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Selective Preparation of C_{2v}-Symmetric Hexaphenylbenzene Derivatives through Sequential Suzuki Coupling

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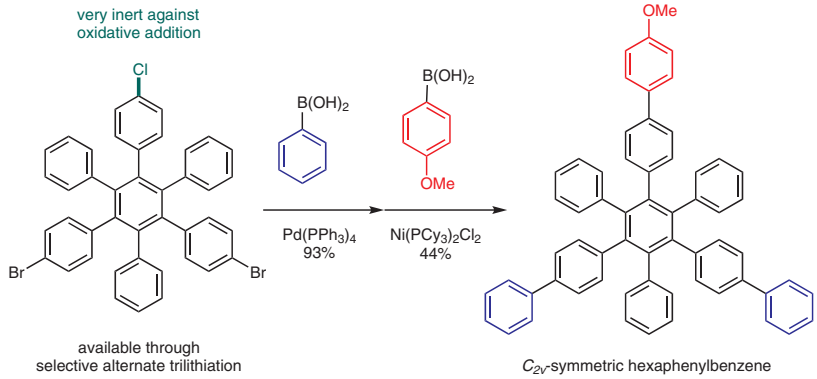

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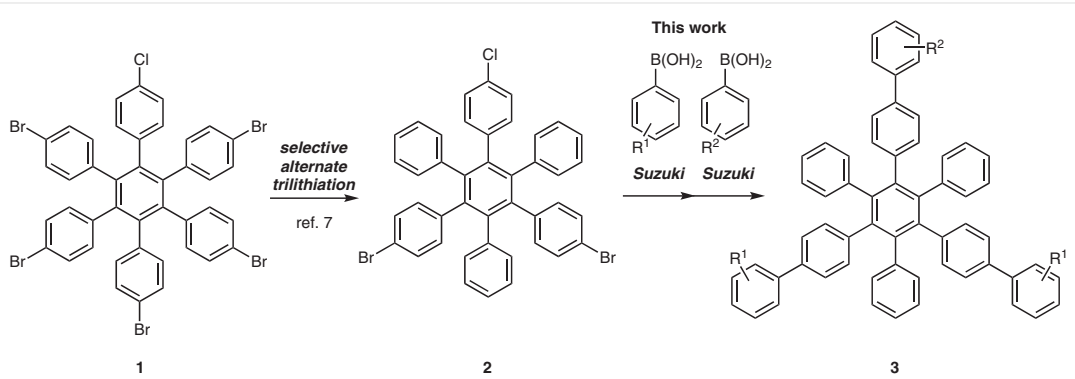
Abstract We have developed effective reaction conditions for the Suzuki cross-coupling of chlorinated hexaphenylbenzene derivatives. A chloro group on a hexaphenylbenzene framework exhibits a low reactivity to Suzuki cross-coupling, and only nickel catalysts bearing alkyl-substituted phosphine ligands achieved the coupling. With this as a key step, we succeeded in the selective preparation of a C_{2v}-symmetric hexaphenylbenzene derivative containing two kinds of aryl group.

Key words hexaphenylbenzene, Suzuki coupling, cross-coupling, nickel catalysis, aryl chlorides, regioselectivity

Hexaphenylbenzene (HPB) is a rigid C_6-symmetric molecular framework that has been adopted as a core structure of various materials.[1] It is also important as a precursor of large polycyclic aromatic hydrocarbon derivatives such as hexa-*peri*-benzocoronene.[2] To maximize the potential of the HPB framework, it is crucial to introduce appropriate substituents in a desired arrangement. Among the various substitution patterns for HPB, a C_{2v}-symmetric one with two kinds of substituent in an alternate pattern is interesting for its potential use as a building unit for polyphenylene dendrimers.[3] This C_{2v}-symmetric pattern has also been used in HPB-based amphiphiles.[4] Despite their utility, C_{2v}-symmetric HPB derivatives are difficult to prepare by conventional methods[5] or even by modern protocols.[6]

