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COMMUNICATION

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

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Tatsuo Kojima* and Shuichi Hiraoka*

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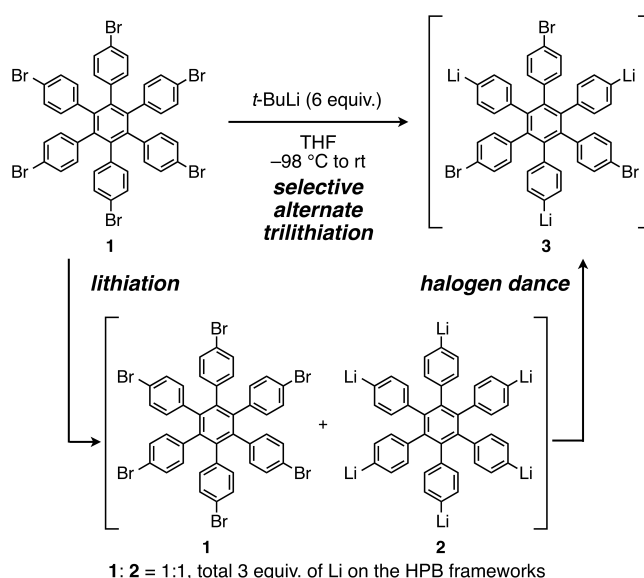
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We report mesityllithium and *p*-(dimethylamino)phenyllithium as new valuable lithiating reagents, which realize Br/Li exchange reaction of bromoarenes at relatively high temperature in THF. With these reagents, we established the general and practical 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 alkyllithiums 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 alkyllithium 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 precursor of large PAH derivatives such as *peri*-hexabenzocoronene, which are employed in various fields.⁵ The HPB framework itself has been also 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



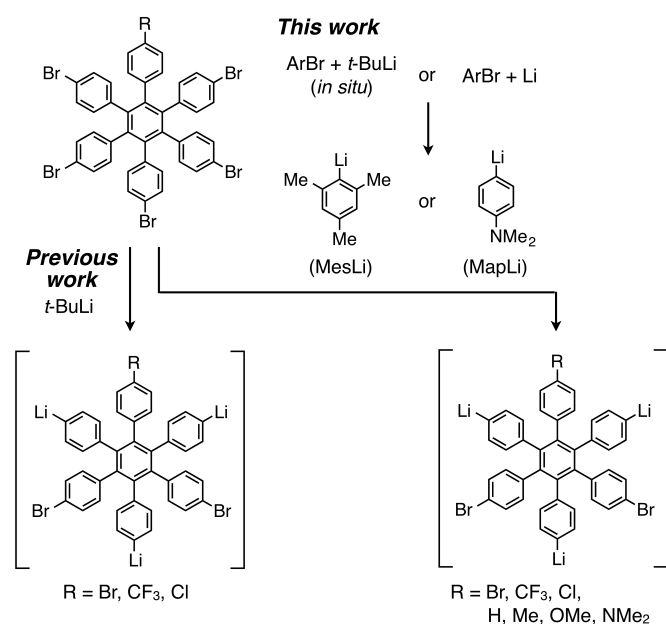
Scheme 1 Selective alternate trilithiation of compound **1** and its Mechanism.

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 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 into pentabrominated HPB derivatives possessing various substituents, the alternate selectivity significantly depended on the substituent (Scheme 2). One possible

* Department of Basic Science, Graduate School of Arts and Sciences, The University of Tokyo, 3-8-1 Komaba, Meguro-ku, Tokyo, Japan. E-mail: chiraoka@mail.ecc.u-tokyo.ac.jp, kojima@mail.ecc.u-tokyo.ac.jp

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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 trithiation 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 *t*-BuLi in THF at the lithiation stage. In that 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 enough stable in THF are required.⁷ Herein we report mesityllithium (MesLi) and *p*-(dimethylamino)phenyllithium (MapLi) as new useful lithiating reagents that possess both the sufficient stability in THF and the enough lithiating ability. With these reagents, we succeeded in the selective alternate trithiation of a broader range of HPB derivatives in practical ways (Scheme 2).

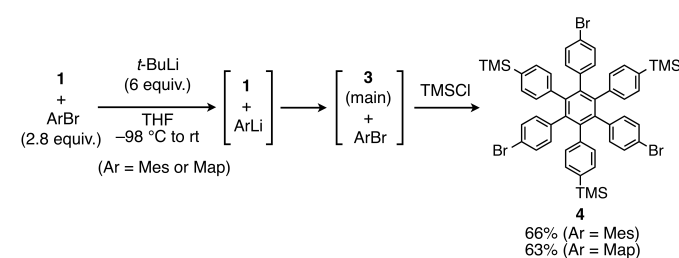


Scheme 2 Selective alternate trithiation of HPB derivatives with MesLi or MapLi.

