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One-Pot Synthesis of Symmetrical and Unsymmetrical Diarylmethanes via Diborylmethane

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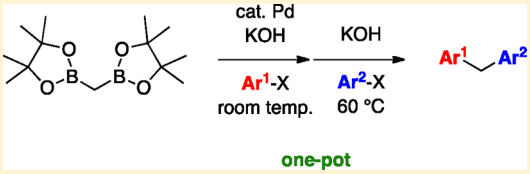
Supporting Information

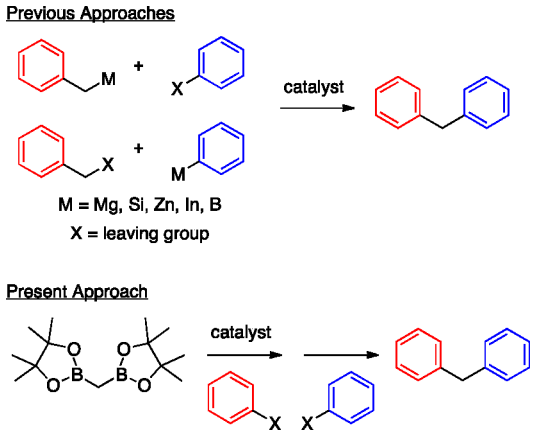
ABSTRACT: A one-pot synthesis of diarylmethanes from air-stable diborylmethane via the Suzuki−Miyaura cross-coupling reaction is described. The present approach realizes the synthesis of various symmetrical and unsymmetrical diarylmethanes in good to excellent yields.



INTRODUCTION

Diarylmethanes are an important class of molecules in medicinal chemistry.[1] Although the one-pot synthesis of diarylmethanes is an indispensable approach, the incorporation of desired aryl units into a methylene unit for the synthesis of unsymmetrical diarylmethanes in a single reaction vessel is difficult to achieve. The typical procedure for the synthesis of diarylmethanes is the cross-coupling reaction of benzyl halides with aryl nucleophiles or aryl halides with benzylic nucleophiles (Scheme 1).[2] The stepwise cross-coupling of silylmethylstannane with arylhalides reported by Itami et al. is an advanced approach to the synthesis of unsymmetrical diarylmethanes.[3] These procedures require the preparation of the corresponding benzyl halides and benzyl nucleophiles as intermediates at each step. Therefore, a one-pot approach starting from stable dimetallomethane derivatives with commercially available aryl halides is needed for the preparation of unsymmetrical diarylmethanes in synthetic organic chemistry.

Scheme 1. Concept of One-Pot Synthesis of Diarylmethanes



RESULTS AND DISCUSSION

We previously reported the use of air-stable diborylmethane derivatives for the regiospecific and chemoselective Suzuki−Miyaura cross-coupling reaction (SMC) at room temperature.[4] The reaction proceeds under ambient conditions and gives benzylboronate derivatives without a subsequent cross-coupling reaction into diarylmethanes. Since various examinations of the SMC showed that alkylboronic acid pinacol esters were not suitable organoboron compounds for achieving a high yield due to the slow generation of a borate intermediate, even in the presence of a strong or specific base such as TlOH, there is only one example of the use of *B*-benzyl-9-borabicyclo-[3.3.1]-nonane derivatives as organoboron compounds for the efficient synthesis of diarylmethanes.[5] Benzyl boronic acid pinacol esters bearing β-C−H bonds have recently been reported to give the products in moderate yields in the presence of a relatively large amount of catalyst, ligands, and a stoichiometric amount of Ag_2O as a base.[6] In this context, we embarked on our strategy for the use of diborylmethane **1** as a methylene unit (Table 1). Although the SMC of diborylmethane **1** (1 equiv) and 1-bromo-4-methylbenzene (**2a**) (2.2 equiv) in the presence of $Pd[P(t\text{-}Bu)_3]_2$ (10 mol %) and KOH (2 equiv) at room temperature gave the benzylboronate **3a** in good yield, the desired diarylmethane **4a** was not obtained at all. In contrast, subsequent heating at 60 °C in the second coupling step gave the desired product **4a** in low yield, and a considerable amount of benzylboronate **3a** remained. When we added KOH (3 equiv) after we confirmed the consumption of diborylmethane **1**, the second coupling reaction took place smoothly at 60 °C

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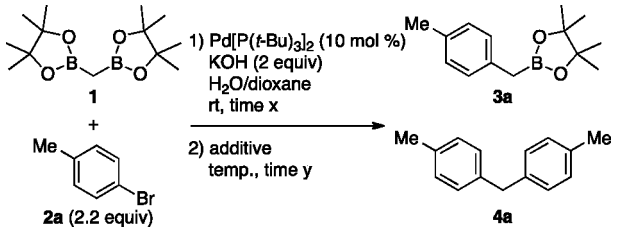
Table 1. Conditions for Symmetrical Diarylmethanes



entry	additive	temp (°C)	time *x*, *y* (h)	yield (%)[a]
1	none	rt	5, 24	**3a**, 80; **4a**, –
2	none	60	5, 14	**3a**, 76; **4a**, 14
3	KOH (3 equiv)	60	5, 15	**3a**, –; **4a**, 91
4[b]	KOH (3 equiv)	60	5, 12	**3a**, –; **4a**, >98
5[c]	none	60	10, –	**3a**, –; **4a**, 59

[a]NMR yields. [b]KOH (1.5 equiv) was used at the initial coupling reaction. [c]The reaction of **1** and **2a** was carried out in the presence of KOH (5 equiv) at 60 °C for 10 h from the beginning of the reaction.

