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"Buttressing Effect" in the Halogen-Lithium Exchange in *ortho*-Bromo-*N,N*-dimethylanilines and Related Naphthalenes

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Dedicated to Professor Alexander F. Pozharskii on the occasion of his 85th birthday.

Non-covalent interactions such as coordination of an organolithium reagent by a directing group and steric repulsion of substituents strongly affect the halogen-lithium exchange process. Here we present the manifestation of the "buttressing effect" – an indirect interaction between two substituents issued by the presence of a third group – and its influence on the ease and selectivity of the bromine-lithium exchange and the reactivity of formed aryllithiums. The increase of the size of the "buttressing" substituent strongly affects the conformation of a NMe_2 group, forcing it to hinder *ortho*-bromine and thus slowing down the exchange. In naphthalene substrates bearing two bromines, this suppresses regioselectivity of the reaction. The "buttressing effect" forces formed aryllithiums to deaggregate, thus boosting their reactivity. This facilitates the decomposition via protolisys by ethereal solvents even at low temperatures and in some cases initiates fast Wurtz-Fittig coupling.

Introduction

Pioneered by Wilhelm Schlenk in 1917, organolithium reagents drastically elevated their role in synthetic chemistry over the past hundred years and solidified their position among the most versatile and widely used reagents in organic synthesis.[1–5] The reason of such prosperity is a low cost, the simplicity of handling (operations at temperatures of liquid ammonia or dry ice under argon atmosphere are a common practice nowadays) and generally clean, selective and high-yielding reactivity. Solvents used in organolithium chemistry are typically mixtures of low-boiling alkanes and ethers, which can be removed in an energy-efficient way by distillation. Recent advances in the field allowed the use of nonconventional media such as deep eutectic solvents[6] and gels,[7] as well as the application of flow processes.[8–11] Although lithium must be removed from industrial wastewater after product separation, this disadvantage is more than compensated by the abovementioned advantages of organolithium reagents. It is no surprise that nowadays, it is almost impossible to imagine an industrial multistep synthesis of biologically active and natural compounds without the utilization of organolithiums during one process step at least.[12,13] This naturally stimulates research on the novel synthetic approaches and selective reactivity of organolithiums.

Today, the halogen-lithium exchange, first developed by Karl Ziegler,[14] regains its status as one of the most important and versatile methods for the synthesis of organolithiums.[15] Effective utilisation of this approach for the preparation of complex organolithiums, which are desirable for the synthesis of biologically active and natural compounds, requires a deep understanding of the factors controlling the ease and selectivity of this process. It is no surprise that to date, key features of the halogen-lithium exchange were thoroughly investigated, especially in the benzene series. It has been shown that heteroatomic groups capable of coordinating metal (so-called directing groups) facilitate the halogen exchange in the *ortho*-position, thus providing regioselective functionalization (Scheme 1a).[16–20] At the same time, the charge overload and realization of an "electron sink" (the possibility to utilize excess electrons) significantly control the ease and regioselectivity of halogen exchanges. For example, the halogen substitution in 4-bromo-*N,N*-dimethylaniline requires a higher temperature and longer exposure time in comparison with 2-bromo isomer, due to the electronic "resistance" provided by the conjugation of the NMe_2 group with the aromatic ring (Scheme 1b).[3,21,22] This conjugation can also serve as a driving force for regioselectivity: being generally not noticeable for small molecules, it strongly manifests itself in rigid structures like naphthalenediamine **1**, forcing the halogen-lithium exchange towards the product with the best conjugation, even though it means a poor saturation

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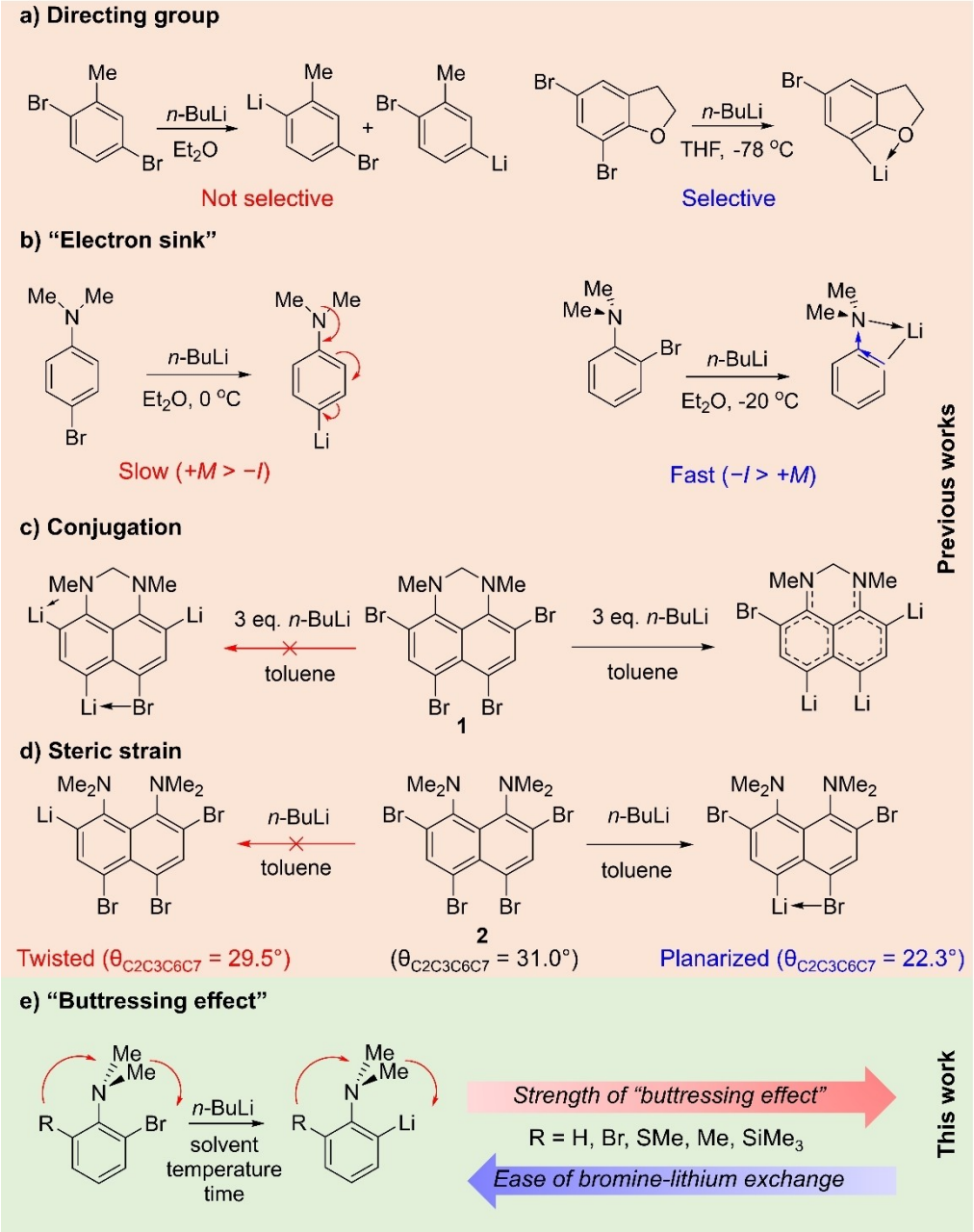
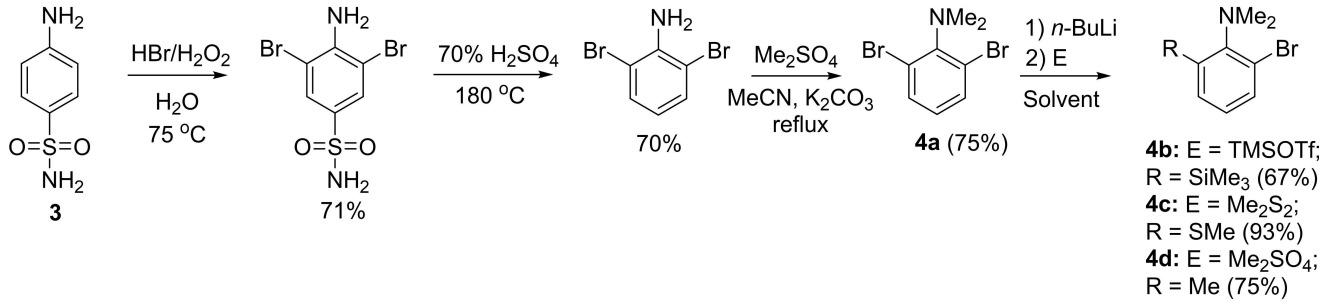


Scheme 1. Factors controlling the Br→Li exchange. Directing groups bearing lone electron pairs coordinate organolithium reagents, providing excellent *ortho*-selectivity (a). The presence of strong electron donating groups in the aromatic core suppresses the halogen-lithium exchange in *para*-position (b). The conformational change after the substitution of *ortho*-bromine allows the effective conjugation of the NMe group with the aromatic core, which in turn facilitates the *ortho*-exchange (c). Planarization of twisted naphthalene ring facilitates the exchange *para*-bromine (d). This work's finding: the increase of steric pressure of the bulky substituent affects the conformation of the NMe_2 group, forcing it to sterically hinder the neighbouring bromine and suppresses the halogen-lithium exchange (d)

of the lithium coordination sphere via intramolecular interactions (Scheme 1c).[23]

Finally, steric strain plays a key role in the halogen-lithium exchange. It is especially pronounced in the naphthalene series where rigidity of the fused aromatic system significantly elevates the impact of steric repulsion. Thus, in our recent paper, we have shown that the directing effect of dimethylamino groups in naphthalenediamine **2** can be completely suppressed by the steric strain of the twisted molecule (Scheme 1d).[24]

However, in the benzene series, the impact of steric effects on the halogen-lithium exchange is generally less manifested and poorly studied. Chemical intuition suggests that the presence of a bulky substituent in the *ortho*-position to the halogen atom will slow the process down. At the same time, it is less obvious how the conformational mobility of this substituent affects the steric availability of the neighboring



Scheme 2. Highly effective synthesis of model 6-substitued-2-bromo-*N,N*-dimethylanilines **4** starting from commercially available sulfanilamide **3**.

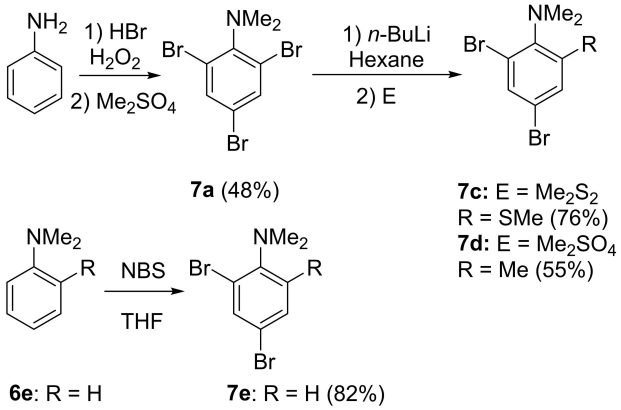
halogen atom in the presence of a second substituent in *ortho*-position to the first one. This complex situation manifests itself in the case of 2,3-disubstituted-1-halobenzenes: the halogen atom is in proximity with the substituent in position 2, which is influenced by the steric pressure of the substituent in position 3. This indirect interaction (so-called "buttressing effect") plays an important role in the reactivity of organic and organometallic species.[25–27] For instance, it dramatically enhances the basicity of naphthalene proton sponges.[28,29] Keeping the demand of polyfunctionalised organolithiums for the synthesis of complex organic molecules and natural products in mind, the understanding of the influence of "buttressing effect" on the ease and selectivity of halogen-lithium exchanges becomes crucial for the rational planning of synthetic sequences. Therefore, we present the very first study of the manifestation of the "buttressing effect" in the bromine-lithium exchange in 6-substituted-2-bromo-*N,N*-dimethylanilines and related dimethylaminonaphthalenes (Scheme 1e) and its impact on the ease and regioselectivity of the process. Using an intertwined approach between an experimental treatment of bromoanilines with organolithiums and quantum chemical modeling of the structure of lithioanilines, we, for the first time, propose a clear correlation between the size of "buttressing" substituent and the ease of the halogen-lithium exchange.

