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Selective Alternate Derivatization of the Hexaphenylbenzene Framework through a Thermodynamically Controlled Halogen Dance

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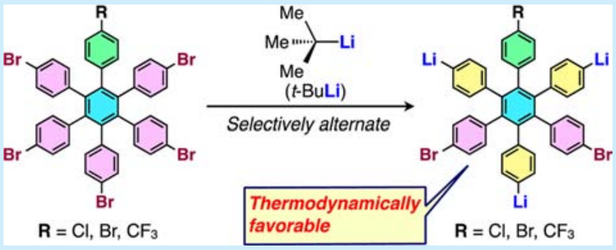
Supporting Information

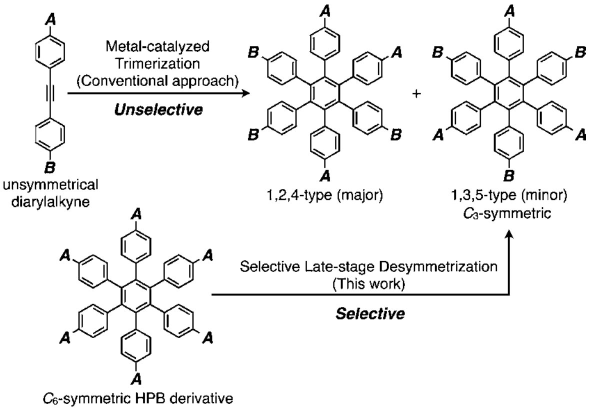
ABSTRACT: We report a practical synthetic protocol and mechanistic details for the selective alternate derivatization of the hexaphenylbenzene (HPB) framework through a thermodynamically controlled halogen dance. The stability of the alternately trilithiated species of HPB is interpreted by the through-space interaction at the *ipso*-carbons of the phenyl groups of the HPB framework. By using this approach, C_3-symmetric and lower-symmetric HPB derivatives possessing two or three kinds of substituents on the periphery have become easily and practically available.



Hexaphenylbenzene (HPB) is a versatile precursor of hexabenzocoronene (HBC) and its extended analogues, i.e. partial fragments of graphene, which play an important role in a wide range of emerging fields.[1] The very strong aggregation ability of HBC has been often employed to construct well-defined nanostructures.[2,3] HPB itself has also been exploited as a rigid molecular scaffold in liquid crystal,[4] organic electronic materials,[5] chromophores,[6] ligands,[7] amphiphiles,[8] and molecular receptors.[9] To regulate the electronic and physical properties of HPB and HBC derivatives, the introduction of proper substituents in an appropriate symmetry is vitally required. Especially, HPB and HBC derivatives with C_3-symmetry, which possess two kinds of substituents arranged in an alternate pattern on the periphery, are established as an invaluable class.[3,7a,8,10]

Despite their importance, almost all C_3-symmetric HPB derivatives have been prepared so far by an inefficient synthetic protocol based on trimerization of unsymmetrical diarylalkynes with two different substituents (Scheme 1).[11] In principle, this protocol inevitably affords a greater amount of the undesired "1,2,4-type" isomer than the desired "1,3,5-type" isomer because the former one is statistically preferred. Furthermore, the isolation of the desired isomer is quite difficult because these isomers have similar chemical properties. Accordingly, a conceptually different approach has long been demanded. For example, if the selective replacement of three of the chemically equivalent six peripheral substituents of the C_6-symmetric HPB framework in an alternate manner is realized (Scheme 1), the synthesis of C_3-symmetric HPB derivatives should be greatly improved. Herein, we report a late-stage desymmetrization approach for the selective synthesis of alternately functionalized HPB derivatives utilizing a thermodynamically controlled ArBr/ArLi exchange reaction, a halogen dance. It is also found that this approach enables us to achieve the synthesis of HPB derivatives with a substitution pattern that is completely unavailable by any conventional approaches.