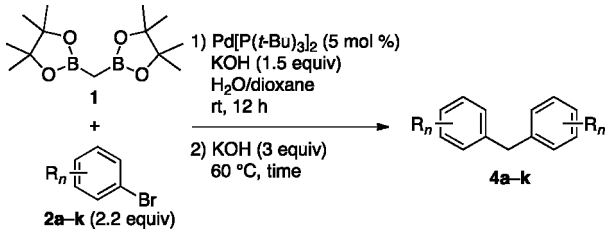
and gave the desired product **4a** in high yield (entry 3). The use of KOH (1.5 equiv) at the initial coupling improved the yield of product **4a** (entry 4). The first reaction temperature was important; the reaction at 60 °C from the beginning of the reaction in the presence of KOH (5 equiv) diminished the yield of product **4a** with the decomposition of **1** and **3a**; protodeboronation proceeded (entry 5).

A wide variety of aryl halides could participate in the reaction to give symmetrical diarylmethanes under the optimized conditions. The reaction of diborylmethane **1** and arylbromides **2a–k** was carried out in the presence of $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %) and KOH (1.5 equiv) at room temperature; after the first coupling reaction, KOH (3 equiv) was added and the reaction mixture was heated at 60 °C (Table 2). We obtained diarylmethanes derived from aryl bromides **2a–e** bearing an electron-donating or -withdrawing substituent at the 4-position (entries 1–5).[7] Aryl bromides **2f** and **2g** bearing a substituent at the 3-position participated in the reaction to give the corresponding products **4f** and **4g**, which are typically difficult to synthesize regioselectively via the conventional Friedel–Crafts approach (entries 6 and 7). The sterically hindered *ortho*-substituted diarylmethanes **4h–j** could be obtained (entries 8–10). Furthermore, bulky disubstituted aryl bromides **2k** gave the desired product **4k** in moderate yield (entry 11).

Modification of the reaction conditions for the synthesis of unsymmetrical diarylmethanes was explored (Scheme 2). The complete consumption of diborylmethane **1** or Ar^1Br at the first coupling is important for decreasing side-products; remaining **1** would lead to the generation of **4-Ar^1$_2$** and **4-Ar^2$_2$** at the second coupling reaction. We initially focused on the amount of KOH to complete the first coupling reaction of diborylmethane **1** (1 equiv) with 1-bromo-4-methylbenzene (**2a**) (1 equiv) (Table 3). The reaction of **1** and **2a** was conducted in the presence of $Pd[P(t\text{-}Bu)_3]_2$ (10 mol %) and KOH in dioxane at room temperature. The amount of KOH is critical, and the optimum conditions gave **3a** in high yield when KOH (2 equiv) was used (entry 3).

We examined the one-pot synthesis of unsymmetrical diarylmethane derivatives (Table 4). After the first coupling reaction of diborylmethane **1** and 1-bromo-4-methylbenzene (**2a**), as shown in entry 3 of Table 3, 1-bromo-4-methoxybenzene (**2c**) (2 equiv) and KOH (3 equiv) were added. However, the reaction gave the desired product **5a** in

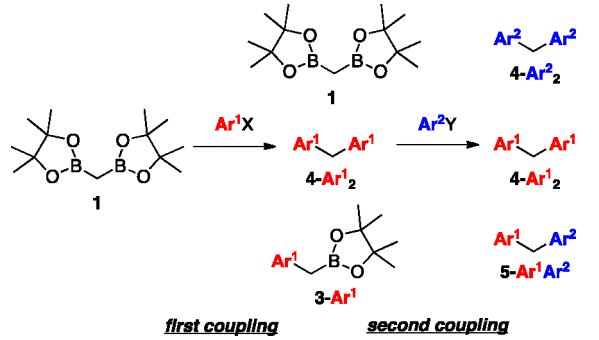
Table 2. Synthesis of Symmetrical Diarylmethanes



entry[a]	ArBr	time (h)	product	yield (%)
1	**2a**, R = Me	12	**4a**	89 (82)[b]
2	**2b**, R = H	4	**4b**	66
3	**2c**, R = OMe	5	**4c**	87
4	**2d**, R = F	7	**4d**	78
5	**2e**, R = Cl	2	**4e**	54
6	**2f**, R = Me	5	**4f**	70
7	**2g**, R = OMe	4	**4g**	65
8	**2h**, R = Me	2	**4h**	55
9	**2i**, R = OMe	3	**4i**	46
10	**2j**, R = *i*-Pr	3	**4j**	41
11	**2k**	4.5	**4k**	58

[a]The reaction of **1** (0.2 mmol), aryl bromide **2** (0.44 mmol), KOH (0.3 mmol, 8 N aq), $Pd[P(t\text{-}Bu)_3]_2$ (0.01 mmol, 5 mol %) was carried out in dioxane (2 mL). After 12 h stirring at room temperature, KOH (0.6 mmol, 8 N aq) was added. Then the reaction mixture was stirred at 60 °C. [b]The yield of the reaction in larger scale using **1** (1 mmol) and **2a** (2.2 mmol) was described in parentheses.