Results and Discussion

Model systems. For the investigation of the manifestation of the "buttressing effect" and its influence on the halogen-lithium exchange, the 2,3-disubstitued-1-halobenzenes and 1,8-disubstituted-8-halonaphthalenes are the perfect models. These compounds possess a "buttressing" substituent in *ortho*- and *peri*-position to the NMe_2 group, which strongly affects its conformation. With this in mind, we have selected 6-substituted-2-bromo-*N,N*-dimethylanilines and 8-substituted-2-bromo-1-dimethylaminonaphthalenes for this study. The presence of the dimethylamino group is highly beneficial since its conformation is strongly affected by the neighbouring *ortho*- and *peri*-substituents. Being "buttressed" by this substituent, NMe_2 group sterically shields *ortho*-bromine and affects the halogen-lithium exchange. This impact can be tuned by varying the size of the "buttressing" substituent, which allows the establishment of correlations between the bulkiness of the substituent and the ease and selectivity of the halogen-lithium exchange.

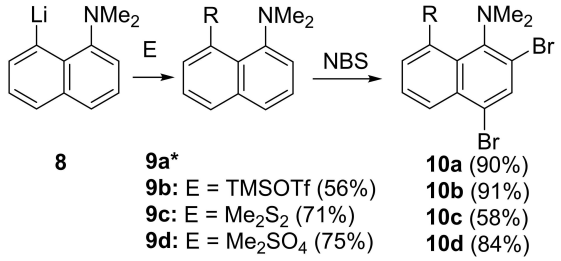
For the synthesis of the key compound of this research – 2,6-dibromo-*N,N*-dimethylaniline **4a** – we have developed a simple and efficient three stage approach based on the bromination of commercially available sulfanilamide **3**, followed by desulfonation in the presence of sulfuric acid and alkylation with dimethyl sulfate (Scheme 2). Further treatment of **4a** with *n*-butyllithium and electrophiles allowed us to prepare 6-substituted 2-bromo-*N,N*-dimethylanilines **4b–d** with good yields, despite some complications (see below).

For the regioselectivity studies, we performed the synthesis of 2,4-dibromo-*N,N*-dimethylanilines **7**. 6-Subsituted dibromoanilines **7c** and **7d** were prepared via subsequent treatment of 2,4,6-tribromide **7a** with *n*-BuLi in hexane and a suitable electrophile (Scheme 3). Our attempts to prepare a similar compound containing a $SiMe_3$ substituent using trimethylsilyl chloride or triflate under various conditions have failed: no Si-containing species were observed in the final reaction mixture. We also tested the possibility to access dibromides **7** via bromination of corresponding dimethylanilines **6**. 2,4-Dibromide **7e** was successfully prepared by direct bromination of *N,N*-dimethylaniline with NBS. In contrast, bromination of **6b** (R = $SiMe_3$) and **6c** (R = SMe) with NBS or HBr/DMSO provided unsatisfactory results: **6b** underwent *ipso*-substitution of the $SiMe_3$ group with the formation of **7e**, while **6c** transformed



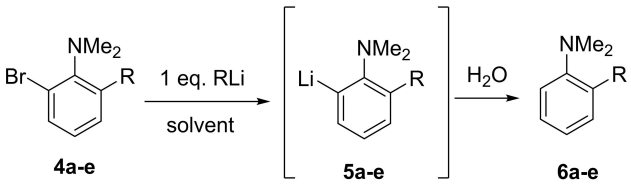
Scheme 3. High yielding synthesis of model 2,4-dibromo-*N,N*-dimethylanilines **7c-d**. Attempts to prepare **7b** (R = $SiMe_3$) have failed (see text for details).

into an inseparable complex mixture, probably due to the competition between directing effects of the NMe_2 and SMe groups. Attempts of bromination of **4b–d** with NBS or HBr/DMSO at various conditions also failed by leaving the starting material unreacted. This seems to be issued by the electron deficiency of the benzene ring originating from poor conjugation with the NMe_2 group and the strong $-I$-effect of bromine.



a: R = H; **b**: R = $SiMe_3$; **c**: R = SMe; **d**: R = Me

Scheme 4. Simple and highly efficient synthesis of model 2,4-dibromo-1-dimethylaminonapthalenes **10**. ***9a** is available commercially and used for the preparation of **8** (see experimental part in SI).



a: R = Br; **b**: R = $SiMe_3$; **c**: R = SMe; **d**: R = Me; **e**: R = H

Scheme 5. General approach to the bromine-lithium exchange. The formation of lithioanilines **5** is determined by quenching them with water to give easily NMR detectable anilines **6**.

Additionally, 2,4-dibromo-1-dimethylaminonaphthalenes **10** were synthesized via the bromination of corresponding 1-dimethylaminonaphthalenes **9** with NBS (Scheme 4). The latter were obtained with excellent yields via the reaction of easily available lithionaphthalene **8**[30] with suitable electrophiles.

The impact of the "buttressing effect" on the ease of the bromine-lithium exchange. The bromine-lithium exchange experiments were performed in hexane, diethyl ether, and tetrahydrofuran at different temperatures. In a typical experiment, the corresponding aryl bromide was treated with *n*-BuLi or *tert*-BuLi and the resulting reaction mixture was quenched with degassed water (Scheme 5).

Our experiments started with the most extreme case of **4b** containing the largest substituent R = TMS. When **4b** is treated with *n*-butyllithium in *n*-hexane or diethyl ether at −25 °C, no signs of a halogen-metal exchange are observed even after 24 h (Table 1, runs 1,2). Increasing the reaction temperature to 5 °C allows a noticeable but incomplete conversion (runs 3,4). Switching to tetrahydrofuran as a solvent allows a significant improvement in conversion even at −25 °C (runs 5,6). Increasing the temperature to 25 °C provides a much better but still incomplete conversion (runs 7–9). We believe that the steric shielding of bromine by methyl groups enhanced by the strong "buttressing effect" of TMS group prevents the effective attack of bulky aggregates of *n*-butyllithium. The latter is hexameric in hexane and tetrameric in diethyl ether.[31] The transition to THF facilitates the deaggregation of *n*-butyllithium to dimer, thus increasing the reactivity. In fact, the use of less aggregated *tert*-butyllithium allows a better conversion already at −25 °C (runs 10–12). Increasing the reaction temperature to 5 °C leads to 100% conversion to the target product **6b** in *n*-hexane (run 13). Replacing the solvent with diethyl ether at 5 °C leads to a decrease in conversion with *tert*-BuLi, which is due to the destruction of the organometallic reagent under these con-

Table 1. Bromine-lithium exchange in **4b**. *n*-BuLi provides the best conversion in ethereal solvents at elevated temperatures. However, formed lithioderivative **5b** is unstable under these conditions. The best results are achieved using *tert*-BuLi in hexane providing both excellent conversion of **4b** and stability of **5b**.

Run	RLi	Aggregation of RLi[a]	Solvent	T, °C	Time	**4b**:**6b** ratio
1	*n*-BuLi	hexamer	hexane	−25	24 h	1:0
2	*n*-BuLi	tetramer	Et_2O	−25	24 h	1:0
3	*n*-BuLi	hexamer	hexane	5	24 h	1:0.6
4	*n*-BuLi	tetramer	Et_2O	5	24 h	1:0.7
5	*n*-BuLi	dimer	THF	−25	24 h	1:3.3
6	*n*-BuLi	dimer	THF	5	24 h	1:3.3
7	*n*-BuLi	hexamer	hexane	25	24 h	1:1
8	*n*-BuLi	tetramer	Et_2O	25	24 h	1:6
9	*n*-BuLi	dimer	THF	25	24 h	1:5
10	*t*-BuLi	tetramer	hexane	−25	24 h	1:0.32
11	*t*-BuLi	dimer	Et_2O	−25	24 h	1:1
12	*t*-BuLi	monomer	THF	−25	24 h	1:1.6
13	*t*-BuLi	tetramer	hexane	5	24 h	0:1
14	*t*-BuLi	dimer	Et_2O	5	24 h	1:3

[a] In the solvent used for reaction.[31]

ditions: *tert*-butyllithium starts reacting with diethyl ether already at 0 °C (run 14).[32]

In contrast to **4b**, unsubstituted at position 6 bromoaniline **4e** undergoes a fast halogen-lithium exchange already in hexane at −25 °C (Table 2, run 1).

The transition from **4e** to **4c**, containing conformationally mobile methylthio substituent leads to a slowdown of the reaction of **4c** with *n*-butyllithium. Thus, in hexane at −25 °C only trace amounts of the product **6c** can be detected (run 2). Usage of diethyl ether and THF leads to a significant increase of the product content up to a quantitative conversion in tetrahydrofuran (runs 3,4). We were not able to investigate the conversion at a higher temperature to the full extent. Thus, in hexane at 25 °C, a quantitative conversion is achieved already after 2 min (line 5). On the contrary, usage of diethyl ether and especially tetrahydrofuran gives poorly reproducible results and an incomplete conversion (lines 6,7). We attribute this result to the relative ease of metalation of the SMe group in such solvents, as it was recently demonstrated.[33]

Treatment of aniline **4d**, which contains a conformationally rigid methyl substituent, with *n*-BuLi leads to a much more difficult halogen-metal exchange in comparison with **4c**. Thus, at −25 °C, only trace amounts of **6d** are observed in hexane and in diethyl ether (runs 8,9). Switching to tetrahydrofuran allows to achieve significant conversion already after 2 minutes (run 10). Increasing the temperature to 25 °C provides an almost quantitative conversion after 2 minutes, regardless of the solvent (lines 11–13).

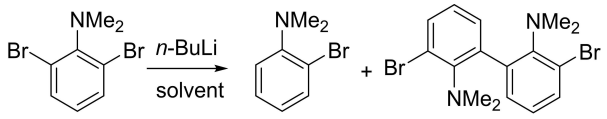
The reactivity of **4a**, containing two bromine atoms in *ortho*-positions to NMe_2 group, towards *n*-BuLi in *n*-hexane is by far superior to **4b-d**, however, it is noticeably inferior to the unsubstituted bromoaniline **4e** (Table 3, runs 1–3). Surprisingly, switching the solvent to diethyl ether results in the formation of yet another product – biphenyl **12** – already after 2 minutes at −25 °C (run 4), which becomes the major component (together with traces of **6a**) of the reaction mixture after 24 h (run 5). Considering the reaction conditions, the formation of **12** occurs via an uncatalyzed cross-coupling reaction between the initially formed **5a** and the starting material **4a**. This transformation – a variation of the Wurtz-Fittig reaction – is a common side-reaction in the synthesis of organolithiums. However, it normally manifests itself in the presence of alkyliodides at elevated temperatures. Spontaneous cross-couplings between arylbromides and aryllithiums at a low temperature were never encountered before, to our knowledge. We believe that the inability of NMe_2 to effectively conjugate with the aromatic ring in combination with a strong -*I*-effect of all substituents facilitates the coupling reaction. Indeed, among all studied bromoanilines, only **4a** gives corresponding biphenyl upon treatment with *n*-BuLi.

