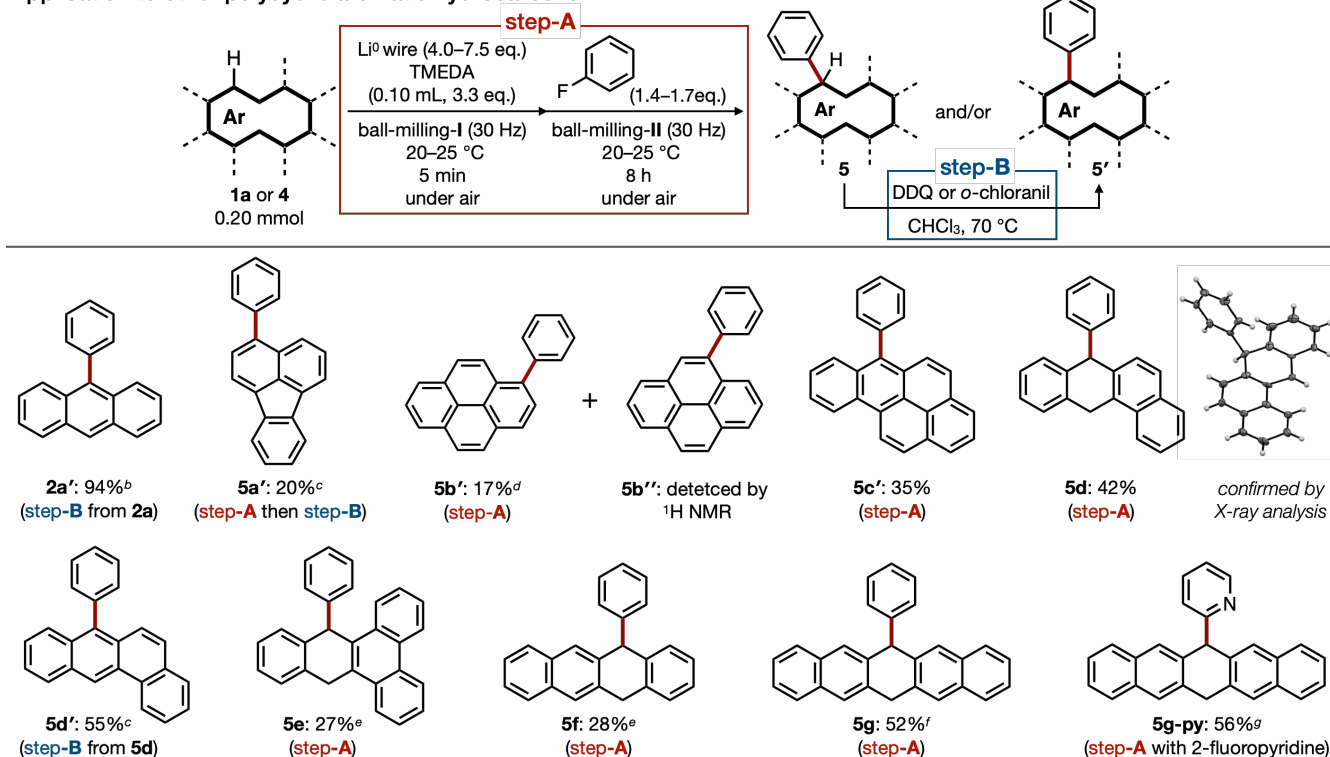


Figure 4. Substrate scope in arylation of PAHs and oxidation of dihydroanthracene to anthracene derivatives. ^a Isolated yield. ^b Step-B is conducted with *o*-chloranil (2.0 eq.) in benzene (10 mL). ^c step-B is conducted with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (4 eq.) after the ball-milling-II. ^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 (**4a**), pyrene (**4b**), benzo[*a*]pyrene (**4c**), benzo[*f*]tetraphene (**4e**), tetracene (**4f**), and pentacene (**4g**) were used as starting materials.

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 Figure 2E, we hypothesized that this reaction mainly proceeds via the dianion species of PAHs and that each reactive site can be formed by disproportionational HOMO coefficients and NBO charges in each peripheral carbon atom of the PAH dianions (Figure 5).¹⁷ 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**, **4a**, **4b**, and **4d–4g**. In the case of the dianions of **4c**, 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 potential¹⁸ of the same dianionic PAHs also supported this regioselectivity (see SI for details).