Scheme 2. Possible Products of One-Pot Synthesis of Diarylmethanes



moderate yield along with symmetrical diarylmethanes **4a** and **4c** (entry 1). Further examination of the reaction conditions showed that the use of diborylmethane **1** (2 equiv) and 1-bromo-4-methylbenzene (**2a**) (1 equiv) at the first coupling reaction, 1-bromo-4-methoxybenzene (**2c**) (4 equiv) in the

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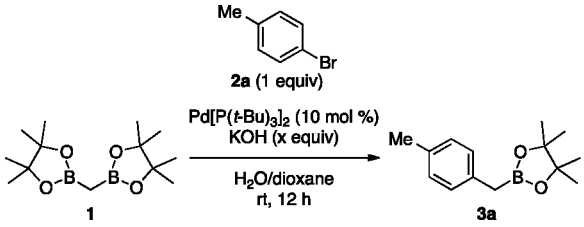
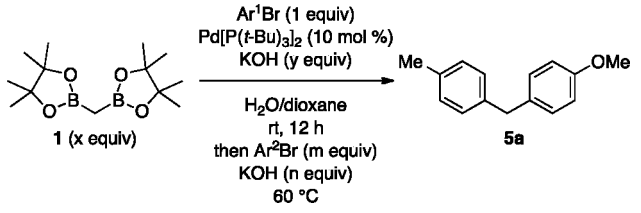
Table 3. Preliminary Screening of Conditions for First Coupling



entry	x	yield (%)[a]
1	1.0	36
2	1.5	78
3	2.0	92
4	2.5	57

[a]NMR yields.

Table 4. Conditions for Unsymmetrical Diarylmethanes



entry	Ar^1Br	Ar^2Br	x	y	m	n	yield (%)[a]
1	**2a**	**2c**	1	2	2	3	71
2			2	2	4	5	84
3	**2c**	**2a**	2	2	4	4	88
4			2	2	4	5	92
5			2	2	4	6	94
6			2	2	3	6	94

[a]NMR yields.

presence of additional KOH (5 equiv) at the second coupling reaction gave the product **5a** in high yield (entry 2). The excess amount of KOH in the second coupling reaction could destroy diborylmethane **1**; thus, the further coupling reaction of **1** with **2c** did not proceed.[4] When 1-bromo-4-methoxybenzene (**2c**) for the first coupling reaction and 1-bromo-4-methylbenzene (**2a**) for the second coupling reaction were used, the desired product **5a** was obtained in an improved yield of 88% (entry 3). After we examined the amount of base and **2a**, we decided to use the optimum conditions for the further screening of aryl bromides (entries 4−6).

We examined the sequential one-pot coupling reaction of various aryl halides under the optimum reaction conditions (Table 5). The coupling reactions using 1-bromo-4-methoxybenzene (**2c**) and 4-substituted aryl bromides gave the desired products **5a−e** in moderate to excellent yields (entries 1−5). Notably, the electron-withdrawing group can be tolerated in the second coupling reaction. Other substituted aryl bromides bearing sterically hindered substituents gave the desired products **5f−k** in good yields (entries 6−11). Heteroaryl bromides are suitable reactants: 2-bromothiophene (**2r**), 3-bromothiophene (**2s**), 3-bromofuran (**2t**), 2-bromopyridine (**2u**), and 3-bromopyridine (**2v**) were good coupling partners. There were no considerable byproducts; decomposition of the benzylboronate intermediate during the reaction decreased the yield of products when less-reactive aryl bromides were used in the second coupling reaction.

Representative results with other combinations of arylbromides are shown in Table 6. The reaction of diborylmethane **1**, 1-bromo-4-methylbenzene (**2a**), and 1-bromo-4-(trifluoromethyl)benzene (**2m**) or 3-bromothiophene (**2s**) gave the desired product **5q** or **5r** in respective yields of 88 or 82% (entries 1 and 2). The reaction of diborylmethane **1**, 1-bromo-4-fluorobenzene (**2d**), and 1-bromo-4-(trifluoromethyl)benzene (**2m**) gave the desired product **5s** in 77% yield (entry 3). Sterically hindered aryl bromides gave the products in reduced yields; the representative results using 1-bromo-2-methoxybenzene (**2i**) and 1-bromo-2-methylbenzene (**2h**) gave the desired product **5t** in 44% yield (entry 4).

We next examined the one-pot cross-coupling of diborylmethane **1** with an aryl bromide and benzyl bromide or cinnamyl halides. The reaction of diborylmethane **1** and benzyl bromide (**6a**), cinnamyl bromide (**6b**), or cinnamyl chloride (**6c**) was carried out under the same reaction conditions as for diarylmethane derivatives (Scheme 3). We previously reported that the cross-coupling reaction between diborylmethane **1** and benzyl bromide or allyl bromide derivatives proceeded efficiently.[4] The reaction of **1**, **2c**, and benzyl bromide (**6a**) gave the desired product **7a** in 67% yield. The reaction of **1**, **2c**, and cinnamyl bromide (**6b**) or cinnamyl chloride (**6c**) proceeded to give the corresponding product **7b** in 47 or 66% yield. The unreacted **6b** or **6c** was recovered after 24 h.