Even more unexpected is the influence of the amount of used *n*-BuLi in the formation of biphenyl **12**. Thus, increasing the load of *n*-BuLi to 1.5 equiv. provides no traces of **12**, while a large amount of unreacted **4a** is still present in the reaction mixture together with **6a** (runs 6–10). We assume that this somewhat counterintuitive result originates from the formation of the stable mixed organolithium aggregate **5a**·*n*-BuLi, the bulkiness of which prohibits further reaction with **4a**, thus preventing the formation of **12** (Scheme 6). The fact that a noticeable amount of **4a** stays unreacted even in the presence of an excess of *n*-BuLi at a low temperature is in agreement with the previously discussed behavior of **4c–d**. The concept of the mixed aggregate **5a**·*n*-BuLi formation suppressing cross-coupling is in agreement with the abovementioned experiments in *n*-hexane. In this media **5a** should exist in the form of self-associates (tetramers or dimers), which sterically hinders *ipso*-carbon and prevents cross-coupling. Transition to diethyl ether or THF results in the deaggregation of most aryllithiums to monomers, especially sterically strained ones,[31,34] facilitating further transformation, such as Wurtz-Fittig reaction. Usage of

Table 2. Bromine-lithium exchange in **4c–e** with *n*-BuLi. The strengthening of the "buttressing effect" via the increase of the size of substituent R slows down the halogen-lithium exchange.

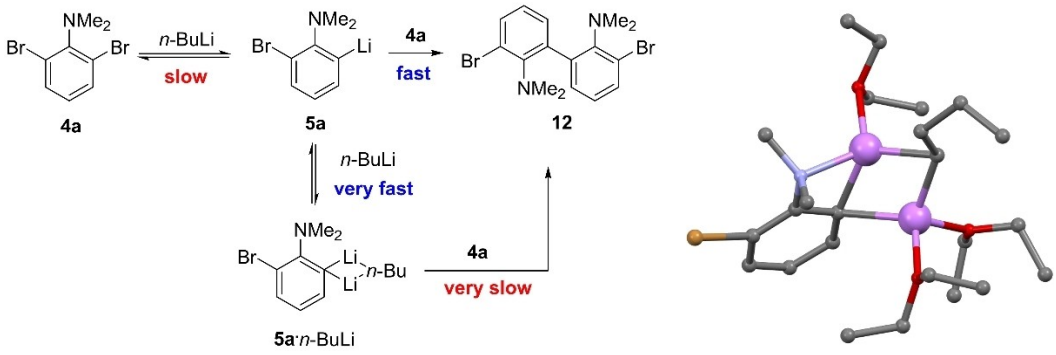
Run	Compound	R	Solvent	T, °C	Time	**4:6** ratio
1	**4e**	H	hexane	−25	24 h	0:1
2	**4c**	SMe	hexane	−25	24 h	1:0.1
3	**4c**	SMe	Et_2O	−25	24 h	1:0.5
4	**4c**	SMe	THF	−25	24 h	1:4.9
5	**4c**	SMe	hexane	25	2 min	0:1
6	**4c**	SMe	Et_2O	25	2 min	1:1.4
7	**4c**	SMe	THF	25	2 min	1:1
8	**4d**	Me	hexane	−25	24 h	1:0.1
9	**4d**	Me	Et_2O	−25	24 h	1:0.1
10	**4d**	Me	THF	−25	2 min	1:0.9
11	**4d**	Me	hexane	25	2 min	1:4.1
12	**4d**	Me	Et_2O	25	2 min	0:1
13	**4d**	Me	THF	25	2 min	0:1

Table 3. Bromine-lithium exchange in **4a** with *n*-BuLi. Initially formed lithioaniline **5a** undergoes fast spontaneous coupling with **4a**, giving biphenyl **12**. Utilization of the excess of *n*-BuLi suppresses biphenyl formation.



4a **6a** **12**

Run	*n*-BuLi, equiv.	Solvent	T, °C	Time	**4a:6a:12** ratio
1	1	hexane	−25	2 min	1:0.04:0
2	1	hexane	−25	24 h	1:0.6:0
3	1	hexane	25	2 min	0.2:1:0
4	1	Et_2O	−25	2 min	1:0.4:0.05
5	1	Et_2O	−25	24 h	0:0.06:1
6	1.1	Et_2O	−25	24 h	0:0.3:1
7	1.2	Et_2O	−25	24 h	0:0.7:1
8	1.3	Et_2O	−25	24 h	0.1:0.4:1
9	1.4	Et_2O	−25	24 h	0.3:0.6: 1
10	1.5	Et_2O	−25	24 h	0.6:1:0



Scheme 6. Proposed mechanism of biphenyl **12** formation upon treatment of **4a** with *n*-BuLi and its suppression in the presence of the excess of *n*-BuLi (left). Optimized geometry of heterodimer **5a**·*n*-BuLi·3Et_2O – B3LYP-GD3BJ/6-311++G(d,p) (right). Hydrogen atoms are omitted for clarity.

THF as a solvent results in the formation of an extremely complex mixture of products even after 2 minutes of exposure. That is why no further experiments with **4a** in THF were performed.

Altogether we have demonstrated the clear impact of the "buttressing effect" on the bromine-lithium exchange in 2-bromo-6-substituted-*N,N*-dimethylanilines. An increase of the size of the substituent in position 6 gradually suppresses the reaction ($SiMe_3 > Me > SMe > Br > H$). However, this issue can be overcome by using less aggregated organolithiums i.e. *tert*-BuLi in hexane or *n*-BuLi in THF.

The impact of the "buttressing effect" on the stability of lithioanilines towards protolysis by solvent. For the further discussion it is important to state that the high basicity of organolithiums allowing their interactions with weak CH-acids is related to the possibility to deaggregate in solutions. As a result, the formation of monomeric species significantly boosts their reactivity and vice versa strong association suppresses it. For instance, even though as a monomer, methyllithium is more basic than phenyllithium by more than 10 pK_a units in gas phase, in solutions in THF at 0.5 M concentration, it is of inferior reactivity due to the higher aggregation state.[35] That is why, common CH-lithiation techniques involve the usage of ethereal solvents or coordinative additives (such as TMEDA) to facilitate the deaggreation of organolithium reagents. With this in mind, in the further discussion, our attention is focused on the possibility of **5** to deaggregate to monomers and the structural features of the latter.

Aromatic organolithiums are usually stable in ethers even at elevated temperatures, with the exception of electron-enriched and poorly aggregated systems, such as lithium-1,8-bis(dimethylamino)naphthalenes.[34] For instance, phenyllithium is commercially available in a form of solutions in ethers and demonstrates stability for months if stored at 2–8 °C. With this in mind, one would expect a similar stability of lithioanilines studied in this work. However, the manifestation of the "buttressing effect" does not only hinder the halogen-lithium exchange but also affects the stability of formed lithiated species.

To support our experimental findings, the geometries and energies of studied lithiated species were calculated for their monomeric and dimeric complexes with THF considering the possibility of intramolecular coordination of the lithium atom by the NMe_2 group (Figure 1). Higher aggregates were not considered, since phenyllithiums predominantly exist in dimeric or monomeric form in ethereal media, as it was shown in multiple papers by Hans Reich.[36–38] Among all studied lithioanilines, only the formation of dimer (**5b**·THF_2)$_2$ is unfavorable: the dimeric structure does not correspond to the minima on potential energy surface and the optimization ends up with two independent monomers **5b**·THF_2 (Figure 1, Figure S63 in SI). At the same time, the steric pressure of the TMS group inverts the NMe_2 group, which makes coordination with the neighboring lithium atom thermodynamically unfavorable. As a result, among the studied monomers of lithioanilines only **5b** benefits from the introduction of the third THF molecule to the coordination sphere of lithium accompanied with the disruption of the $Me_2N \rightarrow Li$ interaction: the $\Delta\Delta G$ for the transition **5b**·2THF→**5b**·3THF is −0.38 kcal/mol, for all other cases the $\Delta\Delta G$ for this conformational transformation has positive values.

To experimentally test the stability of obtained lithiated species towards protolysis by solvent under reaction conditions after *in situ* preparation, they were treated with dry DMF to yield corresponding aldehydes **11** (Table 4). When protolysis took place, anilines **6** were observed in the reaction mixture together with aldehydes **11**. We find the introduction of the CHO group better than simple deuteration since it provides aldehydes **11**, which are much easier distinguished from anilines **6** in NMR spectra. DMF generally provides an excellent conversion of organolithiums into the corresponding aldehydes, even in the case of sterically hindered molecules.[30,39,40] It should be noted that at lower temperatures, the reaction of **5** with DMF in *n*-hexane is incomplete after 24 hours. That is why this data is not included in Table 4.

We have found that all studied lithioanilines **5** demonstrate excellent stability in *n*-hexane even at an elevated temperature, thus providing complete transformation to the corresponding aldehydes **11** upon treatment with dry DMF.

Transition to diethyl ether and THF dramatically changes the reaction outcome. 6-Unsubstituted-2-lithioaniline **5e** demonstrates good stability in Et_2O at low and elevated temperatures and provides good yields of aldehyde **11e** upon treat-

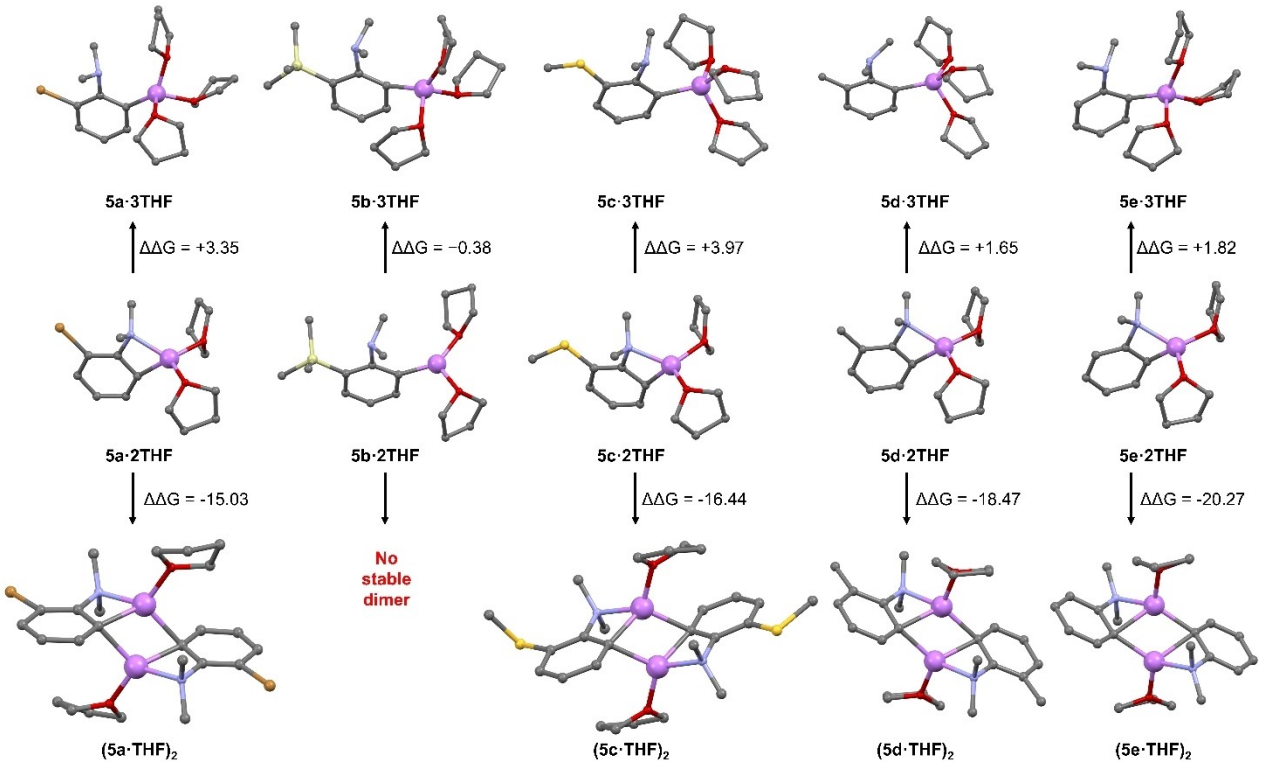
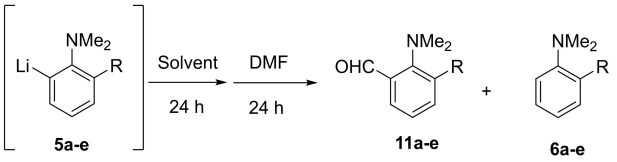