The alternative lithiating reagent to *t*-BuLi should satisfy the following requirements: (1) a 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 candidate is 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 trithiated species **3** selectively (Figure S1).¹⁰ This is due to the 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.

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 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 an aryllithium was confirmed by equilibration experiments with PhLi (Scheme S2). While the thermodynamic instability of MesLi and MapLi was once discussed sixty years ago,¹² they have never been employed as the lithiating reagent in the Br/Li exchange reaction as far as we know.^{13,14}

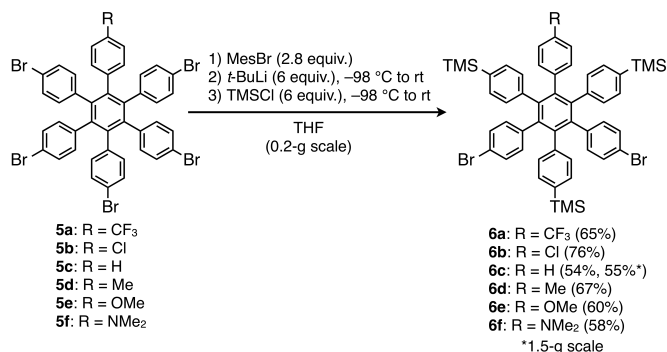
We first investigated the effectiveness of MesLi and MapLi for the selective alternate trithiation of the HPB framework with compound **1**. Considering the practical utility, we prepared MesLi and MapLi *in situ* by adding 6.0 equiv. of *t*-BuLi into the suspension of compound **1** in the presence 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 (Figure S2). 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 with the selective alternate trithiation 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 trithiated species **3**. The utility of MesLi and MapLi was clearly in contrast with the attempted trithiation with *in situ* prepared PhLi and *p*-F₃CC₆H₄Li, which did not afford compound **4** as the main product (Figure S3).



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

On the basis of the success of the selective alternate trithiation of compound **1** with MesLi, we attempted the trithiation of compounds **5a-f** with MesLi (Scheme 4). In particular, the selective alternate trithiation 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 the 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 trithiation of compound **6c** 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.

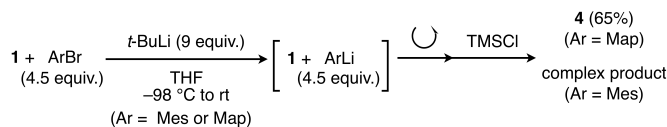


Scheme 4 Selective alternate trithiation of HPB derivatives **5a-f**

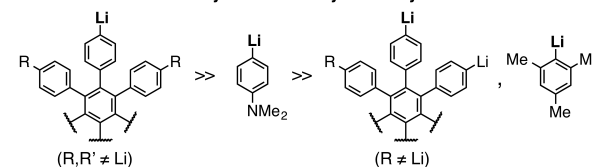
The significant difference between MesLi and MapLi was found when more than 3 equiv. of the ArLi reagent were added to the HPB derivatives (Scheme 5). The use of 4.5 equiv. of MapLi for **1** afforded almost the same crude product as that with 3.0 equiv. of MapLi (Figure S4), and compound **4** was isolated in 65% yield. On the other hand, the use of 4.5 equiv. of MesLi resulted in the “overlithiation” of the HPB framework and the complex mixture was obtained (Figure S4). 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 trithiate 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). Therefore, only MapLi selectively afforded the alternately trithiated 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.

Considering the relative thermodynamic stability of the lithiated species, we have developed a practical protocol of the selective alternate derivatization of the HPB framework (Scheme 6). At first, we efficiently prepared 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 the quench with TMSCl to afford the alternately TMS-substituted

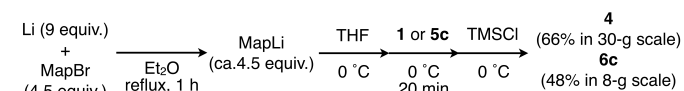
compound **4** or **6c**. The sufficient stability of MapLi in the ethereal solvents realizes all of the reaction steps over 0 °C.¹⁶ It is notable that one can synthesize various C₃- or C_{2v}-symmetrical HPB derivatives selectively without the necessity of the severe control of the stoichiometry of the lithiating reagent.



The order of the thermodynamic stability as an aryllithium



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



Scheme 6 Practical protocol of the selective alternate trithiation of the HPB frameworks

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 trithiation 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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