In conclusion, we achieved the one-pot synthesis of various diarylmethane derivatives via the Suzuki−Miyaura cross-coupling reaction of diborylmethane derivative. The reaction can be controlled by adjusting the reaction temperature and the amount of base. The synthesis of unsymmetrical diarylmethanes required the use of 2 equiv of diborylmethane **1** for complete consumption of the first arylbromides, and excess base in the second coupling reaction to negate the excess diborylmethane **1**; a trace amount of symmetrical diarylmethanes were generated from the second arylbromides. The present one-pot procedure is a convenient approach to the synthesis of densely functionalized diarylmethanes, which are useful compounds in organic synthesis.

EXPERIMENTAL SECTION

Synthesis of Di-*p*-tolylmethane (4a).[8] To a solution of diborylmethane **1** (53.6 mg, 0.200 mmol), 1-bromo-4-methylbenzene (**2a**) (76.4 mg, 0.44 mmol, 2.2 equiv), and $Pd[P(t\text{-}Bu)_3]_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 12 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be >98% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4a** in 0.174 mmol, 89% yield (34.8 mg/39.3 mg); the reaction using **1** (0.98 mmol) and **2a** (2.34 mmol) gave the product **4a** in 0.809 mmol, 82% yield (158.7 mg/193.8 mg).

Synthesis of Diphenylmethane (4b).[9] To a solution of diborylmethane **1** (52.8 mg, 0.197 mmol), *p*-bromobenzene (**2b**) (68.5 mg, 0.44 mmol, 2.2 equiv), and $Pd[P(t\text{-}Bu)_3]_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (71 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 4 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 77% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard.

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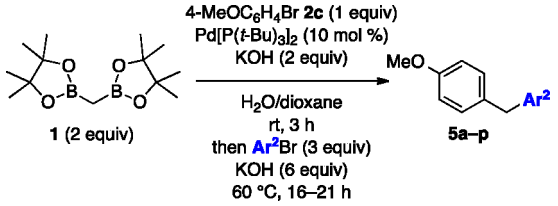
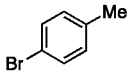
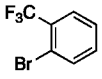
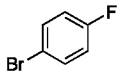
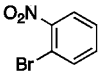
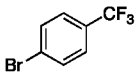
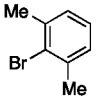
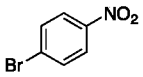
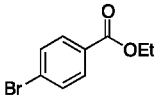
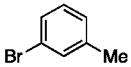
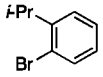
Table 5. Synthesis of Unsymmetrical Diarylmethanes



entry[a]	Ar^2Br	time (h)	yield (%)	entry[a]	Ar^2Br	time (h)	yield (%)
1	 **2a**	16	**5a**, 94 (87)[b]	9	 **2p**	16	**5i**, 71
2	 **2d**	16	**5b**, 91	10	 **2q**	16	**5j**, 61
3	 **2m**	16	**5c**, 80	11	 **2k**	16	**5k**, 73
4	 **2n**	16	**5d**, 75	12	 **2r**	16	**5l**, 83
5	 **2o**	24	**5e**, 43	13	 **2s**	16	**5m**, 93
6	 **2f**	16	**5f**, 94	14	 **2t**	16	**5n**, 74
7	 **2h**	16	**5g**, 83	15	 **2u**	21	**5o**, 50
8	 **2j**	16	**5h**, 79	16	 **2v**	16	**5p**, 80

[a]The reaction of **1** (0.4 mmol), aryl bromide **2** (0.2 mmol), KOH (0.4 mmol, 8 N aq), $Pd[P(t\text{-}Bu)_3]_2$ (0.02 mmol, 10 mol %) was carried out in dioxane (2 mL). After 3 h stirring at room temperature, another **2** (0.6 mmol) and KOH (1.2 mmol, 8 N aq) were added. Then the reaction mixture was stirred at 60 °C. [b]The yield of the reaction in larger scale using **1** (2 mmol), **2c** (1 mmol), and **2a** (3 mmol) was described in parentheses.

Purification by silica gel column chromatography (hexane) gave the product **4b** in 0.130 mmol, 66% yield (21.8 mg/33.1 mg).

Synthesis of Bis(4-methoxyphenyl)methane (4c).[10] To a solution of diborylmethane **1** (52.7 mg, 0.197 mmol), 1-bromo-4-methoxybenzene (**2c**) (82.1 mg, 0.44 mmol, 2.2 equiv), and $Pd[P(t\text{-}Bu)_3]_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 5 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be >98% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **4d** in 0.171 mmol, 87% yield (38.9 mg/44.9 mg).