Figure 1. Optimized geometries of studied lithiated species. Monomers of **5b** in contrast to other lithioanilines demonstrate no tendency for the intramolecular coordination of the Li atom. Dimers of **5a**, **5c**, **5d** and **5e** show comparable stability, while dimer of **5b** does not correspond to the minimum on potential energy surface (see Figure S63 in SI). B3LYP-GD3BJ/6-311++G(d,p). Hydrogen atoms are omitted for clarity. Free Gibbs energy change values (ΔΔG, kcal/mol) are given

Table 4. The stability of **5** towards protolysis by solvent is checked by quenching with DMF. If preliminary protonation takes place, anilines **6** are observed in the final reaction mixture together with aldehydes **11**



5a-e **11a-e** **6a-e**

a: R = Br; **b**: R = $SiMe_3$; **c**: R = SMe; **d**: R = Me; **e**: R = H

Compound	**11**:**6** ratio			
	Hexane	Et_2O		THF
	25 °C	−25 °C	25 °C	−25 °C
5a	1:0	–[a]	–[b]	–[c]
5b	1:0	–[d]	0:1	0:1
5c	1:0	0:1	0:1	0:1[e]
5d	1:0	1:0	0:1	1:0[e]
5e	1:0	1:0	1:0[e]	–[f]

[a] due to the rapid cross-coupling with the starting material under these conditions aldehyde **11** was not detected (see table 3), however the formation of biphenyl **12** allows to indirectly determine the stability of **5a** towards protolysis by solvent: the ratio of **12**:**6e** is 1:0.4; [b] the formation of **12** is facilitated at higher temperatures intercepting protolysis: ratio **12**:**6e** is 1:0; [c] due to the complexity of the reaction of **4a** with *n*-BuLi in THF, stability tests for **5a** in this solvent were not performed; [d] **5b** cannot be generated under these conditions (see run 2, Table 1); [e] additional minor products were also detected; [f] the reaction mixture is very complex, however neither **11e** nor **6e** are present.

ment with DMF. This is in agreement with a previously published experiment using different electrophiles.[41,42] However, generation of **5e** in THF at −24 °C followed by storing the resulted mixture for 24 hours and then treating with DMF results in the formation of complex mixture, where neither **6e** nor **11e** can be detected. In contrast, lithioaniline **5b**, relatively easily formed by treatment of **4b** with *n*-butyllithium in tetrahydrofuran at −25 °C or in diethyl ether at 25 °C, decomposes rapidly under these conditions. Thus, the addition of dimethylformamide to the reaction mixture after 24 hours yields only **6b** with no traces of the expected aldehyde **11b**. We believe that the steric strain of **5b**, facilitated by the "buttressing effect", prevents the effective self-association of **5b**, therefore shifting the equilibrium to the formation of monomers. Together with the inability for intramolecular chelation of lithium this dramatically increases the basicity of **5b**, making its behavior in THF more like alkyllithiums rather than aryllithiums.

Even more peculiar is the situation with lithioanilines **5c** and **5d**. While they both show instability in Et_2O at elevated temperatures, their behavior at −25 °C is different. For instance, after 24 hours in THF or Et_2O, **5c** completely decomposes providing no aldehyde **11c** upon treatment with DMF. At the same time, **5d** is rather stable under these conditions. According to quantum chemical calculations, the stability of the dimers of **5c** and **5d** is comparable (Figure 1), thus the content of monomers in their solution should also not deviate

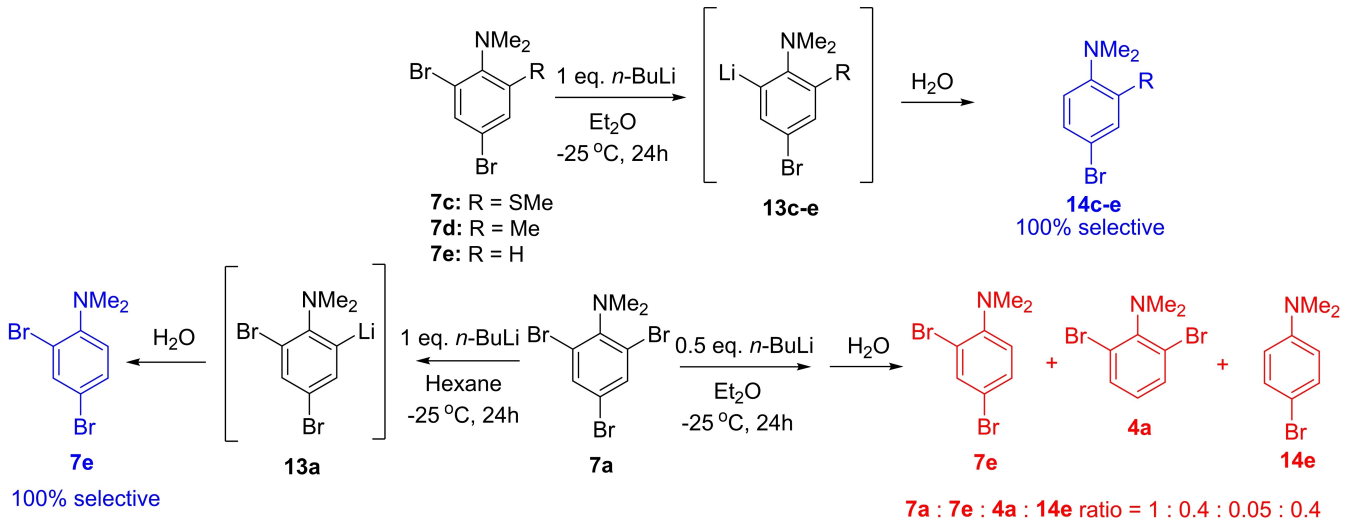
dramatically. Even though the "buttressing effect" provided by the rigid Me group is stronger than the one provided by the conformationally flexible SMe group (see impact on the halogen-lithium exchange above), it seems to be overpowered by electron donating properties of the latter. As a result, despite lesser steric strain, **5c** exhibits much higher basicity than **5d**, thus allowing it to effectively deprotonate THF even at a low temperature.

Since compound **5a** undergoes a fast Wurtz-Fittig reaction with the formation of biphenyl **12** in ethereal solvents, the interpretation of the stability tests of **5a** is a complex matter. For instance, the generation of **5a** from **4a** and *n*-BuLi in Et_2O at −25 °C over 24 hours and further treatment with dry DMF provides a mixture of **12** and **6e** with a relative ratio 1:0.4 and no traces of aldehyde **11a**. Increasing the temperature to 25 °C makes **12** the only reaction product. Thus, while it is clear that the Wurtz-Fittig reaction occurs much faster at a higher temperature, it does not allow the estimation of the basicity of **5a**.

Altogether, the manifestation of the "buttressing effect" noticeably decreases the stability of studied lithioanilines towards protolysis by using an ethereal solvent. Thus, unlike most phenyllithiums, our lithioanilines **5** undergo rapid decomposition in THF and, in some cases, in Et_2O even at low temperatures. This finding makes the choice of solvent for the generation of aryllithiums exhibiting the "buttressing effect" a crucial task for the effective utilisation of these compounds for further synthesis. In general, a higher aggregation state in *n*-hexane together with its low CH-acidity provides excellent stability of lithioanilines **5**. Even though their generation in this media can be quite challenging, their stability and good reactivity towards electrophiles makes this media the most suitable for further synthetic applications. The latter was proven on the example of effective synthesis of aldehydes **11** with good isolated yields (see experimental part).

The impact of the "buttressing effect" on the regioselectivity of bromine-lithium exchange. The third important question we address in this work is how the "buttressing effect" influences the regioselectivity of the halogen-lithium exchange. We have found that 2,4-dibromoanilines **7c-e**, upon treatment with *n*-BuLi in diethyl ether, undergo a selective exchange of bromine in *ortho*-position to the NMe_2 group (Scheme 7, top). Since **7e** bears no bulky substituent in position 6, its NMe_2 group is not influenced by the "buttressing effect" and provides a directing effect in a similar manner as it is shown in Scheme 1a. At the same time, it is rather surprising that **7c** and **7b**, bearing bulky "buttressing" substituents, also undergo a selective exchange of the *ortho*-bromine atom. We believe that in this case the exchange of the *ortho*-bromine atom is sterically not hindered enough by the "buttressing effect", therefore allowing the "electron sink" effect (see Scheme 1b) to overrule it. The exchange of bromine in *para*-position would result in a less beneficial charge distribution, while the exchange of *ortho*-bromine is stabilized by the intramolecular coordination of lithium (see Figure 1) and electron withdrawing properties of *para*-bromine.

The reaction of tribromide **7a** is more complex (Scheme 7, bottom). While treatment with 1 equiv. of *n*-BuLi in hexane makes **7e** the only product, performing this reaction in Et_2O results in a simultaneous displacement of both *ortho*-bromines. Even if 0.5 equiv. of *n*-BuLi are used at −25 °C, the final mixture consists of the initial **7a**, dibromide **7e**, and 4-bromo-*N,N*-dimethylaniline **14e** as the major components. The formation of **14e** under these conditions is surprising and seems to originate from the initial formation of **13a**, which enhanced basicity allows protonation by Et_2O with the formation of **7e**. The latter undergoes further selective exchange of *ortho*-bromine giving **14e** after quenching the reaction mixture with water. Nevertheless, it is possible to observe the formation of 2,6-dibromide **4a** – the product of the *para*-bromine exchange. This result originates from two major outcomes of the



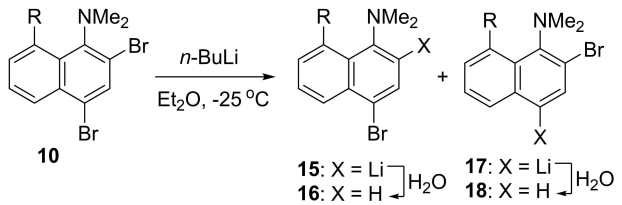
Scheme 7. Reaction of dibromoanilines **7c–e** with *n*-BuLi at −25 °C in Et_2O demonstrates negligible impact of "buttressing" effect on the regioselectivity. **7a** shows similar result in hexane, however, demonstrates noticeable exchange of *para*-bromine in Et_2O.

"buttressing effect" provided by bromine. First, the steric pressure of bromine atoms prevents the conjugation of the NMe_2 group with the benzene ring, thus disabling its negative effect on the halogen-lithium exchange in *para*-position (see Scheme 1). Second, it sterically hinders the halogen-lithium exchange in *ortho*-position, thus facilitating the exchange in *para*-position.

In summary, the impact of the "buttressing effect" on the halogen-lithium exchange regioselectivity in dibromoanilines is rather neglectable.