We recently developed a method for the selective alternate trilithiation of brominated HPB derivatives through a thermodynamically controlled halogen dance,[7] and have overcome the synthetic hurdle for C_{2v}-symmetric HPB derivatives (Scheme 1). One of the products, with both bromo and chloro groups on the HPB framework, could serve as a common precursor to various C_{2v}-symmetric HPB derivatives, owing to the different reactivities of aryl bromide and aryl chloride groups in metal-catalyzed cross-coupling reactions.[8,9] However, we encountered a low reactivity of the C–Cl moiety on the HPB framework in the Suzuki cross-coupling reaction. Here, we report an effective method for



Scheme 1 Selective preparation of a C_{2v}-symmetric HPB derivative containing two kinds of aryl group through selective alternate trilithiation of HPB derivative **1** and sequential Suzuki coupling

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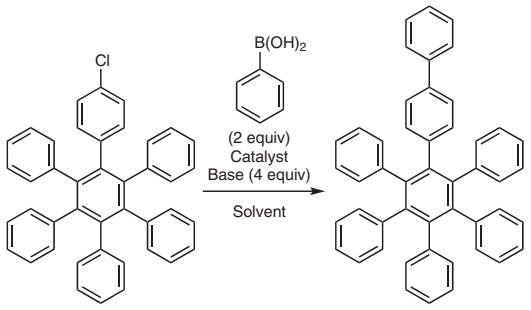
Suzuki cross-coupling of the chloro group on the HPB framework. By using this condition, we selectively prepared a C_{2v}-symmetric HPB derivative containing two kinds of aryl group (Scheme 1).

We screened several sets of conditions for the Suzuki cross-coupling of the chlorinated HPB **4** with phenylboronic acid (Table 1).[10] No cross-coupling reaction of a chloro group on HPB has previously been reported. We found that compound **4** was completely recovered in the presence of palladium catalysts bearing bulky or electron-rich phosphines such as SPhos,[11] PCy_3,[12,13] or $P(t\text{-}Bu)_3$,[13] which are known to be effective in Suzuki cross-coupling reactions of aryl chlorides (Table 1, entries 1–3). Taking successful examples of Suzuki cross-coupling reaction of brominated HPB derivatives[14] into consideration, we attributed this low reactivity to difficult oxidative addition of the C–Cl moiety of compound **4**. Our attention then shifted to Ni catalysts, which are known to promote oxidative addition more readily than do Pd catalysts.[15] Whereas Ni catalysts with aryl-substituted phosphine ligands such as DPPP,[16] PPh_3,[17] or DPPF[18] did not work at all (entries 4–8), more-electron-rich Ni catalysts with alkyl-substituted phosphine ligands, such as PCy_3[19] or 1,2-bis(dicyclohexylphosphino)ethane (DCYPE),[20] afforded the coupled product **5** when an appropriate base and solvent were used (entries 9–13). The optimized conditions involved a combination of $Ni(PCy_3)_2Cl_2$ and K_3PO_4 in THF or 1,4-dioxane (entries 9 and 10). The moderate yields under these conditions are due to the recovery of the starting material **4** (34% for entry 9, 45% for entry 10). Although the reason for this is unclear, no further improvement of the conversion was achieved, even on doubling the amount of the Ni catalyst.

Table 1 Optimization of a Suzuki Coupling of HPB Derivative **4**[a]