NBO charges (HOMO coefficients)

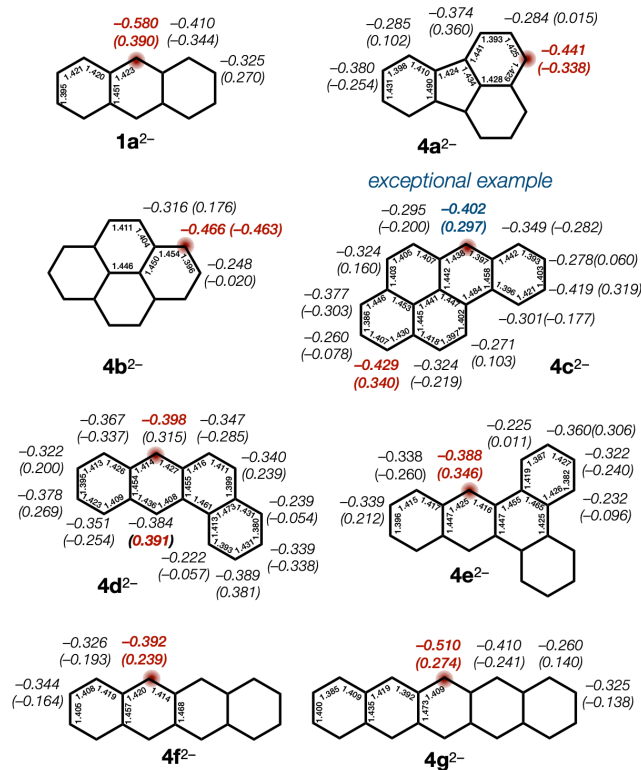


Figure 5. NBO charges and HOMO coefficients (in brackets) of PAH dianions calculated at B3LYP/6-31+G(d,p) level of theory. Red-colored values represent the positive or negative largest values of the HOMO coefficient and negative largest NBO charge. Red-colored

circles represent the experimental arylation positions. The bond lengths (Å) are shown inside structures.

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 (**6**) was obtained in 27% isolated yield (Figure 6A). This multi-fold arylation can be also applied to pentacene, affording 6,6,13,13-tetra(pyridin-2-yl)-6,13-dihydropentacene (**7**) in a 24% isolated yield (Figure 6B). 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 (Figure 6C), followed by diarylation to afford **3d**, as shown in Figure 3B. Compound **3d** was considered to process more acidic benzylic protons (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 **7**. Single crystals of **6** and **7** were also obtained by recrystallization from CHCl₃/hexane (for **6**) and MeOH/Et₂O (for **7**), 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.

