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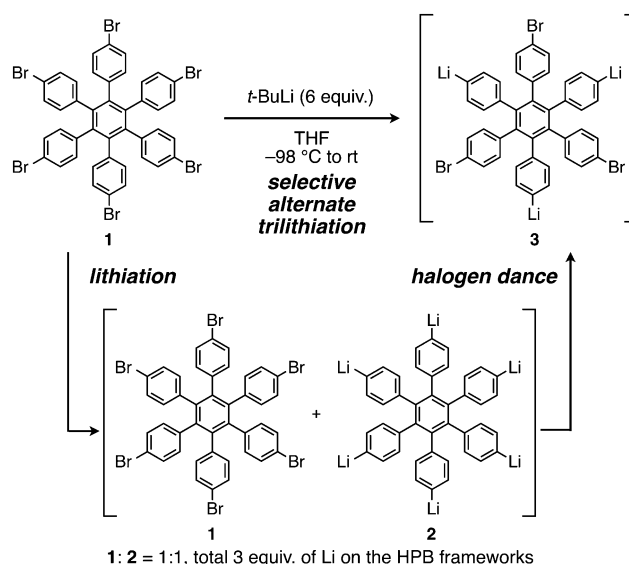
Mesityllithium and *p*-(dimethylamino)phenyllithium for the selective alternate trilithiation of the hexaphenylbenzene framework†

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We report mesityllithium and *p*-(dimethylamino)phenyllithium as new valuable lithiating reagents, which realize Br/Li exchange reaction of bromoarenes at relatively high temperature in THF. With these reagents, we established the general and practical protocols for the selective alternate trilithiation of the hexaphenylbenzene framework.

Halogen–lithium exchange reaction with *t*-BuLi or *n*-BuLi in ethereal solvents is one of the most versatile methods to selectively derivatize aromatic frameworks.¹ The reaction should be performed at low temperature due to the instability of the alkyl-lithiums especially in THF.² While the exchange reaction normally proceeds very rapidly even at low temperature, the restriction of the reaction temperature sometimes limits the scope and the practicality of the reaction. In the case of the halogen–lithium exchange reaction of substrates with extremely low solubility such as halogenated polyaromatic hydrocarbon (PAH) derivatives,³ the rate of the reaction is so sluggish at low temperature that higher reaction temperature is required. However, the reaction could fail due to the decomposition of the alkylolithium reagent at elevated temperature.

Recently we reported the selective alternate trilithiation of hexabrominated hexaphenylbenzene (HPB) derivative **1** (Scheme 1).⁴ HPB derivatives are the most versatile precursors of large PAH derivatives such as hexa-*peri*-hexabenzocoronene, which are employed in various fields.⁵ The HPB framework itself has also been utilized as a rigid molecular scaffold in a broad range of applications.⁶ These aspects have highly motivated the development of the effective method for the selective functionalization of the HPB framework. Our lithiation reaction can efficiently achieve the alternate substitution pattern on the HPB framework, which has been inaccessible by conventional synthetic approaches. We disclosed that this reaction proceeds in two stages: the lithiation stage and the halogen dance stage. At the initial part

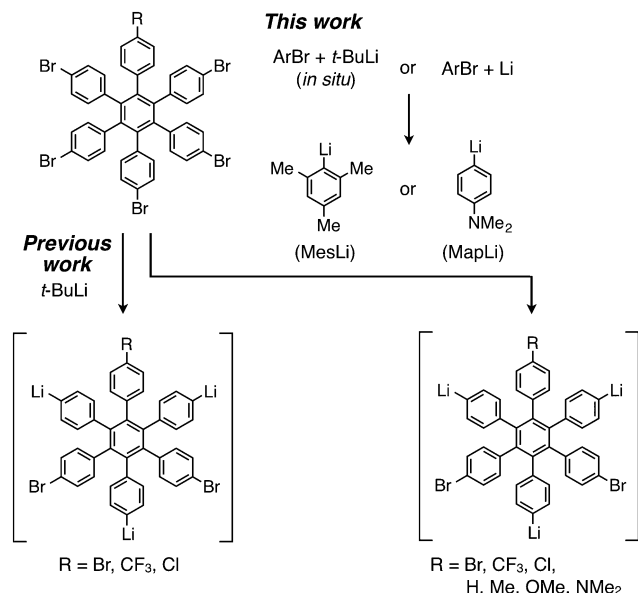


Scheme 1 Selective alternate trilithiation of compound **1** and its mechanism.