Synthesis of Bis(4-fluorophenyl)methane (4d).[11] To a solution of diborylmethane **1** (53.6 mg, 0.200 mmol), 1-bromo-4-fluorobenzene (**2d**) (74.8 mg, 0.43 mmol, 2.2 equiv), and $Pd[P(t\text{-}Bu)_3]_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 6.5 h and

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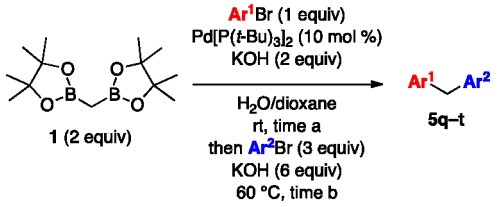
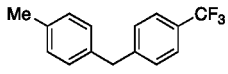
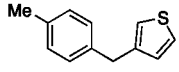
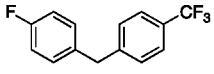
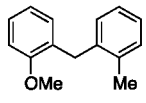
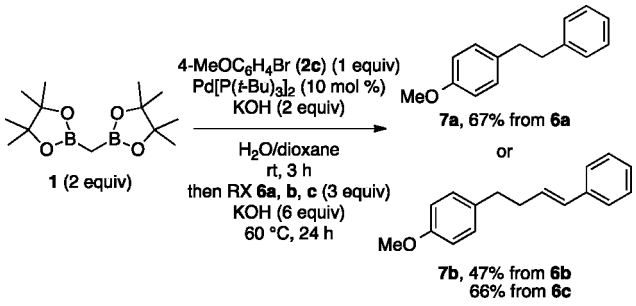
Table 6. Other Combination of Aryl bromides



entry[a]	Ar^1Br, Ar^2Br	time a, b (h)	product (%)
1	**2a, 2m**	7, 16	 **5q**, 88
2	**2a, 2s**	7, 16	 **5r**, 82
3	**2d, 2m**	4, 16	 **5s**, 77
4	**2i, 2h**	5, 16	 **5t**, 44

[a]The reaction of **1** (0.4 mmol), aryl bromide **2** (0.2 mmol), KOH (0.4 mmol, 8 N aq), Pd[P(*t*-Bu)$_3$]$_2$ (0.02 mmol, 10 mol %) was carried out in dioxane (2 mL). After 3 h stirring at room temperature, another **2** (0.6 mmol) and KOH (1.2 mmol, 8 N aq) were added. Then the reaction mixture was stirred at 60 °C.

Scheme 3. Benzylation and Allylation



passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 86% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4d** in 0.155 mmol, 78% yield (31.7 mg/40.8 mg): ^{1}H, ^{13}C NMR chemical shifts, and HRMS were literature known; ^{19}F NMR ($CDCl_3$, 466 MHz) δ −117.0; IR (neat, cm^{-1}) 3041, 2925, 1507, 1224, 819.

Synthesis of Bis(4-chlorophenyl)methane (4e). To a solution of diborylmethane **1** (53.1 mg, 0.198 mmol), 1-bromo-4-chlorobenzene (**2e**) (84.2 mg, 0.44 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.2 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 2 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 65% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4e** in 0.107 mmol, 54% yield (25.3 mg/47.0 mg); white solid: mp 50 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.23 (m, 4H), 7.08 (m, 4H), 3.91 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.1, 132.2, 130.3, 128.8, 40.6; IR (neat, cm^{-1}) 3031, 2923, 2858, 1091, 806; HRMS (FAB, positive) *m*/*z* calcd for $C_{13}H_{10}Cl_2$ 236.0160, found 236.0157.

Synthesis of Di-*m*-tolylmethane (4f). To a solution of diborylmethane **1** (53.6 mg, 0.200 mmol), 1-bromo-3-methylbenzene (**2f**) (74.8 mg, 0.44 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.2 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 5 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 74% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4f** in 0.141 mmol, 70% yield (27.6 mg/39.3 mg); yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (m, 2H), 7.02−6.95 (m, 6H), 3.90 (s, 2H), 2.31 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.3, 138.1, 129.8, 128.4, 126.9, 126.1, 42.0, 21.5; IR (neat, cm^{-1}) 3021, 2922, 2863, 1459, 1377, 771, 693; HRMS (FAB, positive) *m*/*z* calcd for $C_{15}H_{16}$ 196.1252, found 196.1244.

Synthesis of Bis(3-methoxyphenyl)methane (4g).[12] To a solution of diborylmethane **1** (54.2 mg, 0.202 mmol), 1-bromo-3-methoxybenzene (**2g**) (81.3 mg, 0.43 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (73 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 4 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 71% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **4g** in 0.131 mmol, 65% yield (30.0 mg/46.2 mg): NMR chemical shifts were literature known; IR (neat, cm^{-1}) 3006, 2937, 2835, 1260, 774, 692; HRMS (FAB, positive) *m*/*z* calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1148.

Synthesis of Di-*o*-tolylmethane (4h).[13] To a solution of diborylmethane **1** (53.4 mg, 0.199 mmol), 1-bromo-2-methylbenzene (**2h**) (74.5 mg, 0.44 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 2 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 63% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4h** in 0.109 mmol, 55% yield (21.4 mg/39.1 mg).

Synthesis of Bis(2-methoxyphenyl)methane (4i).[12] To a solution of diborylmethane **1** (52.5 mg, 0.196 mmol), 1-bromo-2-methoxybenzene (**2i**) (81.5 mg, 0.44 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (35 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (71 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 3 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 50% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **4i** in 0.0898 mmol, 46% yield (20.5 mg/44.7 mg): NMR chemical shifts were literature known; IR (neat, cm^{-1}) 3066, 3026, 2838, 1458, 1244, 751; HRMS (FAB, positive) *m*/*z* calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1157.