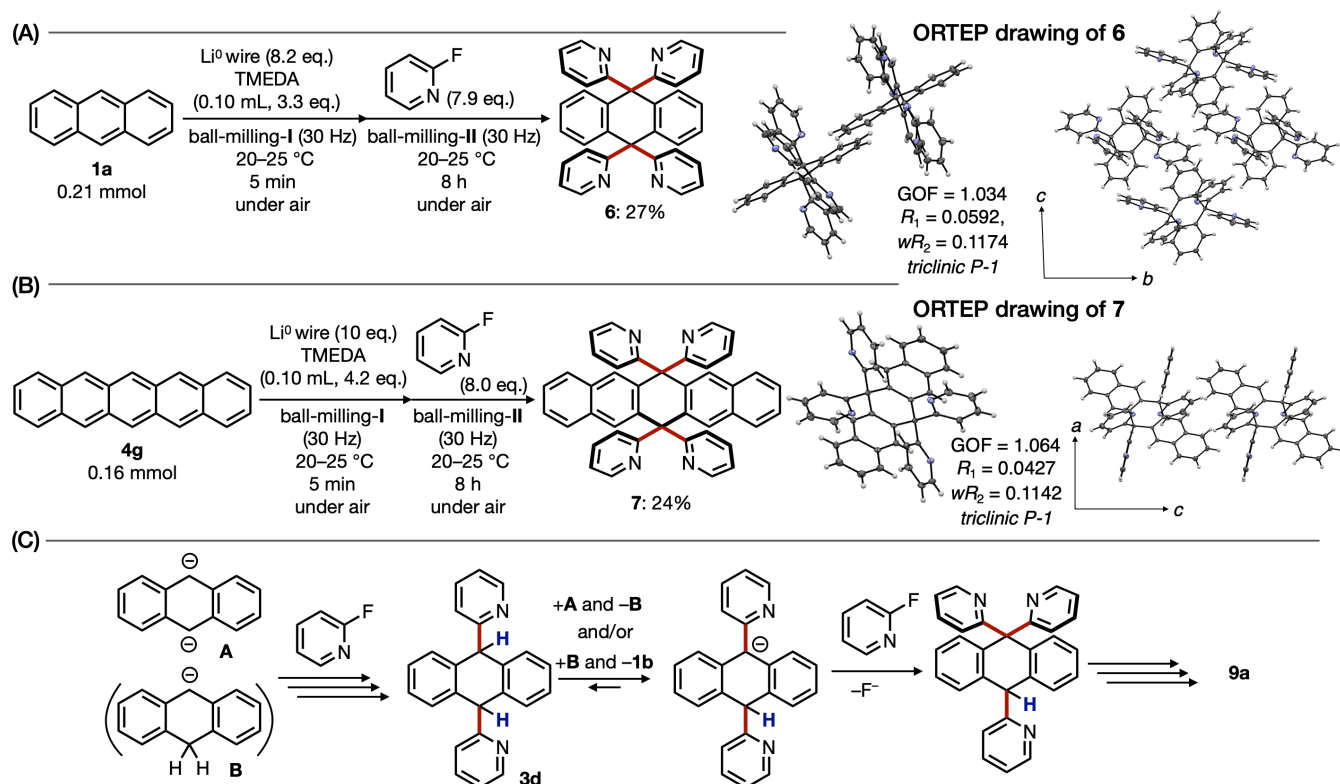


Figure 6. (A) Four-fold arylation of anthracene for synthesis (A) tetrapyridinylidihydroanthracene **6**, and (B) tetrapyridinylidihydropentacene **7**. (C) Proposed reaction mechanism.

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

Finally, to apply current mechanochemical arylation for nanographene synthesis, we attempted *fissure-region*¹⁹ annulative π -extension (*fissure-APEX*) reaction by combining previously developed lithium(0)-mediated mechanochemical cyclodehydrogenation.¹⁰ Grinding fluoranthene (**4a**) with lithium(0) wire and 1-fluoronaphthalene afforded 3-(1-naphthalenyl)fluoranthene (**8**) in an 18% yield. **8** was converted to the perylene derivative (**9**) using the mechanochemical cyclodehydrogenation method that we previously reported. The one pot C–H arylation and cyclodehydrogenation was attempted with pyrene (**4b**) and afforded **10** as an orange solid in a 6% yield. While the yield was not unsatisfactory, this reaction is considered the first example of one-pot *fissure-region* APEX. Further investigations on the conditions of *fissure-region* APEX reaction are ongoing in our laboratory (Figure 7).

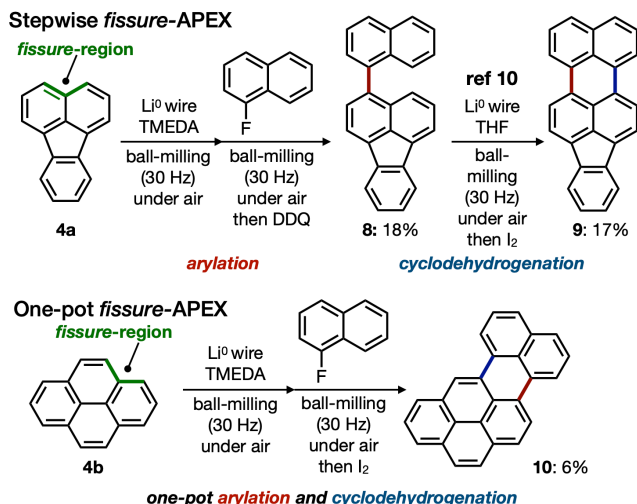


Figure 7. *Fissure-APEX* reactions via lithium-mediated mechanochemical arylation and cyclodehydrogenation. For detailed reaction conditions, see SI.