4 **5**

Entry	Catalyst (mol%)	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1[c]	$Pd(OAc)_2$ (5) SPhos (10)	K_3PO_4[d]	toluene	100	14	0
2[e]	$Pd_2(dba)_3$ (2.5) $PCy_3{\cdot}HBF_4$ (6)	K_3PO_4	1,4-dioxane	80	22	0
3[e]	$Pd_2(dba)_3$ (2.5) $P(t\text{-}Bu)_3{\cdot}HBF_4$ (6)	K_3PO_4	THF	80	30	0
4	$Ni(dppp)Cl_2$ (5)	K_3PO_4	1,4-dioxane	100	66	0
5	$Ni(dppp)Cl_2$ (5)	K_3PO_4	THF	80	42	0
6	$Ni(dppp)Cl_2$ (5)	K_3PO_4	toluene	100	42	0
7	$Ni(PPh_3)_2Cl_2$ (10)	K_3PO_4	THF	80	44	0
8	$Ni(dppf)Cl_2$ (10)	K_3PO_4	THF	80	62	0
9	$Ni(PCy_3)_2Cl_2$ (10)	K_3PO_4	THF	80	60	66
10	$Ni(PCy_3)_2Cl_2$ (10)	K_3PO_4	1,4-dioxane	100	51	55
11	$Ni(PCy_3)_2Cl_2$ (10)	K_3PO_4	toluene	100	28	0
12	$Ni(PCy_3)_2Cl_2$ (10)	CsF	THF	80	38	0
13	$Ni(dcype)Cl_2$ (10)	K_3PO_4	THF	80	75	25

[a] Compound **4** (0.10 g) and solvent (1 mL) were used.
[b] Determined by ^1H NMR.
[c] With 1.1 equivalents of $PhB(OH)_2$.
[d] With 2.0 equivalents of K_3PO_4.
[e] With 1.5 equivalents of $PhB(OH)_2$.

The inertness of compound **4** against oxidative addition of a metal center might be related to the geometrical structure of the HPB framework (Figure 1). HPB derivatives adopt a propeller conformation because of steric repulsion between the adjacent aryl groups, especially around the central part of the framework.[21] During oxidative addition of a metal center to an aryl halide, the metal center approaches the C–X bond, interacting with the π-orbitals of the aryl ring of an aryl halide.[22] In the case of the HPB derivatives such as compound **4**, both sides of the π-orbitals of the aryl rings are sterically covered by the adjacent aryl groups. This geometrical characteristic of the HPB framework, combined with the intrinsic low reactivity of aryl chlorides, hampers oxidative addition of a metal catalyst, thereby demanding electron-rich Ni catalysts.

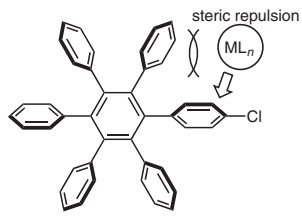


Figure 1 Difficult oxidative addition of a metal catalyst to a C–Cl bond on the HPB framework

We selectively prepared a C_{2v}-symmetric HPB derivative **8** possessing two kinds of aryl group on the HPB framework (Scheme 2). HPB derivative **1** was selectively trilithiated in an alternate pattern to afford compound **6** containing three TMS groups.[7] The introduction of the TMS groups enabled us to isolate compound **6** by crystallization. The TMS groups in **6** were then protodesilylated under acidic conditions.[23] Though the direct protonation of the trilithio species deriving from compound **1** afforded compound **2** as the main product, it was difficult to separate compound **2** from small amounts of its isomers generated during the lithiation step. Compound **2** was then subjected to sequential