Synthesis of Bis(2-isopropylphenyl)methane (4j). To a solution of diborylmethane **1** (51.7 mg, 0.193 mmol), 1-bromo-2-isopropylbenzene (**2j**) (86.1 mg, 0.43 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (35 μL, 0.3 mmol, 1.5 equiv) at room temperature. After

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12 h stirring at room temperature, 8 N KOH aq (70 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 2.5 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 49% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4j** in 0.0792 mmol, 41% yield (20.0 mg/48.7 mg); yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.30 (m, 2H), 7.25−7.20 (m, 2H), 7.10−7.05 (m, 2H), 6.88−6.84 (m, 2H), 4.08 (s, 2H), 3.13 (sept, J = 6.8 Hz, 2H), 1.21 (d, J = 6.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.0, 137.5, 129.8, 126.7, 125.8, 125.2, 35.3, 29.0, 23.7; IR (neat, cm^{-1}) 3026, 2961, 2873, 1382, 1035, 758; HRMS (FAB, positive) m/z calcd for $C_{19}H_{24}$ 252.1878, found 252.1883.

Synthesis of Bis(2,6-dimethylphenyl)methane (4k). To a solution of diborylmethane **1** (54.4 mg, 0.203 mmol), 2-bromo-1,3-dimethylbenzene (**2k**) (78.3 mg, 0.42 mmol, 2.2 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5.1 mg, 10 μmol, 5 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (36 μL, 0.3 mmol, 1.5 equiv) at room temperature. After 12 h stirring at room temperature, 8 N KOH aq (72 μL, 0.6 mmol, 3 equiv) was added. The mixture was stirred at 60 °C for 4.5 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 61% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane) gave the product **4k** in 0.118 mmol, 58% yield (26.4 mg/45.5 mg); white solid: mp 93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04−6.93 (m, 6H), 4.01 (s, 2H), 2.12 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.9, 136.9, 128.7, 125.8, 31.9, 21.0; IR (neat, cm^{-1}) 3061, 3026, 2924, 2852, 768; HRMS (FAB, positive) m/z calcd for $C_{17}H_{20}$ 224.1565, found 224.1564.

Synthesis of 1-Methoxy-4-(4-methylbenzyl)benzene (5a).[14] To a solution of diborylmethane **1** (111.3 mg, 0.42 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (38.2 mg, 0.204 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (49 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (147 μL, 1.2 mmol, 6 equiv) and 1-bromo-4-methylbenzene (**2a**) (106.7 mg, 0.62 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5a** in 0.192 mmol, 94% yield (40.8 mg/43.4 mg); the reaction using **1** (531.7 mg, 2.0 mmol, 2 equiv), **2c** (186.2 mg, 1 mmol), and **2a** (510.8 mg, 3.0 mmol, 3 equiv) gave the product **5a** in 0.866 mmol, 87% yield (183.8 mg/211.3 mg).

Synthesis of 1-(4-Fluorobenzyl)-4-methoxybenzene (5b).[10] To a solution of diborylmethane **1** (106.3 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.2 mg, 0.199 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.3 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (143 μL, 1.2 mmol, 6 equiv) and 1-bromo-4-fluorobenzene (**2d**) (103.0 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5b** in 0.182 mmol, 91% yield (39.3 mg/43.0 mg): ^{1}H, ^{13}C NMR chemical shifts, IR, and HRMS were literature known; ^{19}F NMR ($CDCl_3$, 466 MHz) δ −117.4.

Synthesis of 1-(4-Methoxybenzyl)-4-(trifluoromethyl)-benzene (5c).[15] To a solution of diborylmethane **1** (106.3 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.1 mg, 0.198 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (143 μL, 1.2 mmol, 6 equiv) and 1-bromo-4-(trifluoromethyl)benzene (**2m**) (132.2 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5c** in 0.159 mmol, 80% yield (42.3 mg/52.8 mg): ^{1}H and ^{13}C NMR chemical shifts were literature known; ^{19}F NMR ($CDCl_3$, 466 MHz) δ −62.2; IR (neat, cm^{-1}) 2934, 2838, 1248, 1123, 1037, 814; HRMS (FAB, positive) m/z calcd for $C_{15}H_{13}F_3O$ 266.0918, found 266.0916.

Synthesis of 1-Methoxy-4-(4-nitrobenzyl)benzene (5d). To a solution of diborylmethane 1 (105.5 mg, 0.39 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (36.8 mg, 0.197 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.3 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (142 μL, 1.2 mmol, 6 equiv) and 1-bromo-4-nitrobenzene (**2n**) (119.1 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 10/1) gave the product **5d** in 0.148 mmol, 75% yield (36.0 mg/47.9 mg); orange oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, J = 8.4 Hz, 2H), 7.34−7.31 (m, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.02 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 149.5, 146.5, 131.3, 130.0, 129.6, 123.8, 114.3, 55.4, 41.0; IR (neat, cm^{-1}) 2954, 2930, 2837, 1250, 859, 828; HRMS (FAB, positive) m/z calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0907.