Conclusion

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 and a rare example of carbon–carbon bond formation reaction between carboanions and fluoroarenes via S_NAr. Unlike previous solution-based Birch reductive functionalizations, the newly 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 new methodology is useful not only as a formal direction arylation method for unfunctionalized aromatics, but also a complementary arylation method for conventional cross-coupling reaction. Further investigations into the reaction mechanism is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge on the ChemRxiv website. Experimental procedures, ¹H and ¹³C NMR spectra, data characterization of all new compounds, optical properties, and computational data.

Accession Code

CCDC numbers of *anti-3e* (2374003), *syn-3e* (2374004), **6** (2374002) and **7** (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.

AUTHOR INFORMATION

Corresponding Author

* ito.hideto.p4@f.mail.nagoya-u.ac.jp (H.I.)

* kenichiro.itami@riken.jp (K.I.)

ACKNOWLEDGMENT

This study was supported by the Sumitomo Foundation, Foundation of Public Interest of Tatematsu, Kondo Memorial Foundation, NAGAI Foundation of Science & Technology (to H.I.), and JST-CREST (JPMJCR19R1 to A.Y.). Y.T. thanks the Interdisciplinary Frontier Next-Generation Researcher Program of the Tokai Higher Education and Research System for the fellowships. We thank Dr. Keigo Yamada (Nagoya Univ.) and Mr. Takato Mori (Nagoya Univ.) for helping the X-ray diffraction analysis. The computations were performed at the Research Center for Computational Science, Okazaki, Japan (Project Nos. 23-IMS-C061 and 24-IMS-C059). The authors declare no competing financial interests.