The transition to naphthalenes **10**, where substituent R is in much closer proximity to the NMe_2 group, makes the influence of the "buttressing effect" more pronounced. For instance, the reaction of dibromide **10d**, containing the Me substituent, proceeds slower under the same conditions and leads to the formation of a mixture of **16d** and **18d** together with unreacted **10d** (Table 5, run 7). The fact that the product of the *ortho*-bromine exchange **16d** absolutely dominates in the reaction mixture demonstrates the balance between thermodynamic and kinetic features. On the one hand, the "buttressing effect" slows down the halogen-lithium exchange in the *ortho*-position to the NMe_2 group, therefore making 4-lithioderivative **17d** the kinetically favorable product. On the other hand, the displacement of bromine in the *ortho*-position reduces the steric strain of the molecule, making 2-lithioisomer **15d** the thermodynamically favorable product. Reducing the reaction time leaves more starting material and keeps the relative ratio of products unchanged (run 8). Similar behavior is demonstrated by **10c** containing the SMe group (runs 5, 6). However, in all experiments, a noticeable amount of **9c** – the result of the double bromine-lithium exchange – is observed. Decreasing the amount of *n*-BuLi to 0.5 equivalents suppresses the double bromine exchange drastically and increases the amount of the product of the *para*-bromine exchange: **16c**:**18c** ratio is 2:1 (run 6).

Table 5. Bromine-lithium exchange in **10** with *n*-BuLi



Run	Compound	R	*n*-BuLi, equiv.	Time	**10:16:18:9** ratio
1	**10a**	H	1	24 h	0:1:0:0
2	**10b**	$SiMe_3$	1	2 min	0.9:1:0:0
3	**10b**	$SiMe_3$	1	24 h	0:1:0:0
4	**10c**	SMe	1	24 h	0.3:1:0.2:0.3
5	**10c**	SMe	1	2 min	0.5:1:0.2:0.1
6	**10c**	SMe	0.5	24 h	1:0.4: 0.2:0
7	**10d**	Me	1	24 h	0.2:1:0.2:0
8	**10d**	Me	1	2 min	0.4:1:0.2:0

In contrast, dibromide **10a**, bearing no bulky substituent in the *peri*-position, similarly to **7e**, expectedly undergoes a selective exchange of *ortho*-bromine with the formation of **15a** upon treatment with *n*-BuLi in diethyl ether (run 1)

The transition to **10b** containing the $SiMe_3$ group expectedly slows the reaction down. Thus, after 2 minutes, 90% of the starting material remains unreacted (run 2). Nevertheless, after 24 hours, the conversion is complete and **16b** is the only component of the reaction mixture (run 3). Such unexpected regioselectivity supports the abovementioned concept of the balance between thermodynamics and kinetics: the extreme bulkiness of the $SiMe_3$ group makes the displacement of *ortho*-bromine especially thermodynamically favorable.

In total, for 2,4-dibromo-1-dimethylaminonaphthalenes the influence of "buttressing effect" on the regioselectivity of bromine-lithium exchange is well manifested for medium size "buttressing" substituents such as Me and SMe. The transition to smaller (H) or much larger (TMS) functional groups allows the impact of "buttressing effect" on the regioselectivity to be overruled by the directing group effect (in the case of **10a**) and steric strain (in the case of **10b**).

Conclusions

In this paper, we have demonstrated the role of the "buttressing effect" in the ease and regioselectivity of bromine-lithium exchange in 2-bromo-*N*,*N*-dimethylanilines and 2-bromo-1-dimethylaminonaphthalenes, bearing bulky substituents in *ortho*- and *peri*-positions to the NMe_2 group. In general, the influence of the "buttressing effect" is twofold. On the one hand, the steric pressure of the "buttressing" substituent affects the conformation of the neighboring NMe_2 group and increases the steric pressure of the latter on the *ortho*-bromine atom. This hinders the interaction of the bromine atom with organolithium reagents by slowing down the halogen-lithium exchange process. The bigger the "buttressing" substituent is, the slower the reaction will be. On the other hand, the dependence of the regioselectivity on the size of the "buttressing" substituent is less linear. Thus, in the naphthalene series, medium size moieties (Me, SMe) suppress the exchange in *ortho*-position of the NMe_2 group, thus making the exchange in *para*-position more favorable. At the same time, the small hydrogen substituent and the large $SiMe_3$ group provide selective *ortho*-exchange. The first one – due to the stabilization of the corresponding lithioarene via intramolecular Li→NMe_2 coordination, the second one – due to the removal of steric strain upon exchange of bulky bromine to small lithium. In the benzene series, the influence of the "buttressing effect" on the regioselectivity of the halogen-lithium exchange is weaker and is generally overruled by other effects, such as saturation of the coordination sphere of Li via the coordination with NMe_2 group. In contrast, the influence of the "buttressing effect" on the stability of corresponding lithioanilines is strongly manifested. Thus, the increase of the size of the "buttressing" substituent facilitates the deaggregation of lithiated species in ethereal solutions by unraveling their strong basicity and nucleophilicity.

This results in rapid decomposition via protolisys by CH-acidic Et_2O and THF in some cases even at low temperatures. In the case of 2-lithio-dibromo-*N,N*-dimethylaniline, this reactivity boost leads to unprecedented fast Wurtz-Fittig coupling with 2,6-dibromo-*N,N*-dimethylaniline and results in the formation of corresponding biphenyl. The understanding of the "buttressing effect" allowed us to find the most optimal conditions for effective synthesis of studied aryllithiums and to tame their reactivity for the effective utilization in organic synthesis. These findings should help researchers to carefully plan multistep synthetic procedures involving usage of sterically hindered organolithiums.

Experimental section

GENERAL

Hexane, diethyl ether and tetrahydrofuran were dried over sodium/benzophenone. Liquid-state NMR experiments were performed using a Bruker Avance iii NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) at the Center for Magnetic Resonance, St. Petersburg State University Research Park. Chemical shifts are referenced to TMS for ^{1}H and ^{13}C. HR-ESI mass-spectra were obtained on a BRUKER maXis spectrometer equipped with an electrospray ionization (ESI) source (methanol was used as the solvent) at the Chemical Analysis and Materials Research Centre, St. Petersburg State University Research Park. The instrument was operated in positive mode using an m/z range of 50–1200. The capillary voltage of the ion source was set at 4000 V. The nebulizer gas pressure was 1.0 bar, and the drying gas flow was set to 4.0 L/min.

COMPUTATIONS

The calculations were performed using the Gaussian16 C.01 software package.[43] Geometry optimizations with standard convergence criteria and vibrational harmonic frequencies calculation were performed at the spin-restricted B3LYP-GD3BJ/6-311++G(d,p) level of theory. The Grimme dispersion correction D3 with zero damping was included.[44] All structures were checked on the absence of imaginary vibrational frequencies. Solvent effects were accounted by adding THF molecules in the first coordination sphere of lithium atom. Computational resources were provided by the Computer Center of Saint-Petersburg University Research Park (http://www.cc.spbu.ru/).

SYNTHESIS

4-Amino-3,5-dibromobenzenesulfonamide: HBr (48% aqueous solution, 35.34 mL, 0.312 mol, 2.5 equiv.) and of H_2O_2 (37% aqueous solution, 15.84 mL, 0.250 mol, 2 equiv.) were added to a stirred at 70 °C solution of 4-amino-3-bromobenzenesulfonamide **3** (21.45, g 0.125 mol) in water (365 mL). The reaction mixture was stirred at 75 °C for 40 min. The hot suspension was filtered off. The residue was recrystallized from 95% EtOH to yield 4-amino-3,5-dibromobenzenesulfonamide (28.86 g, 71%) as a peach crystals. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.07$ (s, 2 H), 7.25 (s, 2 H), 7.80 (s, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 106.6$, 129.9, 133.2, 146.3 ppm. HRMS (ESI): *m/z* calcd. for $C_6H_5{}^{79}Br_2N_2O_2S^-$ [M–H$^+$]: 326.8443, found 326.8443, *m/z* calcd. for $C_6H_5{}^{79}Br^{81}BrN_2O_2S^-$ [M–H$^+$]: 328.8423, found 328.8427, *m/z* calcd. for $C_6H_5{}^{81}Br_2N_2O_2S^-$ [M–H$^+$]: 330.8403, found 330.8408.

2,6-Dibromoaniline: A solution of 4-amino-3,5-dibromobenzenesulfonamide (5 g, 0.015 mol) in H_2SO_4 (70% aqueous solution, 25 mL) was stirred at 180 °C for 3 h. The mixture was cooled to room temperature, diluted with water (25 mL) and filtered off. The crude product was dissolved in CH_2Cl_2 (150 mL) and washed with water (3×150 mL). The organic phase was separated and evaporated to dryness to yield 2,6-dibromoaniline (2.655 g, 70%) as a white needles. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.58$ (s, 2 H), 6.51 (t, $J =$ 8.0 Hz, 1 H), 7.39 (d, $J = 8.0$ Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl3): $\delta = 108.9$, 119.4, 131.8, 142.0 ppm.

*2,6-Dibromo-N,N-dimethylaniline (**4a**)*: K_2CO_3 (13.66 g, 0.099 mol, 2 equiv.) and Me_2SO_4 (16.39 mL, 0.173 mol, 3.5 equiv.) were added to a stirred at 90 °C solution of 2,6-dibromoaniline (12.26 g, 0.049 mol) in MeCN (50 mL). The reaction mixture was stirred at 90 °C for 2 h and then at 75 °C for 12 h. The mixture was coolled to room temperature and the product was extracted with *n*-hexane (3×20 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness. The crude product was distilled under 5 torr ($T_b = 110$ °C) to yield **4a** (11.61 g, 85%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.92$ (s, 6 H), 6.86 (t, $J = 7.9$ Hz, 1 H), 7.53 (d, $J = 7.9$ Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 41.8$, 125.9, 127.3, 132.9, 148.5 ppm.

6-Substituted 2-bromo-N,N-dimethyl-anilines (general procedure): *n*-Butyllithium (1.6 M solution in hexanes, 3.36 mL, 5.37 mmol, 1.5 equiv.) was added via syringe to a solution of 2,6-dibromo-*N,N*-dimethylaniline **4a** (1 g, 3.58 mmol) in dry *n*-hexane (30 mL) in flame-dried flask under argon atmosphere at −24 °C. Resulted mixture was stirred for 24 h at the same temperature. Corresponding electrophile was added via syringe: solution of TMSOTf (1.95 mL, 10.74 mmol, 3 equiv.) in dry Et_2O (30 mL) for **4b**, neat dry Me_2S_2 (0.950 mL,10.74 mmol, 3 equiv.) for **4c**, neat dry Me_2SO_4 (1.02 mL, 10.76 mmol, 3 equiv.) for **4d**. The reaction mixture was stirred for 24 h at −24 °C and 24 h at room temperature and then was treated with aqueous ammonia (30 mL). The products were extracted with *n*-hexane (3×10 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness.

2-Bromo-N,N-dimethyl-6-trimethylsilylaniline (**4b**): was purified by TLC on SiO_2 with *n*-hexane as the eluent. The fraction with $R_f = 0.7$ gave **4b** (634 mg, 60%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.28$ (s, 9 H), 2.85 (s, 6 H), 7.07 (t, $J = 7.5$ Hz, 1 H), 7.41 (dd, $J = 7.3$, 1.5 Hz, 1 H), 7.54 (dd, $J = 7.9$, 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.1$, 43.1, 123.1, 127.2, 134.1, 135.9, 145.3, 155.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{11}H_{18}{}^{79}BrNSi^+$ [M+H$^+$]: 272.0465, found 272.0450, *m/z* calcd. for $C_{11}H_{18}{}^{81}BrNSi^+$ [M+H$^+$]: 274.0444, found 274.0435.