Synthesis of Ethyl 4-(4-methoxybenzyl)benzoate (5e). To a solution of diborylmethane **1** (107.4 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.4 mg, 0.200 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.3 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (144 μL, 1.2 mmol, 6 equiv) and ethyl 4-bromobenzoate (**2o**) (138.8 mg, 0.61 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 24 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5e** in 0.0858 mmol, 43% yield (23.2 mg/54.1 mg); yellow solid: mp 42 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.97 (s, 2H), 3.78 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7, 158.2, 147.0, 132.4, 130.0, 129.9, 128.9, 128.4, 114.1, 60.9, 55.4, 44.1, 14.4; IR (neat, cm^{-1}) 2932, 2836, 1719, 1247, 1034, 801, 668; HRMS (ESI, positive) m/z calcd for $C_{17}H_{18}NaO_3$ [M + Na]$^+$ 293.1154, found 293.1142.

Synthesis of 1-Methoxy-4-(3-methylbenzyl)benzene (5f).[16] To a solution of diborylmethane **1** (105.2 mg, 0.39 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (36.7 mg, 0.196 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.1 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (141 μL, 1.2 mmol, 6 equiv) and 1-bromo-3-methylbenzene (**2f**) (100.8 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5f** in 0.185 mmol, 94% yield (39.2 mg/41.7 mg): ^{1}H NMR chemical shifts are literature known; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.0, 141.6, 138.1, 133.5, 129.9, 129.7, 128.4, 126.8, 125.9, 113.9, 53.3, 41.1, 21.5; IR (neat, cm^{-1}) 3006, 2912, 2834, 1464, 1248, 819, 788, 695; HRMS (FAB, positive) m/z calcd for $C_{15}H_{16}O$ 212.1201, found 212.1210.

Synthesis of 1-Methoxy-4-(2-methylbenzyl)benzene (5g).[17] To a solution of diborylmethane **1** (105.2 mg, 0.39 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (36.8 mg, 0.197 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.3 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (142 μL, 1.2 mmol, 6 equiv) and 1-bromo-2-methylbenzene (**2h**) (100.1 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5g** in 0.163 mmol, 83% yield (34.5 mg/41.8 mg): ^{1}H and ^{13}C NMR chemical shifts were literature known; IR (neat, cm^{-1}) 3010, 2953, 2838, 1247, 1037, 812, 747; HRMS (FAB, positive) m/z calcd for $C_{15}H_{16}O$ 212.1201, found 212.1194.

Synthesis of 1-(2-Isopropylbenzyl)-4-methoxybenzene (5h). To a solution of diborylmethane **1** (108.4 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (38.3 mg, 0.205 mmol), and Pd[P(*t*-

Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (49 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (147 μL, 1.2 mmol, 6 equiv) and 1-bromo-2-isopropylbenzene (**2j**) (121.1 mg, 0.61 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5h** in 0.161 mmol, 79% yield (38.8 mg/49.2 mg); yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.28 (m, 1H), 7.26−7.21 (m, 1H), 7.15−7.07 (m, 2H), 7.03−7.00 (m, 2H), 6.82−6.78 (m, 2H), 4.00 (s, 2H), 3.77 (s, 3H), 3.14 (sept, J = 6.8 Hz, 1H), 1.13 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.1, 147.2, 137.7, 133.4, 130.5, 129.6, 126.9, 125.7, 125.6, 113.8, 55.3, 38.0, 29.0, 23.9; IR (neat, cm^{-1}) 3061, 2961, 2832, 1362, 1037, 805, 760; HRMS (FAB, positive) m/z calcd for $C_{17}H_{20}O$ 240.1514, found 240.1504.

Synthesis of 1-(4-Methoxybenzyl)-2-(trifluoromethyl)-benzene (5i). To a solution of diborylmethane **1** (106.7 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.3 mg, 0.199 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (144 μL, 1.2 mmol, 6 equiv) and 1-bromo-2-(trifluoromethyl)benzene (**2p**) (133.1 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5i** in 0.142 mmol, 71% yield (37.7 mg/53.1 mg); yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.12 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.3, 140.1, 132.0, 131.8, 131.7, 130.2, 128.7 (J_2 = 29.8 Hz), 126.2, 125.9 (J_3 = 6.0 Hz), 124.7 (J_1 = 274.1 Hz), 114.0, 55.3, 37.0 (J_4 = 2.4 Hz); ^{19}F NMR ($CDCl_3$, 466 MHz) δ −59.5; IR (neat, cm^{-1}) 2929, 2843, 1247, 1121, 1037, 805, 767; HRMS (FAB, positive) m/z calcd for $C_{15}H_{13}F_3O$ 266.0918, found 266.0907.

Synthesis of 1-Methoxy-4-(2-nitrobenzyl)benzene (5j).[18] To a solution of diborylmethane **1** (105.7 mg, 0.39 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (36.8 mg, 0.197 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (142 μL, 1.2 mmol, 6 equiv) and 1-bromo-2-nitrobenzene (**2q**) (119.1 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 10/1) gave the product **5j** in 0.120 mmol, 61% yield (29.1 mg/47.9 mg): ^{1}H, ^{13}C NMR chemical shifts, and HRMS were literature known; IR (neat, cm^{-1}) 2954, 2836, 1526, 1350, 1247, 1035, 862, 800, 766.