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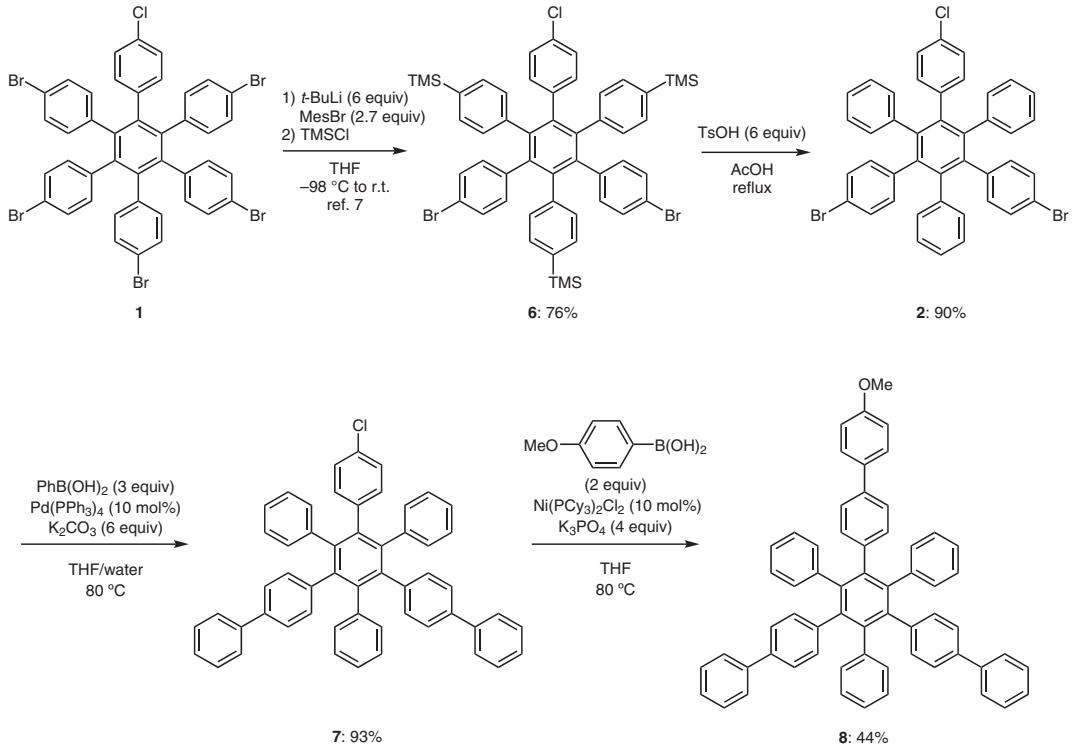

Scheme 2 Preparation of HPB derivative **8**

Suzuki cross-coupling. The first coupling with phenylboronic acid in the presence of $Pd(PPh_3)_4$ as a catalyst occurred exclusively at the Br moieties, even with excess phenylboronic acid, and the diarylated HPB derivative **7** was obtained in high yield.[24] The second Suzuki coupling between the C–Cl moiety of compound **7** and 4-methoxyphenylboronic acid afforded the C_{2v}-symmetric HPB derivative **8** (44%) with 30% recovery of compound **7**.[25] This result demonstrates the utility of our protocol in selectively affording C_{2v}-symmetric HPB derivatives containing two kinds of aryl group, which are difficult to prepare by other protocols.

In conclusion, we have developed effective reaction conditions for the Suzuki cross-coupling of chlorinated HPB derivatives. The aryl chloride moiety on the HPB framework exhibits a low reactivity to Suzuki cross-coupling, and only Ni catalysts bearing alkyl-substituted phosphine ligands were capable of inducing this reaction. With this as a key step, we succeeded in the selective introduction of two kinds of aryl group onto the periphery of a HPB skeleton to give a C_{2v}-symmetric HPB derivative. This protocol should be applicable to the development of new HPB derivatives bearing multiple functional groups or HPB-based large carbon clusters.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610024.