of the reaction, the lithiation stage, exactly half of substrate **1** is hexalithiated by *t*-BuLi due to the low solubility of **1**, most of which is precipitated at the beginning and dissolved gradually during the warming process. The total equivalent of Li on the HPB frameworks is determined in this stage. Then the halogen dance reaction, the reversible ArBr/ArLi exchange reaction, redistributes Br and Li on the HPB frameworks to selectively afford alternately trilithiated species **3** under thermodynamic control. When this reaction was applied in pentabrominated HPB derivatives possessing various substituents, the alternate selectivity significantly depended on the substituent (Scheme 2). One possible reason for the dependency on the substituents could be the different solubility of the substrates because the slower dissolution of the precipitated starting material was observed during the warming process in the case of the HPB derivatives with which the selective alternate trilithiation failed. If the dissolution of the substrate is too slow, the three equivalents of lithiation of the HPB frameworks cannot be completed due to the competitive decomposition of

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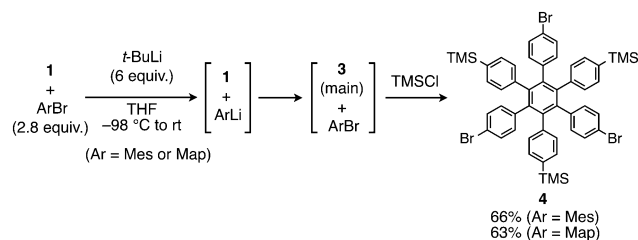


Scheme 2 Selective alternate trilithiation of HPB derivatives with MesLi or MapLi.

t-BuLi in THF at the lithiation stage. In this case, the system should reach an undesired equilibrium, where the average equivalent of Li on the HPB frameworks is less than three. To overcome this problem, lithiating reagents that are stable enough in THF are required.⁷ Herein we report mesityllithium (MesLi) and *p*-(dimethylamino)phenyllithium (MapLi) as new useful lithiating reagents that possess both sufficient stability in THF and enough lithiating ability. With these reagents, we succeeded in the selective alternate trilithiation of a broader range of HPB derivatives in practical ways (Scheme 2).

The alternative lithiating reagent to *t*-BuLi should satisfy the following requirements: (1) sufficient stability in THF, (2) an enough lithiating ability, and (3) the bromide concomitantly formed by Br/Li exchange has less reactivity or an effective quenching pathway like *t*-BuBr.⁸ For this reason, *n*-BuLi is not suitable because of the high reactivity of *n*-BuBr. The promising candidates are aryllithiums (ArLi) because they are more stable in THF than alkylolithiums⁹ and because aryl bromides produced by Br/Li exchange would be inert against the generated lithiated species. For the efficient lithiation of bromoarenes, the ArLi reagent should be thermodynamically much less stable than the aryllithiums produced by Br/Li exchange. Indeed, the lithiation of **1** with 3.0 equiv. of PhLi did not yield alternately trilithiated species **3** selectively (Fig. S1, ESI†).¹⁰ This is due to a similar thermodynamic preference of PhLi and the lithiophenyl group on the HPB framework. The distribution of Li is not biased onto the HPB frameworks in the lithiation stage, and hence the total equivalent of Li on the HPB framework is less than three during the halogen dance stage.