Scheme 1. Synthetic Approaches to Alternately Substituted HPB Derivatives



To our surprise, from thoroughly surveying the literature, we found one example reported by Rathore et al.[12] a decade ago which included an alternately substituted HPB derivative that was accidentally produced in high yield through lithiation of C_6-symmetric hexakis(*p*-bromophenyl)benzene (**1**) by using 7.2 equiv of *t*-BuLi followed by electrophilic trapping with benzophenone. Although this reaction seems promising for the synthesis of C_3-symmetric HPB derivatives, its mechanistic details and versatility have remained unexplored. Thus,

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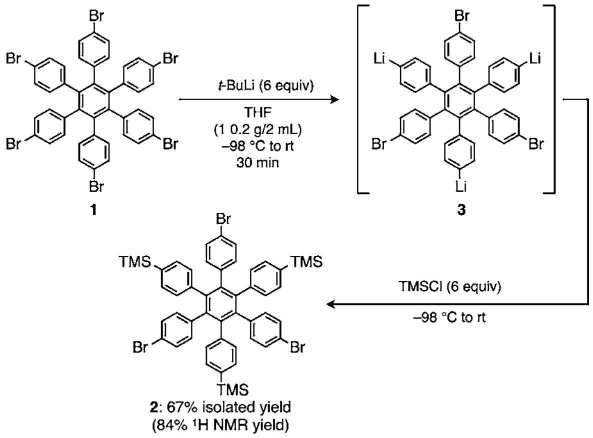
modifying Rathore's conditions, we added 6.0 equiv of *t*-BuLi into the suspension of **1** in THF at −98 °C, warmed it to rt to obtain a clear solution, and then quenched it with trimethylsilyl chloride (TMSCl) at −98 °C. HPB derivative **2** was selectively generated (^{1}H NMR yield: 84%) and isolated in 67% yield after recrystallization (Scheme 2). This reproducible result indicates the selective generation of the C_3-symmetric alternately trilithiated species **3** before quenching.

Scheme 2. Selective Alternate Trilithiation of Compound 1



To clarify the reaction mechanism, we monitored the composition of the reaction mixture by electrophilic trapping of lithiated intermediates with TMSCl at −98 °C. The ^{1}H NMR spectra of the resulting crude mixture at various times are shown in Figure 1. The product obtained 2.5 min after removal of the cooling bath was a 1:1 mixture of starting material **1** and compound **4** derived from hexalithiated species **5** (Figure 1a). During the warming process, the ratio of **5** progressively decreased, and via a rather complex mixture (Figure 1b and c), finally the alternately trilithiated species **3** became the main component of the reaction mixture, which did not contain **5** at all (Figure 1d). This result indicates that alternately trilithiated species **3** is not a kinetic product but is produced from **1** and "overlithiated" species **5** during the warming process.

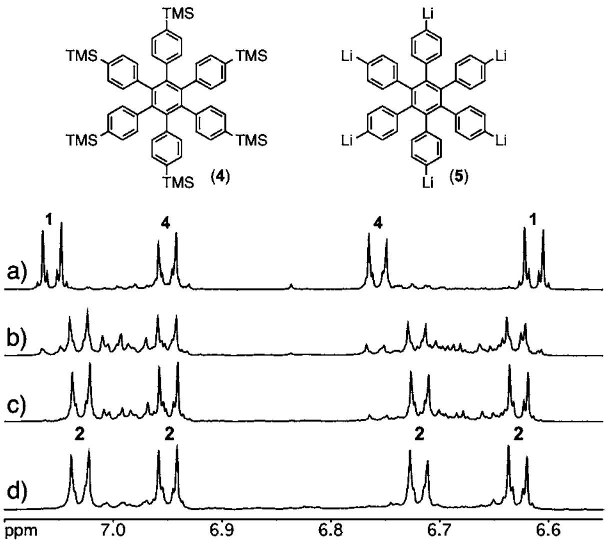
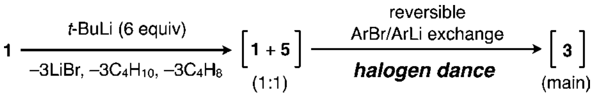


Figure 1. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of the crude mixture obtained by quenching with TMSCl at various times: (a) 2.5 min, (b) 5 min, (c) 7.5 min, (d) 30 min after removal of the cooling bath.