*2-Bromo-6-(thiomethyl)-N,N-dimethylaniline (**4c**)*: Yellow oil, yield: 852 mg (97%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3 H), 2.88 (s, 6 H), 6.98 (dd, $J = 7.9$, 1.6 Hz, 1 H), 7.03 (t, $J = 7.8$ Hz, 1 H), 7.27 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.6$, 41.2, 122.2, 123.4, 127.3, 129.2, 144.6, 145.8 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{13}{}^{79}BrNS^+$ [M+H$^+$]: 245.9947, found 245.9943, *m/z* calcd. for $C_9H_{13}{}^{81}BrNS^+$ [M+H$^+$]: 247.9926, found 247.9922.

*2-Bromo-N,N,6-trimethylaniline (**4d**)*: Yellow oil, yield: 733 mg (96%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3 H), 2.88 (s, 6 H), 6.91 (t, $J =$ 7.7 Hz, 1 H), 7.12 (dd, $J = 7.5$, 1.5 Hz 1 H), 7.40 (dd, $J = 7.9$, 1.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.4$, 42.0, 124.6, 126.1, 130.1, 131.4, 140.1, 149.1 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{13}{}^{79}BrN^+$ [M+H$^+$]: 214.0226, found 214.0225, *m/z* calcd. for $C_9H_{13}{}^{81}BrN^+$ [M+H$^+$]: 216.0205, found 216.0205.

*2,4,6-Tribromo-N,N-dimethylaniline (**7a**)*:[45] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.85$ (s, 6 H), 7.64 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 41.8, 118.7, 126.6, 135.4, 148.2 ppm.

6-Subsituted 2,4-dibromo-N,N-dimethylanilines (general procedure): *n*-Butyllithium (1.6 M solution in hexanes, 0.2 mL, 0.32 mmol) was added via syringe to a solution of 2,4,6-tribromo-*N*,*N*-dimethylaniline **7a** (114 mg, 0.32 mmol) in dry *n*-hexane (5 mL) in flame-dried flask under an argon atmosphere at −24 °C. Resulted mixture was stirred for 24 h at the same temperature.

Corresponding electrophile was added via syringe: Me_2S_2 (0.04 mL, 0.45 mmol, 1.4 equiv.) for **7c**, Me_2SO_4 (0.04 mL, 0.45 mmol, 1.4 equiv.) for **7d**. The products were extracted with *n*-hexane (3×15 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness. The residue was purified by column chromatography on SiO_2 (1×15 cm) with *n*-hexane/CH_2Cl_2 (3:1, v/v) as the eluent.

*2,4-Dibromo-N,N-dimethyl-6-methylthioaniline (**7c**)*: Yellowish oil, R_f = 0.6, yield: 60 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.81 (s, 6 H), 7.02 (d, J = 2.1 Hz, 1 H), 7.39 (d, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 41.2, 120.0, 123.8, 125.0, 131.3, 145.1, 146.8 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{12}{}^{79}Br_2NS^+$ [M + H$^+$]: 323.9052, found 323.9057, *m/z* calcd. for $C_9H_{12}{}^{79}Br^{81}BrNS^+$ [M + H$^+$]: 325.9032, found 325.9036, *m/z* calcd. for $C_9H_{12}{}^{81}Br_2NS^+$ [M + H$^+$]: 327.9011, found 327.9015.

*2,4-Dibromo-N,N,6-trimethylaniline (**7d**)*: Colourless oil, R_f = 0.8, yield: 52 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 2.82 (s, 6 H), 7.24 (d, J = 2.2 Hz, 1 H), 7.51 (d, J = 2.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 42.0, 118.2, 125.2, 132.9, 133.7, 141.8, 148.5 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{12}{}^{79}Br_2N^+$ [M + H$^+$]: 291.9331, found 291.9335, *m/z* calcd. for $C_9H_{12}{}^{79}Br^{81}BrN^+$ [M + H$^+$]: 293.9311, found 293.9316, *m/z* calcd. for $C_9H_{12}{}^{81}Br_2N^+$ [M + H$^+$]: 295.9291, found 295.9296.

8-Substituted 1-dimethylaminonaphthalenes (general procedure): *n*-Butyllithium (1.6 M solution in hexanes, 8.22 mL,13.16 mmol, 4.5 equiv.) was added via syringe to a solution 1-dimethylaminonaphthalene **9a** (500 mg, 2.92 mmol) in dry Et_2O (25 mL) in flame-dried flask under argon atmosphere at room temperature. Resulted mixture was stirred for 48 h at the same temperature. Corresponding electrophile was added via syringe: TMSOTf (2.65 mL, 14.62 mmol, 5 equiv.) for **9b**, Me_2S_2 (1.29 mL,14.62 mmol, 5 equiv.) for **9c**, MeI (0.91 mL, 14.62 mmol, 5 equiv.) for **9d**. Resulted mixture was stirred for 24 h at the room temperature and treated with water (10 mL). The products were extracted with *n*-hexane (2×30 mL), the solvent was evaporated to dryness. The residue was purified by column chromatography on Al_2O_3 (2×20 cm) with *n*-hexane as the eluent.

*N,N-Dimethyl-8-(trimethylsilyl)naphthalen-1-amine (**9b**)*: Colourless oil, R_f = 0.9, yield: 398 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (s, 9 H), 2.63 (s, 6 H), 7.32 (dd, J = 7.5, 1.2 Hz, 1 H), 7.39–7.49 (m, 2 H), 7.64 (dd, J = 8.1, 1.3 Hz, 1 H), 7.81 (dd, J = 8.1, 1.3 Hz, 1 H), 7.86 (dd, J = 6.8, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.3, 47.4, 116.3, 125.2, 125.3, 125.6, 129.4, 134.6, 135.0, 135.8, 136.6, 153.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{22}NSi^+$ [M + H$^+$]: 244.1517, found 244.1515.

*N,N-Dimethyl-8-(thiomethyl)naphthalen-1-amine (**9c**)*: Colourless oil, R_f = 0.6, yield: 450 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 2.74 (s, 6 H), 7.20 (d, J = 7.5 Hz, 1 H), 7.31 (dd, J = 7.4, 1.3 Hz, 1 H), 7.36–7.46 (m, 2 H), 7.57 (dd, J = 8.1, 1.1 Hz, 1 H), 7.61 (dd, J = 8.1, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 45.7, 118.4, 120.6, 124.2, 125.3, 125.7, 126.0, 128.5, 136.1, 137.4, 151.9 ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NS^+$ [M + H$^+$]: 218.0998, found 218.1004.

*N,N,8-Trimethylnaphthalen-1-amine (**9d**)*: Colourless oil, R_f = 0.8, yield: 406 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.76 (s, 6 H), 3.01 (s, 3 H), 7.23 (dd, J = 7.4, 1.3 Hz, 1 H), 7.26–7.30 (m, 1 H), 7.35 (dd, J = 8.0, 7.0 Hz, 1 H), 7.40 (t, J = 7.7 Hz, 1 H), 7.57 (dd, J = 8.1, 1.3 Hz, 1 H), 7.64–7.74 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 45.8, 116.4, 124.6, 125.3, 125.4, 127.0, 129.2(7), 129.3(3), 135.2, 136.5, 152.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}N^+$ [M + H$^+$]: 186.1278, found 186.1282.

*Synthesis of bromoarenes **7e**, **10a-10d**, **13e**, **16a–16d** with N-bromosuccinimide (general procedure)*: A solution of NBS (178 mg, 1 mmol, 1 equiv.) or (356 mg, 2 mmol, 2 equiv.) in THF (15 mL) was added dropwise to a stirred solution of NMe_2-substituted arene (1 mmol) in THF (5 mL) at room temperature. The reaction mixture was stirred for 30 min and the solvent was evaporated to dryness. The residue was treated with *n*-hexane (30 mL) and filtered off. The filtrate was evaporated to dryness to give corresponding bromoarenes without further purifications.

*2,4-Dibromo-N,N-dimethylaniline (**7e**)*: Colourless oil, yield: 227 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (s, 6 H), 6.93 (d, J = 8.6 Hz, 1 H), 7.35 (dd, J = 8.6, 2.3 Hz, 1 H), 7.68 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.1, 115.3, 119.7, 121.6, 131.0, 136.0, 151.2 ppm. HRMS (ESI): *m/z* calcd. for for $C_8H_{10}{}^{79}Br_2N^+$ [M + H$^+$]: 277.9175, found 277.9175, *m/z* calcd. for $C_8H_{10}{}^{79}Br^{81}BrN^+$ [M + H$^+$]: 279.9155, found 279.9155, *m/z* calcd. for $C_8H_{10}{}^{81}Br_2N^+$ [M + H$^+$]: 281.9134, found 281.9135.

*2,4-Dibromo-N,N-dimethylnaphthalen-1-amine (**10a**)*: Colourless oil, yield: 296 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (s, 6 H), 7.55–7.66 (m, 2 H), 7.95 (s, 1 H), 8.14–8.26 (m, 1 H), 8.31–8.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.7, 119.3, 119.9, 125.2, 127.4, 127.5, 127.6, 132.2, 134.3, 135.3, 147.2 ppm. HRMS (ESI): *m/z* calcd. for for $C_{12}H_{12}{}^{79}Br_2N^+$ [M + H$^+$]: 327.9331, found 327.9310, *m/z* calcd. for $C_{12}H_{12}{}^{79}Br^{81}BrN^+$ [M + H$^+$]: 329.9311, found 329.9313, *m/z* calcd. for $C_{12}H_{12}{}^{81}Br_2N^+$ [M + H$^+$]: 331.9291, found 331.9295.

*2,4-Dibromo-N,N-dimethyl-8-(trimethylsilyl)naphthalen-1-amine (**10b**)*: Colourless oil, yield: 365 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.33 (s, 9 H), 2.84 (s, 6 H), 7.54 (dd, J = 8.3, 6.9 Hz, 1 H), 7.90–7.99 (m, 2 H), 8.19 (dd, J = 8.3, 1.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.51, 45.9, 117.6, 120.8, 126.7, 128.8, 132.6, 135.3, 137.8, 138.3, 139.7, 148.8 ppm. HRMS (ESI): *m/z* calcd. for for $C_{15}H_{20}{}^{79}Br_2NSi^+$ [M + H$^+$]: 399.9727, found 399.9737, *m/z* calcd. for $C_{15}H_{20}{}^{79}Br^{81}BrNSi^+$ [M + H$^+$]: 401.9706, found 401.9720, *m/z* calcd. for $C_{15}H_{20}{}^{81}Br_2NSi^+$ [M + H$^+$]: 403.9686, found 403.9701.

*2,4-Dibromo-N,N-dimethyl-8-(methylthio)naphthalen-1-amine (**10c**)*: Yellow oil, yield 218 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.40 (s, 3 H), 2.80 (s, 6 H), 7.27 (d, J = 7.7 Hz, 1 H), 7.49 (dd, J = 8.4, 7.7 Hz, 1 H), 7.86–7.98 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 42.1, 121.2, 121.6, 122.5, 123.4, 127.5, 133.3, 133.5, 134.7, 139.0, 146.6 ppm. HRMS (ESI): *m/z* calcd. for for $C_{13}H_{14}{}^{79}Br_2NS^+$ [M + H$^+$]: 373.9209, found 373.9212, *m/z* calcd. for $C_{13}H_{14}{}^{79}Br^{81}BrNS^+$ [M + H$^+$]: 375.9188, found 375.9193, *m/z* calcd. for $C_{13}H_{14}{}^{81}Br_2NS^+$ [M + H$^+$]: 377.9168, found 377.9173.