An efficient way to control the thermodynamic stability of the ArLi reagent is the change of substituents.¹¹ We focused on two aryllithiums, MesLi and MapLi, as the candidates for the new lithiating reagents. As for MesLi, the moderately electron-donating nature of the three Me groups and the ineffective

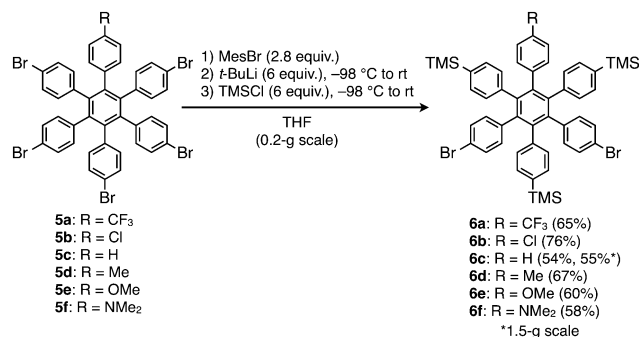


Scheme 3 Selective alternate trilithiation of compound **1** with *in situ* prepared MesLi or MapLi.

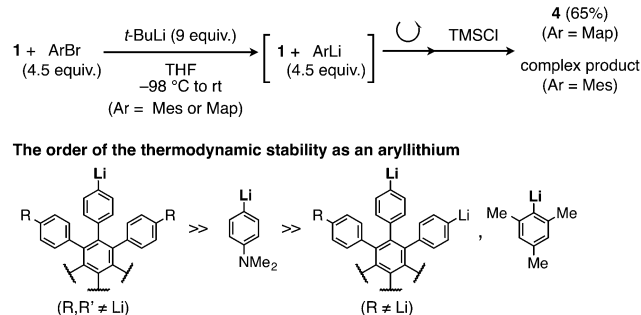
solvation of THF around Li due to the steric hindrance of the two *o*-Me groups should diminish the thermodynamic stability as an aryllithium. As for MapLi, the strongly electron-donating ability of the *p*-NMe₂ group destabilizes the aryllithium. The thermodynamic instability of MesLi and MapLi as aryllithiums was confirmed by equilibration experiments with PhLi (Scheme S2, ESI†). While the thermodynamic instability of MesLi and MapLi was once discussed sixty years ago,¹² they have never been employed as lithiating reagents in the Br/Li exchange reaction as far as we know.^{13,14}

We first investigated the effectiveness of MesLi and MapLi for the selective alternate trilithiation of the HPB framework with compound **1**. Considering the practical utility, we prepared MesLi and MapLi *in situ* by adding 6.0 equiv. of *t*-BuLi into the suspension of compound **1** in the presence of 2.8 equiv.¹⁵ of MesBr or MapBr in THF at $-98\text{ }^{\circ}\text{C}$ (Scheme 3). Due to the low solubility of compound **1**, MesBr or MapBr can be selectively lithiated by *t*-BuLi (Fig. S2, ESI†). This *in situ* preparation of MesLi or MapLi makes the reaction protocol quite simple. Then we warmed the suspension to rt to obtain a clear solution, and thus quenched it with trimethylsilyl chloride (TMSCl). Both MesLi and MapLi afforded the crude mixture containing compound **4** and the used aryl bromide (MesBr or MapBr) as the main components. In the case of MapLi, the recovered MapBr can be removed easily by acid washing. Compound **4** was isolated after recrystallization in 66% and 63% yields, which were almost the same yield as that obtained in the selective alternate trilithiation reaction with *t*-BuLi itself as the lithiating reagent (67%).⁴ This result indicates that all of the 3.0 equiv. of Li on the aryllithiums in the system are selectively distributed on the HPB frameworks and that MesLi and MapLi are thermodynamically much less stable than the lithiophenyl groups of trilithiated species **3**. The utility of MesLi and MapLi was clearly in contrast to the attempted trilithiation with *in situ* prepared PhLi and *p*-F₃CC₆H₄Li, which did not afford compound **4** as the main product (Fig. S3, ESI†).

On the basis of the success of the selective alternate trilithiation of compound **1** with MesLi, we attempted the trilithiation of compounds **5a–f** with MesLi (Scheme 4). In particular, the selective alternate trilithiation of compounds **5c–e** failed previously with *t*-BuLi itself as the lithiating reagent. In contrast, alternately functionalized HPB derivatives **6a–f** were selectively produced with MesLi and were isolated in good yields after recrystallization. We also found that the isolated yields of compounds **6a** and **6b** were improved compared with the previous method with *t*-BuLi itself as the lithiating reagent.⁴ The reaction with *in situ* prepared MesLi is scalable and the selective alternate trilithiation of compound **6c**



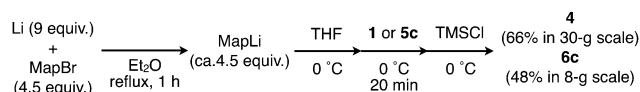
Scheme 4 Selective alternate trilithiation of HPB derivatives 5a–f.