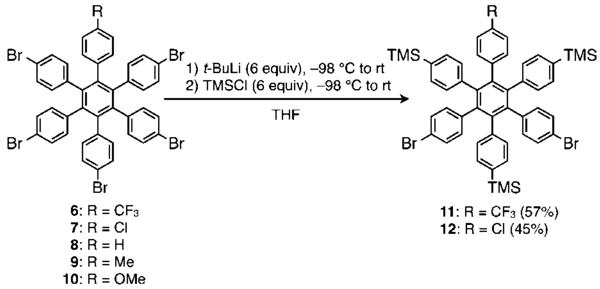
The reversibility of the ArBr/ArLi exchange reaction in THF was demonstrated,[13] and the process leading to a thermodynamic equilibration is known as a halogen dance reaction.[14] The formation of **3** can be interpreted on the basis of the halogen dance (Scheme 3). At the initial stage of the warming process, hexalithiated species **5** is selectively generated. The selective formation of **5** without any other partially lithiated species was attributed to the slower dissolution rate of precipitated **1** than the rate of Br/Li exchange on the dissolved partially lithiated species with *t*-BuLi.[15,16] Then the halogen dance between **1**, **5**, and the various partially lithiated species takes place to afford an equilibrium mixture which contains **3** as a major component. It should be noted that the highly site-selective derivatization based on the halogen dance has been limited to the monocyclic aromatics and quinoline, and there is no example of such high site selectivity to be attained for larger molecular frameworks such as HPB. As far as we know, this is the first report demonstrating that the halogen dance is applicable for the selective derivatization of polyaromatic hydrocarbons.

Scheme 3. Mechanism of Selective Alternate Trilithiation of Compound 1



Considering the statistical unfavorability of the alternate substitution pattern, the alternately trilithiated species **3** should be thermodynamically much more stable than the other trilithiated species. To reveal the origin of the thermodynamic stability of **3** and the versatility of this reaction for other HPB derivatives that can lead to a novel substitution pattern, we subjected brominated HPB derivatives **6**–**10** possessing one substituent (CF_3, Cl, H, Me, or OMe) and five Br atoms to the conditions of trilithiation for compound **1** (Scheme 4). The high alternate selectivity was observed only for **6** and **7**, which contain an electron-withdrawing group (R = CF_3, Cl), to give the products bearing three TMS groups arranged in an alternate manner in 57% and 45% isolated yield, respectively. It should be emphasized that we first realized the synthesis of the low symmetric HPB derivatives with this type of substitution pattern by utilizing the halogen dance. On the other hand, the trilithiation of **8**, **9**, and **10** bearing a hydrogen or an electron-donating group (R = Me, OMe) gave a complex

Scheme 4. Attempted Selective Alternate Trilithiation of HPB Derivatives 6–10



mixture.[17] These results indicate that the substituents of **6−10** strongly affect the alternate selectivity of trilithiation of the HPB framework.

How do the substituents affect the arrangement of Li even though they were distributed onto the different phenyl groups? The direct π-conjugation through the central benzene unit should not be operative owing to the large dihedral angles between the benzene units of the HPB framework. On the other hand, the through-space interaction between the adjacent phenyl groups in the HPB framework has been well recognized on the basis of the effective overlap of the p-orbitals of the *ipso*-carbons of the six phenyl groups (Figure 2a).[18] Therefore it is reasonable that the peripheral substituents effectively affect the stability of the lithiated moieties via a through-space interaction at the *ipso*-carbons. Although the effectiveness of this through-space interaction has been demonstrated experimentally, it has never been applied in the derivatization of the HPB framework.