*2,4-Dibromo-N,N,8-trimethylnaphthalen-1-amine (**10d**)*: Colourless oil, yield: 288 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.86 (s, 6 H), 2.87 (s, 3 H), 7.34–7.40 (m, 1 H), 7.44 (dd, J = 8.4, 7.1 Hz, 1 H), 7.95 (s, 1 H), 8.07–8.16 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 42.2, 121.5, 123.6, 126.8, 127.1, 131.8, 133.4, 134.4, 135.7, 147.4 ppm. HRMS (ESI): *m/z* calcd. for for $C_{13}H_{14}{}^{79}Br_2N^+$ [M + H$^+$]: 341.9488, found 341.9485, *m/z* calcd. for $C_{13}H_{14}{}^{79}Br^{81}BrN^+$ [M + H$^+$]: 343.9468, found 343.9473, *m/z* calcd. for $C_{13}H_{14}{}^{81}Br_2N^+$ [M + H$^+$]: 345.9447, found 345.9457.

*4-Bromo-N,N-dimethylaniline (**13e**)*: Colourless solid, yield: 181 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (s, 6 H), 6.56–6.63 (m, 2 H), 7.27–7.34 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.7, 108.7, 114.3, 131.8, 149.7 ppm. HRMS (ESI): *m/z* calcd. for

$C_8H_{11}{}^{79}BrN^+$ [M+H$^+$]: 200.0070, found 200.0070, *m/z* calcd. for $C_8H_{11}{}^{81}BrN^+$ [M+H$^+$]: 202.0049, found 202.0050.

*4-Bromo-1-dimethylaminonaphthalene (**16a**)*: Colourless oil, yield: 231 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (s, 6 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 7.59–7.69 (m, 2 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 8.30–8.42 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.3, 114.8, 116.5, 124.7, 126.0, 127.2, 127.7, 129.7, 130.2, 132.9, 151.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{12}H_{13}{}^{79}BrN^+$ [M+H$^+$]: 250.0226, found 250.0230, *m/z* calcd. for $C_{12}H_{13}{}^{81}BrN^+$ [M+H$^+$]: 252.0206, found 252.0210.

*4-Bromo-N,N-dimethyl-8-(trimethylsilyl)naphthalen-1-amine (**16b**)*: Colourless oil, yield: 299 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.28 (s, 9 H), 2.57 (s, 6 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 7.52 (dd, *J* = 8.4, 6.8 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.84 (dd, *J* = 6.9, 1.2 Hz, 1 H), 8.18 (dd, *J* = 8.4, 1.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.3, 47.2, 116.4, 118.8, 126.6, 128.4, 129.6, 133.1, 135.9, 136.5, 137.5, 153.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}{}^{79}BrNSi^+$ [M+H$^+$]: 322.0622, found 322.0621, *m/z* calcd. for $C_{15}H_{21}{}^{81}BrNSi^+$ [M+H$^+$]: 324.0601, found 324.0600.

*4-Bromo-N,N-dimethyl-8-(methylthio)naphthalen-1-amine (**16c**)*: Yellow solid, mp 64 − 65 °C (*n*-hexane), yield: 287 mg (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 2.71 (s, 6 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.48–7.54 (m, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 8.02 (dd, *J* = 8.4, 1.1 Hz, 1 H) ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}{}^{79}BrNS^+$ [M+H$^+$]: 296.0104, found 296.0107, *m/z* calcd. for $C_{13}H_{15}{}^{81}BrNS^+$ [M+H$^+$]: 298.0083, found 298.0086

*4-Bromo-N,N,8-trimethylnaphthalen-1-amine (**16d**)*: Colourless oil, yield: 251 mg (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71 (s, 6 H), 2.95 (s, 3 H), 7.02 (d, *J* = 8.1 Hz, 1 H), 7.27–7.33 (m, 1 H), 7.43 (dd, *J* = 8.4, 7.0 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 8.06–8.18 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 45.6, 116.5, 117.8, 126.2, 126.7, 129.5, 130.2, 130.5, 134.2, 135.7, 152.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}{}^{79}BrN^+$ [M+H$^+$]: 264.0383, found 264.0384, *m/z* calcd. for $C_{13}H_{15}{}^{81}BrN^+$ [M+H$^+$]: 266.0362, found 266.0365.

*3-Bromo-2-(dimethylamino)benzaldehyde (**11a**)*: *n*-Butyllithium (1.6 M solution in hexanes, 3.36 mL, 5.37 mmol, 1.5 equiv.) was added via syringe to a solution of 2,6-dibromo-*N,N*-dimethylaniline **4a** (1 g, 3.58 mmol) in dry *n*-hexane (25 mL) in flame-dried flask under an argon atmosphere at −24 °C. Resulted mixture was stirred for 24 h at the same temperature. Dry DMF (0.830 mL,10.74 mmol, 3 equiv.) was added. The reaction mixture was stirred for 24 h at −24 °C and treated with water (30 mL). The products were extracted with *n*-hexane (3×15 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness to give **11a** (790 mg, 97%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.03 (s, 6 H), 7.12 (t, *J* = 7.8, 1 H), 7.77 (m, 2 H), 10.36 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.8, 123.7, 126.2, 128.1, 136.3, 139.8, 153.6, 192.1 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{10}{}^{79}BrNNaO^+$ [M+Na$^+$]: 249.9838, found 249.9890, *m/z* calcd. for $C_9H_{10}{}^{81}BrNNaO^+$ [M+Na$^+$]: 251.9818, found 251.9792. IR (KBr): 1678 (C=O), 2852 (C(O)–H), 2787 (C(O)–H) cm^{-1}.

*2-(Dimethylamino)-3-(trimethylsilyl)benzaldehyde (**11b**): tert*-Butyllithium (1.7 M solution in pentane, 0.44 mL, 0.74 mmol, 2 equiv.) was added via syringe to a solution of 2-bromo-*N,N*-dimethyl-6-(trimethylsilyl)aniline **4b** (100 mg, 0.37 mmol) in dry *n*-hexane (10 mL) in flame-dried flask under an argon atmosphere at 5 °C. Resulted mixture was stirred for 24 h at the same temperature. A solution of dry DMF (0.86 mL, 1.11 mmol, 3 equiv.) in dry Et_2O (10 mL) was added. The reaction mixture was stirred for 24 h at 5 °C and treated with aqueous ammonia (5 mL). The products were extracted with *n*-hexane (3×10 mL). The residue was dissolved in MeOH (10 mL) and a saturated aqueous solution of $Na_2S_2O_5$ (15 mL) was added. Resulted mixture was stirred for 24 h at room temperature and treated with *n*-hexane (3×10 mL). The aqueous-alcohol layer was treated with 50% aqueous NaOH (20 mL) and extracted with *n*-hexane (3×10 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness to give **11b** (57 mg, 70%). a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.32 (s, 9 H), 2.95 (s, 6 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 7.76 (dd, *J* = 7.2, 1.8 Hz, 1 H), 7.95 (dd, *J* = 7.6, 1.8 Hz, 1 H), 10.44 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.01, 46.7, 126.2, 131.7, 136.1, 141.9, 143.2, 161.6, 191.4 ppm. HRMS (ESI): m/z calcd. for $C_{12}H_{20}NOSi^+$ [M+H$^+$]: 222.1309, found 222.1309. IR (KBr): 1686 (C=O), 2789 (C(O)-H), 2833 (C(O)-H) cm^{-1}.

*2-(Dimethylamino)-3-thiomethylbenzaldehyde (**11c**)*: Was prepared similarly to **11a** using *n*-butyllithium (1.6 M solution in hexanes, 0.38 mL, 0.61 mmol, 1.5 equiv.), 2-bromo-6-(thiomethyl)-*N,N*-dimethylaniline **4c** (100 mg, 0.41 mmol) and dry DMF (0.95 mL,1.23 mmol, 3 equiv.). Purified similarly to **11b**. Yellow oil, yield: 60 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.00 (s, 6 H), 7.27 (m, 1 H), 7.35 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.60 (dd, *J* = 7.6, 1.7 Hz, 1 H), 10.34 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6, 43.9, 125.3, 125.9, 130.1, 135.0, 141.5, 152.1, 192.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{10}H_{14}NOS^+$ [M+H$^+$]: 196.0791, found 196.0793. IR (KBr): 1680 (C=O), 2851 (C(O)–H), 2785 (C(O)–H) cm^{-1}.

*2-(Dimethylamino)-3-methylbenzaldehyde (**11d**)*: Was prepared similarly to **11a** using *n*-butyllithium (1.6 M solution in hexanes 0.44 mL, 0.70 mmol, 1.5 equiv.), *2-bromo-N,N,6-trimethylaniline* **4d** (100 mg, 0.47 mmol) and dry DMF (0.11 mL, 1.41 mmol, 3 equiv.). Purified by column chromatography on SiO_2 (2×20 cm) with *n*-hexane/EtOAc (4 : 1, v/v) as the eluent. The yellow fraction with R_f = 0.6 gave 60 mg (78%) of **11d** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 2.99 (s, 6 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 10.38 (s, 1 H), 7.39 (dd, *J* = 7.5, 1.8 Hz, 1 H), 7.67 (dd, *J* = 7.7, 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 44.3, 124.7, 126.8, 134.1, 137.3, 137.5, 154.4, 193.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{10}H_{14}NO^+$ [M+H$^+$]: 164.1070, found 164.1070. IR (KBr): 1680 (C=O), 2852 (C(O)–H), 2787 (C(O)–H) cm^{-1}.

2-Substituted 4-bromo-N,N-dimethylanilines (general procedure): *n*-Butyllithium (1.6 M solution in hexanes, 0.1 mL, 0.16 mmol) was added via syringe to a solution of corresponding dibromoaniline **7** (0.16 mmol) in dry Et_2O (5 mL) in flame-dried flask under an argon atmosphere at −24 °C. Resulted mixture was stirred for 24 h at the same temperature and degassed water (5 mL) was added via syringe. The reaction mixture was stirred for 5 minutes at room temperature. The products were extracted with *n*-hexane (3×15 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness. The residue was purified by column chromatography on SiO_2 (1×15 cm) with *n*-hexane/CH_2Cl_2 (3 : 1, v/v) as the eluent.

*4-Bromo-N,N-dimethyl-2-(methylthio)aniline (**14c**)*: Yellowish oil, R_f = 0.6, yield: 33 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.72 (s, 6 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.17 (d, *J* = 2.2 Hz, 1 H), 7.20 (dd, *J* = 8.4, 2.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 44.3, 117.0, 120.8, 127.1, 127.7, 137.2, 150.1 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{13}{}^{79}BrNS^+$ [M+H$^+$]: 245.9947, found 245.9948, *m/z* calcd. for $C_9H_{13}{}^{81}BrNS^+$ [M+H$^+$]: 247.9927, found 247.9927.

*4-Bromo-N,N,2-trimethylaniline (**14d**)*: Colourless oil, R_f = 0.8, yield:27 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.67 (s, 6 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.21–7.30 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 44.2, 115.3, 120.2, 129.3, 133.8, 134.6, 152.0 ppm. HRMS (ESI): *m/z* calcd. for $C_9H_{13}{}^{79}BrN^+$ [M+H$^+$]: 214.0226, found 214.0228, *m/z* calcd. for $C_9H_{13}{}^{81}BrN^+$ [M+H$^+$]: 216.0206, found 216.0208.