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(9) A combination of an aryl bromide and an aryl iodide is not applicable for the selective sequential Suzuki coupling because both substrates are reactive in the lithiation step.
(10) **Suzuki Coupling Reactions of Compound 4; General Procedure**
A suspension of compound **4** (0.100 g, 0.176 mmol, 1.0 equiv), the appropriate arylboronic acid, base, and catalyst were stirred in a Schlenk tube under N_2 while the reaction was monitored and the yield was determined by ^{1}H NMR.
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(23) **Compound 2**
A suspension of compound **6** (0.500 g, 0.530 mmol) and TsOH (604 mg, 3.18 mmol) in AcOH (5 mL) was refluxed for 1.5 h. H_2O (5 mL) was then poured into the mixture and the resulting precipitate was collected by filtration and washed with MeOH to afford compound **2** as a colorless solid; yield: 0.346 g (90%); mp >300 °C.
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 6.98 (d, *J* = 8.8 Hz, 4 H), 6.92–6.89 (m, 9 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.78–6.75 (m, 6 H), 6.71 (d, *J* = 8.6 Hz, 2 H), 6.66 (d, *J* = 8.6 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 140.66, 140.57, 139.91, 139.89, 139.48, 139.43, 139.39, 138.90, 132.98, 132.61, 131.45, 131.25, 130.00, 127.21, 127.08, 125.90, 119.75. HRMS (ESI-TOF): *m/z* $[M]^+$ calcd for $C_{42}H_{27}{}^{79}Br_2{}^{35}Cl$: 724.0182; found: 724.0168.
(24) **Compound 7**
A solution of compound **2** (0.200 g, 0.275 mmol, 1.0 equiv), $PhB(OH)_2$ (0.101 g, 0.825 mmol, 3.0 equiv), K_2CO_3 (0.228 g, 1.65 mmol, 6.0 equiv), and $Pd(PPh_3)_4$ (31.8 mg, 27.5 µmol, 10 mol%) in THF (2 mL) and H_2O (2 mL) was stirred at 80 °C for 6 h under N_2. The mixture was then extracted with EtOAc (3 × 5mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, hexane to hexane–EtOAc (20:1)] to give a colorless solid; yield: 0.186 g (93%); mp 284–286 °C.
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.44 (d, *J* = 7.2 Hz, 4 H), 7.33 (t, *J* = 7.5 Hz, 4 H), 7.24 (t, *J* = 7.4 Hz, 2 H), 7.13 (d, *J* = 8.4 Hz, 4 H), 6.90–6.80 (m, 21 H), 6.77 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 140.91, 140.80, 140.55, 140.49, 140.40, 140.31, 139.69, 139.33, 139.27, 137.56, 132.80, 131.90, 131.51, 131.47, 131.29, 128.68, 127.03, 126.92, 126.81, 125.62, 125.50, 125.29. HRMS (ESI-TOF): *m/z* $[M]^+$ calcd for $C_{54}H_{37}{}^{35}Cl$: 720.2576; found: 724.2584.
(25) **Compound 8**
A solution of compound **7** (0.100 g, 0.139 mmol, 1.0 equiv), 4-methoxyphenylboronic acid (42.2 mg, 0.278 mmol, 2.0 equiv), K_3PO_4 (0.118 g, 0.556 mmol, 4.0 equiv), and $Ni(PCy_3)_2Cl_2$ (9.60 mg, 13.9 µmol, 10 mol%) in THF (1 mL) was stirred at 80 °C for one week under N_2. The mixture was then extracted with EtOAc (3 × 5 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, hexane to hexane–EtOAc (10:1)] to give a colorless solid [yield: 48 mg (44%)], together with a mixture of compound **7** and 4,4′-dimethoxybiphenyl. Compound **7** [yield: 30 mg (30%); mp 252–253 °C] was recovered after washing this mixture with hexane.
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 7.45 (d, *J* = 7.4 Hz, 4 H), 7.38 (d, *J* = 9.0 Hz, 2 H), 7.33 (t, *J* = 7.8 Hz, 4 H), 7.24 (t, *J* = 7.4 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 4 H), 7.09 (d, *J* = 8.5 Hz, 2 H), 6.90–6.80 (m, 23 H), 3.80 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 158.97, 140.88, 140.71, 140.69, 140.67, 140.60, 140.30, 140.22, 139.94, 139.21, 137.47, 137.09, 133.45, 132.00, 131.97, 131.61, 128.68, 127.82, 127.01, 126.89, 126.82, 125.40, 125.26, 124.79, 114.11, 55.47. HRMS (ESI-TOF): *m/z* $[M]^+$ calcd for $C_{61}H_{44}O$: 792.3392; found: 792.3395.

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