REFERENCES

1. Ito, H.; Ozaki, K.; Itami, K. Annulative π -Extension (APEX): Rapid Access to Fused Arenes, Heteroarenes, and Nanographenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 11144.
2. Roche, S. P.; Porco Jr, J. A. Dearomatization Strategies in the Synthesis of Complex Natural Products. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.
3. (a) Birch, J. A. Reduction by dissolving metals. Part I. *J. Chem. Soc.*, **1944**, 430. (b) Rabideau, P. W.; Marcinow, Z. The Birch Reduction of Aromatic Compounds. *Organic Reactions*, **2004**, *42*, 1. (c) Zimmerman, H. E. A Mechanistic Analysis of the Birch Reduction. *Acc. Chem. Res.* **2012**, *45*, 164.
4. Benkeser, R. A.; Robinson, R. E.; Landesman, H. The True Identity of the Solvated Free Radical "Triphenylsilyl Ethylamine." The Multiple Addition of Lithium to an Aromatic System in Ethylamine. *J. Am. Chem. Soc.* **1952**, *74*, 5699.
5. (a) Lebeuf, R.; Dunet, J.; Beniazza, R.; Ibrahim, D.; Bose, G.; Berlande, M.; Robert, F.; Landais, Y. Birch Reductive Alkylation of Biaryls: Scope and Limitations. *J. Org. Chem.* **2009**, *74*, 6469. (b) Hook, J. M.; Mander, L. N. Recent developments in the Birch reduction of aromatic compounds: applications to the synthesis of natural products. *Nat. Prod. Rep.*, **1986**, *3*, 35. (c) Perez, H.; Melero, C.; Guijarro, A.; Yus, M. The reaction of biphenyl radical anion and dianion with alkyl fluorides. From ET to S_N2 reaction pathways and synthetic applications. *Tetrahedron*. **2009**, *65*, 10769.
6. Melero, C.; Herrera, R. P.; Guijarro, A.; Yus, M. New Modes of Reactivity in the Threshold of the Reduction Potential in Solution. Alkylation of Lithium PAH (Polycyclic Aromatic Hydrocarbon) Dianions by Primary Fluoroalkanes: A Reaction Pathway Complementing the Classical Birch Reductive Alkylation. *Chem. Eur. J.* **2007**, *13*, 10096.
7. Fukazawa, M.; Takahashi, F.; Yorimitsu, H. Sodium-Promoted Borylation of Polycyclic Aromatic Hydrocarbons. *Org. Lett.* **2021**, *23*, 4613.
8. Miwa, K.; Aoyagi, S.; Amaya, T.; Sasamori, T.; Morisako, S.; Kurogi, T.; Yorimitsu, H. Multiply *exo*-Methylated Corannulenes. *Chem. Eur. J.* **2023**, *29*, e202301557.
9. (a) Rodenburg, L.; De Block, R.; Bieze, T. W. N.; Cornelisse, J.; Lugtenburg, J. Reactivity of pyrene dianion and some of its 2-substituted derivatives. *Recl. Trav. Chim. Pays-Bas.* **1988**, *107*, 9. (b) Van loo, M. E.; Lugtenburg, J.; Cornelisse, J. Reactivity of the Acenaphthylene Dianion Towards Electrophiles. *POLYCYCL AROMAT COMP.* **1999**, *14*, 109. (c) Harvey, R. G.; Lindow, D. F.; Rabideau, P. W. Metal-ammonia reduction—XIV: Fluoranthene: Correlation of primary product structure with HMO theoretical prediction. *Tetrahedron*, **1972**, *28*, 2909. (d) Lindow, D. F.; Cortez, C. N.; Harvey, R. G. Metal-Ammonia Reduction. XIII. Regiospecificity of Reduction and Reductive Methylation in the Terphenyl Series. *J. Am. Chem. Soc.* **1972**, *94*, 5406.
10. Fujishiro, K.; Morinaka, Y.; Ono, Y.; Tanaka, T.; Scott, L. T.; Ito, H.; Itami, K. Lithium-Mediated Mechanochemical Cyclodehydrogenation. *J. Am. Chem. Soc.* **2023**, *145*, 8163.
11. Gao, Y.; Kubota, K.; Ito, H. Mechanochemical Approach for Air-Tolerant and Extremely Fast Lithium-Based Birch Reductions in Minutes. *Angew. Chem., Int. Ed.* **2023**, *135*, e202217723.
12. (a) Wang, G. W. Mechanochemical organic synthesis. *Chem. Soc. Rev.* **2013**, *42*, 7668. (b) Kubota, K.; Ito, H. Mechanochemical Cross-Coupling Reactions. *TRENDS CHEM.* **2020**, *2*, 1066.
13. Eisenstein, O.; Milani, J.; Perutz, R. N. Selectivity of C–H Activation and Competition between C–H and C–F Bond Activation at Fluorocarbons. *Chem. Rev.* **2017**, *117*, 8710.
14. Atkins, P.W.; Overton, T. L.; Rourke, J. P.; Weller, M. T.; Armstrong, F. M. *Shriver and Atkins' Inorganic Chemistry, Fifth Edition*, **2010**. Oxford University Press.
15. (a) Kubota, K.; Fukuzawa, Y.; Kondo, K.; Gao, Y.; Ito, H. Highly Efficient and Air-tolerant Calcium-based Birch Reduction Using Mechanochemistry. *Chem. Lett.* **2024**, *53*, upae060. (b) Kondo, K.; Kubota, K.; Ito, H. Mechanochemistry enabling highly efficient Birch reduction using sodium lumps and D-(+)-glucose. *Chem. Sci.* **2024**, *15*, 4452.
16. Housecroft, C. E.; Sharpe, A. G. *Inorganic Chemistry 5th edition*, **2018**, Pearson.

17. (a) Weinhold, F.; Landis, C. R. NATURAL BOND ORBITALS AND EXTENSIONS OF LOCALIZED BONDING CONCEPTS. *Chem. Educ. Res. Pract.* **2001**, *2*, 91. (b) Glendening, E. D.; Landis, C. R.; Weinhold, F. *NBO 6.0: Natural bond orbital analysis program. J. Comput. Chem.* **2013**, *34*, 1429.
18. Singh, U. C.; Kollman, P. A. An approach to computing electrostatic charges for molecules. *J. Comput. Chem.* **1984**, *5*, 129.
19. Dias, J. R. Perimeter Topology of Benzenoid Polycyclic Hydrocarbons. *J. Chem. Inf. Model.* **2005**, *45*, 562.