*2-Bromo-N,N-dimethyl-8-(methylthio)naphthalen-1-amine (**18c**)*: *n*-Butyllithium (1.6 M solution in hexanes, 0.2 mL, 0.32 mmol, 1 equiv.)

was added via syringe to the solution of 2,4-dibromo-*N*,*N*-dimethyl-8-(methylthio)naphthalen-1-amine **10c** (121 mg, 0.32 mmol) in dry Et_2O (5 mL) in flame-dried flask under an argon atmosphere at −24 °C. Resulted mixture was stirred for 24 h at the same temperature and degassed water (5 mL) was added via syringe. The reaction mixture was stirred for 5 minutes at room temperature. The products were extracted with *n*-hexane (3×10 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness. The residue was purified by column chromatography on SiO_2 (1×15 cm) with *n*-hexane/CH_2Cl_2 (3:1, v/v) as the eluent. The first colourless fraction with R_f = 0.70 gave unreacted **10c** (14 mg, 12%). The second colourless fraction with R_f = 0.65 gave **18c** (8 mg, 9%) as yellowish oil. The third colourless fraction with R_f = 0.60 gave **16c** (47 mg, 50%) of, and the fourth colourless fraction with R_f = 0.55 gave **9c** (9 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 2.83 (s, 6 H), 7.20 (d, J = 7.5 Hz, 1 H), 7.37–7.41 (m, 1 H), 7.48–7.53 (m, 2 H), 7.55 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 42.2, 121.5, 122.7, 124.0, 126.4, 128.2, 131.4, 132.8, 135.0, 138.0, 146.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}{}^{79}BrNS^+$ [M + H$^+$]: 296.0104, found 296.0107, *m/z* calcd. for $C_{13}H_{15}{}^{81}BrNS^+$ [M + H$^+$]: 298.0083, found 298.0089.

*2-Bromo-N,N,8-trimethylnaphthalen-1-amine (**18d**)*: Was prepared similarly to **18c**. Was purified by column chromatography on SiO_2 (1×15 cm) with *n*-hexane as the eluent. The first colourless fraction with R_f = 0.8 gave unreacted **10d** (13 mg, 12%). The second colourless fraction with R_f = 0.6 gave **18d** as colourless oil (10 mg, 12%). The third colourless fraction with R_f = 0.55 gave **16d** (55 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.87 (s, 3 H), 2.88 (s, 6 H), 7.28–7.34 (m, 2 H), 7.51 (d, J = 8.7 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H), 7.63 (dd, J = 7.2, 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 42.1, 124.5, 125.7, 127.2, 128.3, 130.6, 130.9, 134.8, 135.1, 135.3, 147.2 ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}{}^{79}BrN^+$ [M + H$^+$]: 264.0383, found 264.0382, *m/z* calcd. for $C_{13}H_{15}{}^{81}BrN^+$ [M + H$^+$]: 266.0362, found 266.0372.

*3,3′-Dibromo-N^2,N^2,N$^{2'}$,N$^{2'}$-tetramethyl-[1,1′-biphenyl]-2,2′-diamine (**12**)*: *n*-Butyllithium (1.6 M solutionin hexanes, 0.09 mL, 0.14 mmol, 1 equiv.) was added via syringe to a solution of 2,6-dibromo-*N*,*N*-dimethylaniline **4a** (40 mg, 0.14 mmol) of in dry Et_2O (5 mL) in flame-dried flask under an argon atmosphere at −24 °C. Resulted mixture was stirred for 24 h at the same temperature and degassed water (5 mL) was added via syringe. The reaction mixture was stirred for 5 minutes at room temperature. The products were extracted with *n*-hexane (3×10 mL). The combined organic extracts were dried with Na_2SO_4 and filtered off. The solvent was evaporated to dryness. Compound **12** was purified by TLC on SiO_2 with *n*-hexane/EtOAc (20:1, v/v) as the eluent. The brown fraction with R_f = 0.7 gave **12** (29 mg, 70%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 12 H), 6.98 (t, J = 7.7 Hz, 2 H), 7.05 (dd, J = 7.7,1.8 Hz, 2 H), 7.56 (dd, J = 7.7, 1.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.3, 123.9, 124.5, 130.9, 133.2, 141.4, 148.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{16}H_{19}{}^{79}Br_2N_2^+$ [M + H$^+$]: 396.9910, found 396.9894, *m/z* calcd. for $C_{16}H_{19}{}^{81}Br^{79}BrN_2^+$ [M + H$^+$]: 398.9889, found 398.9881, *m/z* calcd. for $C_{16}H_{19}{}^{81}Br_2N_2^+$ [M + H$^+$]: 400.9869, found 400.9860.

Supporting Information

NMR spectra data for obtained compounds can be found in the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[1] W. Schlenk, J. Holtz, *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 262–274.
[2] U. Wietelmann, J. Klett, *Zeitschrift für Anorg. und Allg. Chemie* **2018**, *644*, 194–204.
[3] M. Schlosser, in *Organometallics Synth. A Man.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2013**, pp. 1–352.
[4] A. E. H. Wheatley, M. Uchiyama, Eds., *Polar Organometallic Reagents: Synthesis, Structure, Properties and Applications*, John Wiley & Sons Ltd, Chichester, **2022**.
[5] Z. Chai, W. X. Zhang, *Organometallics* **2022**, *41*, 3455–3477.
[6] S. E. García-Garrido, A. Presa Soto, E. Hevia, J. García-Álvarez, *Eur. J. Inorg. Chem.* **2021**, 3116–3130.
[7] P. Slavík, B. R. Trowse, P. O'Brien, D. K. Smith, *Nat. Chem.* **2023**, *15*, 319–325.
[8] F. F. Mulks, B. Pinho, A. W. J. Platten, M. R. Andalibi, A. J. Expósito, K. J. Edler, E. Hevia, L. Torrente-Murciano, *Chem* **2022**, *8*, 3382–3394.
[9] U. Wietelmann, J. Klösener, P. Rittmeyer, S. Schnippering, H. Bats, W. Stam, *Org. Process Res. Dev.* **2022**, *26*, 1422–1431.
[10] M. Power, E. Alcock, G. P. McGlacken, *Org. Process Res. Dev.* **2020**, *24*, 1814–1838.
[11] M. Colella, P. Musci, D. Cannillo, M. Spennacchio, A. Aramini, L. Degennaro, R. Luisi, *J. Org. Chem.* **2021**, *86*, 13943–13954.
[12] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596–2616.
[13] F. Totter, P. Rittmeyer, in *Organometallics Synth.* (Ed.: M. Schlosser), John Wiley & Sons, Inc., Hoboken, NJ, USA, **2013**, pp. 167–194.
[14] K. Ziegler, H. Colonius, *Justus Liebigs Ann. Chem.* **1930**, *479*, 135–149.
[15] J. Clayden, *Organolithiums: Selectivity for Synthesis*, ELSEVIER SCIENCE Ltd, Oxford, **2002**.
[16] G. Voß, H. Gerlach, *Chem. Ber.* **1989**, *122*, 1199–1201.
[17] A. G. Avent, P. B. Hitchcock, G. J. Leigh, M. Togrou, *J. Organomet. Chem.* **2003**, *669*, 87–100.
[18] R. A. Murphy, M. P. Kung, J. Billings, H. F. Kung, *J. Med. Chem.* **1990**, *33*, 171–178.
[19] M. Murakata, T. Ikeda, N. Kimura, A. Kawase, M. Nagase, M. Kimura, K. Maeda, A. Honma, H. Shimizu, *Tetrahedron* **2017**, *73*, 655–660.
[20] H. Gilman, W. Langham, F. W. Moore, *J. Am. Chem. Soc.* **1940**, *62*, 2327–2335.
[21] A. S. Antonov, S. G. Kachalkina, A. F. Pozharskii, G. S. Borodkin, A. Filarowski, *Tetrahedron* **2017**, *73*, 3452–3457.
[22] R. J. Mayer, N. Hampel, A. R. Ofial, *Chem. A Eur. J.* **2021**, *27*, 4070–4080.
[23] A. A. Yakubenko, E. Y. Tupikina, A. S. Antonov, *Chem. A Eur. J.* **2023**, *29*, e202301439.
[24] A. A. Yakubenko, V. V. Karpov, E. Y. Tupikina, A. S. Antonov, *Organometallics* **2021**, *40*, 3627–3636.
[25] Y. Zhang, G. Lavigne, N. Lugan, V. César, *Chem. A Eur. J.* **2017**, *23*, 13792–13801.

[26] M. Decouzon, O. Exner, J. F. Gal, P. C. Maria, *J. Chem. Soc. Perkin Trans. 2* **1996**, *4*, 475–479.
[27] J. Gorecka, C. Heiss, R. Scopelliti, M. Schlosser, *Org. Lett.* **2004**, *6*, 4591–4593.
[28] V. A. Ozeryanskii, A. V. Marchenko, A. F. Pozharskii, A. Filarowski, D. V. Spiridonova, *J. Org. Chem.* **2021**, *86*, 3637–3647.
[29] E. A. Filatova, A. V. Gulevskaya, A. F. Pozharskii, E. A. Ermolenko, V. A. Ozeryanskii, A. D. Misharev, *ChemistrySelect* **2020**, *5*, 9932–9945.
[30] A. S. Antonov, V. G. Bardakov, V. V. V. Mulloyarova, *J. Organomet. Chem.* **2020**, *906*, 121068.
[31] H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130–7178.
[32] P. Stanetty, M. D. Mihovilovic, *J. Org. Chem.* **1997**, *62*, 1514–1515.
[33] A. V. Marchenko, V. A. Ozeryanskii, O. P. Demidov, A. S. Antonov, E. Y. Tupikina, A. F. Pozharskii, *J. Org. Chem.* **2022**, *87*, 16506–16516.
[34] A. S. Antonov, V. V. Karpov, E. Y. Tupikina, P. M. Tolstoy, M. A. Vovk, *Organometallics* **2020**, *39*, 3705–3714.
[35] R. Waack, M. A. Doran, *J. Am. Chem. Soc.* **1969**, *91*, 2456–2461.
[36] H. J. Reich, W. S. Goldenberg, A. W. Sanders, K. L. Jantzi, C. C. Tzschucke, *J. Am. Chem. Soc.* **2003**, *125*, 3509–3521.
[37] K. L. Jantzi, I. A. Guzei, H. J. Reich, *Organometallics* **2006**, *25*, 5390–5395.
[38] H. J. Reich, D. P. Green, M. A. Medina, W. S. Goldenberg, B. Ö. Gudmundsson, R. R. Dykstra, N. H. Phillips, *J. Am. Chem. Soc.* **1998**, *120*, 7201–7210.
[39] A. S. Antonov, A. A. Yakubenko, *Synth.* **2020**, *52*, 98–104.
[40] A. S. Antonov, V. G. Bardakov, A. F. Pozharskii, M. A. Vovk, A. D. Misharev, *J. Organomet. Chem.* **2018**, *855*, 18–25.
[41] L. Klemmer, A. L. Thömmes, M. Zimmer, V. Huch, B. Morgenstern, D. Scheschkewitz, *Nat. Chem.* **2021**, *13*, 373–377.
[42] A. S. Antonov, V. Y. Mikshiev, A. F. Pozharskii, V. A. Ozeryanskii, *Synthesis (Stuttg).* **2014**, *46*, 3273–3282.
[43] D. J. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratch, **2016**.
[44] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.
[45] K. A. Zachariasse, S. I. Druzhinin, V. A. Galievsky, S. Kovalenko, T. A. Senyushkina, P. Mayer, M. Noltemeyer, M. Boggio-Pasqua, M. A. Robb, *J. Phys. Chem. A* **2009**, *113*, 2693–2710.

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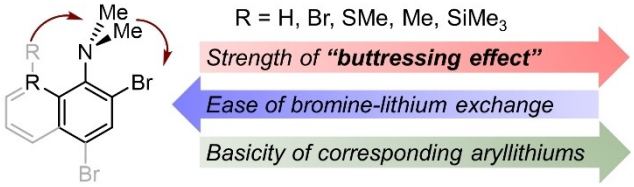

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The manifestation of the "buttressing effect" – an indirect interaction between two substituents issued by the presence of a third group – and its influence on the ease and selectivity of the bromine-lithium exchange and the reactivity of formed aryllithiums is presented. In naphthalene substrates bearing two bromines, the impact on regioselectivity of the reaction is demonstrated.