Scheme 5 Lithiation of compound 1 with an excess amount of MesLi or MapLi.

succeeded at the 1.5 g scale. These successes result from the higher stability of MesLi in THF than *t*-BuLi. This stability realizes the Br/Li exchange reaction of the HPB framework at relatively high temperature, which is required for the dissolution of the low soluble HPB derivatives.

The significant difference between MesLi and MapLi was found when more than 3 equiv. of the ArLi reagent were added to the HPB derivatives (Scheme 5). The use of 4.5 equiv. of MapLi for 1 afforded almost the same crude product as that with 3.0 equiv. of MapLi (Fig. S4, ESI[†]), and compound 4 was isolated in 65% yield. On the other hand, the use of 4.5 equiv. of MesLi resulted in the “over-lithiation” of the HPB framework and the complex mixture was obtained (Fig. S4, ESI[†]). This difference can be interpreted by the relative thermodynamic stability of the aryllithiums, MesLi, MapLi, and the two kinds of lithiophenyl groups on the HPB framework (Scheme 5). The lithiophenyl group that is not adjacent to other lithiophenyl groups on the HPB framework should be much more stable than MapLi and MesLi. This is the reason why 3.0 equiv. of MesLi or MapLi can completely trilithiate the HPB frameworks. In contrast, the lithiophenyl group that is adjacent to other lithiophenyl groups on the HPB framework is expected to be much less stable than MapLi, but comparably stable as MesLi. The thermodynamically higher stability of MapLi than MesLi was confirmed by the equilibration experiment (Scheme S2, ESI[†]). Therefore, only MapLi selectively afforded the alternately trilithiated species 3 regardless of the stoichiometry of the ArLi reagent. This result demonstrates that an ArLi reagent with an appropriate thermodynamic stability can achieve the selective partial lithiation of polybrominated aromatics without special care of the equivalents of the lithiating reagent.



Scheme 6 Practical protocol for the selective alternate trilithiation of the HPB frameworks.

Considering the relative thermodynamic stability of the lithiated species, we have developed a practical protocol for the selective alternate derivatization of the HPB framework (Scheme 6). At first, we efficiently prepared an excess amount of MapLi from MapBr and granular lithium in Et₂O. The appropriate thermodynamic stability of MapLi eliminates the necessity of the determination of the exact yield of MapLi. This direct preparation of the ArLi reagent from granular lithium can avoid the dangerous handling of the highly pyrophoric *t*-BuLi at the large scale. Then, after the addition of THF, HPB derivative 1 or 5c was directly added to the solution of MapLi followed by quenching with TMSCl to afford the alternately TMS-substituted compound 4 or 6c. The sufficient stability of MapLi in the ethereal solvents realizes all of the reaction steps over 0 °C.¹⁶ It is notable that one can synthesize various C_{3v}- or C_{2v}-symmetrical HPB derivatives selectively without the necessity of the severe control of the stoichiometry of the lithiating reagent.

In conclusion, we demonstrated the utility of MesLi and MapLi as new lithiating reagents, which realize Br/Li exchange reaction of bromoarenes at relatively high temperature in THF. With these reagents, we succeeded in the selective alternate trilithiation of various HPB derivatives. These reagents should also be effective for the Br/Li exchange reaction of a wide range of bromoarenes, especially when they have a low solubility such as brominated PAHs. The lithiated species from PAHs, which are difficult to be prepared with conventional lithiating reagents, could realize diverse derivatization of PAH frameworks based on the synthetic utility of organolithiums.¹ We believe that these reagents will be a new general choice of lithiating reagent in Br/Li exchange reactions.

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