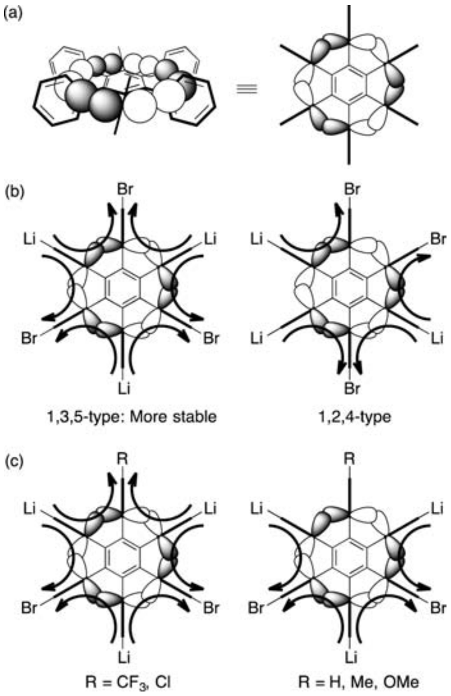


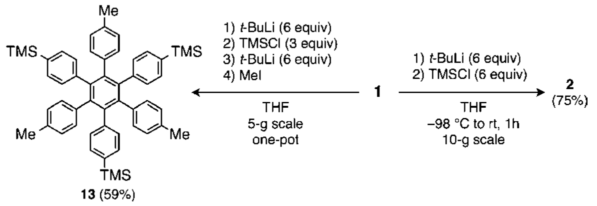
Figure 2. (a) Schematic representation of the through-space interaction at the *ipso*-carbons of the six phenyl groups on the HPB framework. (b) Qualitative comparison of the thermodynamic stability of the two trilithiated regioisomers from compound **1**. (c) Qualitative comparison of the thermodynamic stability of alternately trilithiated species from compounds **6**−**10**. Bold arrows represent the stabilizing interaction of the peripheral substituent via the through-space interaction at *ipso*-carbons.

The substituent effects on the thermodynamic stability of aryllithium were recently pursued by Schlosser et al.[19] They proposed that the proximal σ-polarization and the distal σ/π polarization are the key operative factors to determine the stability of aryllithiums. In the latter, the increased electron density in the σ-framework of the lithiated carbon is reduced by the polarization of the π-cloud. Likewise, in the case of the HPB framework, the extraction of the excessive electron density on the lithiated phenyl groups to the adjacent phenyl groups should be the prominent contribution to the stabilization of the lithiated moieties. Therefore, the substituent effects on the stabilization of the adjacent lithiated phenyl group can be qualitatively deduced from the stability of p-substituted aryllithiums, in which σ/π polarization is the predominant stabilization, and the order is as follows: Br ≈ CF_3 > Cl ≫ H > Me ≈ OMe.[20] Accordingly, it is electron-withdrawing groups, Br, CF_3 and Cl, that stabilize the adjacent lithiated phenyl group preferentially.

On the basis of the above order, we qualitatively interpreted the thermodynamic stability of the alternately trilithiated species. In the case of the "1,3,5-type" alternately trilithiated species obtained from compound **1**, each lithiated moiety can be stabilized by the two Br substituents on the adjacent phenyl groups (Figure 2b). In the case of the "1,2,4-type" trilithiated species, on the other hand, the number of the through-space stabilizing interactions decreases. In addition, the destabilization arising from the electronic repulsion between the two adjacent lithiated phenyl groups might be expected. As a result, the "1,3,5-type" alternately trilithiated species becomes the major component in the equilibrium mixture in spite of its statistical disadvantage. In the same manner, the alternately trilithiated species acquires high stability in the case of the compounds bearing an electron-withdrawing substituent, **6** and **7** (Figure 2c).

This selective late-stage desymmetrization of readily available polybrominated HPBs, **1**,[21] **6**, and **7**, through the halogen dance is quite practicable to obtain alternately functionalized HPB derivatives. For instance, selective alternate introduction of three TMS groups was accomplished in 75% yield after recrystallization at the 10-g scale (Scheme 5). Large-scale sequential trilithiation also succeeded in producing HPB derivative **13** with Me and TMS groups arranged in an alternate pattern, which was difficult to obtain through the conventional trimerization approach because of the tedious separation of the two possible isomers. The synthetic versatility of organolithiums and bromoarenes can effectually expand the availability of HPB derivatives.

Scheme 5. Application of Selective Alternate Trilithiation of Compound 1



In conclusion, we have developed the selective late-stage desymmetrization approach for the alternate derivatization of the HPB framework utilizing a thermodynamically controlled halogen dance. The key for success was the combination of the geometrical characteristics of the HPB framework and the advantageous feature of the halogen dance reaction. This success demonstrates that in some cases a late-stage desymmetrization approach can be more effective than that with prederivatized precursors for the preparation of low-symmetric π-conjugated frameworks. The elucidation of the detail of the stability of the alternately trilithiated species and research toward developing novel HPB derivatives based on this protocol are now underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details for the synthesis, spectral characterizations, and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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