Synthesis of 1-(2,6-Dimethylbenzyl)-4-methoxybenzene (5k). To a solution of diborylmethane **1** (106.3 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.1 mg, 0.198 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (143 μL, 1.2 mmol, 6 equiv) and 2-bromo-1,3-dimethylbenzene (**2k**) (107.8 mg, 0.58 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5k** in 0.145 mmol, 73% yield (32.9 mg/44.9 mg); white solid: mp 61 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12−7.03 (m, 3H), 6.93−6.91 (m, 2H), 6.80−6.76 (m, 2H), 3.99 (s, 2H), 3.76 (s, 3H), 2.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.8, 137.4, 137.2, 131.8, 128.9, 128.2, 126.4, 113.9, 55.3, 34.2, 20.3; IR (neat, cm^{-1}) 2947, 2834, 1511, 1246, 1038, 769; HRMS (FAB, positive) m/z calcd for $C_{16}H_{18}O$ 226.1358, found 226.1358.

Synthesis of 2-(4-Methoxybenzyl)thiophene (5l).[17] To a solution of diborylmethane **1** (106.0 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.0 mg, 0.198 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.3 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (142 μL, 1.2 mmol, 6 equiv) and 2-bromothiophene (**2r**) (97.1 mg, 0.60 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5l** in 0.164 mmol, 83% yield (33.6 mg/40.4 mg); yellow oil: ^{1}H and ^{13}C NMR chemical shifts were literature known; IR (neat, cm^{-1}) 2908, 2834, 1248, 1037, 851, 818; HRMS (FAB, positive) m/z calcd for $C_{12}H_{12}OS$ 204.0609, found 204.0601.

Synthesis of 3-(4-Methoxybenzyl)thiophene (5m).[19] To a solution of diborylmethane **1** (110.8 mg, 0.41 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (38.7 mg, 0.207 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (50 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (149 μL, 1.2 mmol, 6 equiv) and 3-bromothiophene (**2s**) (100.7 mg, 0.62 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5m** in 0.192 mmol, 93% yield (39.2 mg/42.3 mg): ^{1}H and ^{13}C NMR chemical shifts were literature known; IR (neat, cm^{-1}) 3097, 3035, 2834, 1245, 1036, 813, 747; HRMS (FAB, positive) m/z calcd for $C_{12}H_{12}OS$ 204.0609, found 204.0606.

Synthesis of 3-(4-Methoxybenzyl)furan (5n). To a solution of diborylmethane **1** (109.1 mg, 0.41 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (38.4 mg, 0.205 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (49 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (148 μL, 1.2 mmol, 6 equiv) and 3-bromofuran (**2t**) (93.1 mg, 0.63 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5n** in 0.152 mmol, 74% yield (28.7 mg/38.6 mg); orange oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (s, 1H), 7.19 (s, 1H), 7.13 (m, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.23 (s, 1H), 3.80 (s, 3H), 3.71 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.1, 143.1, 139.6, 132.5, 129.6, 124.8, 113.9, 111.3, 55.4, 30.4; IR (neat, cm^{-1}) 3001, 2929, 2836, 1515, 1247, 874, 822, 754; HRMS (FAB, positive) m/z calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0830.

Synthesis of 2-(4-Methoxybenzyl)pyridine (5o).[20] To a solution of diborylmethane **1** (107.3 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.4 mg, 0.200 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (144 μL, 1.2 mmol, 6 equiv) and 2-bromopyridine (**2u**) (94.0 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 21 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/EtOAc = 10/1) gave the product **5o** in 0.101 mmol, 50% yield (20.1 mg/39.8 mg).

Synthesis of 3-(4-Methoxybenzyl)pyridine (5p). To a solution of diborylmethane **1** (105.0 mg, 0.39 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (36.6 mg, 0.196 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (141 μL, 1.2 mmol, 6 equiv) and 3-bromopyridine (**2v**) (92.1 mg, 0.58 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/EtOAc = 10/1) gave the product **5p** in 0.156 mmol, 80% yield (31.0 mg/39.0 mg); yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50−8.44 (m, 2H), 7.47−7.43 (m, 1H), 7.22−7.18 (m, 1H), 7.11−7.08 (m, 2H), 6.86−6.83 (m, 2H), 3.92 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.3, 150.2, 147.7, 137.0, 136.3, 132.0, 129.9, 123.5, 114.2, 55.4, 38.3; IR (neat, cm^{-1}) 3001, 2929, 2835, 1515, 1250, 806, 711; HRMS (FAB, positive) m/z calcd for $C_{13}H_{13}NO$ 199.0997, found 199.1002.

Synthesis of 1-Methyl-4-[4-(trifluoromethyl)benzyl]benzene (5q).[8] To a solution of diborylmethane **1** (108.1 mg, 0.40 mmol, 2

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equiv), 1-bromo-4-methylbenzene (**2a**) (34.5 mg, 0.202 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 7 h stirring at room temperature, 8 N KOH aq (145 μL, 1.2 mmol, 6 equiv) and 1-bromo-4-(trifluoromethyl)benzene (**2m**) (134.2 mg, 0.60 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane) gave the product **5q** in 0.177 mmol, 88% yield (44.2 mg/50.5 mg); colorless oil: ^{1}H, ^{13}C NMR chemical shifts, and HRMS were literature known; ^{19}F NMR ($CDCl_3$, 466 MHz) δ −62.2; IR (neat, cm^{-1}) 2925, 2861, 1515, 1124, 1066, 797.

Synthesis of 3-(4-Methylbenzyl)thiophene (5r).[19] To a solution of diborylmethane **1** (106.7 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methylbenzene (**2a**) (34.0 mg, 0.199 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 7 h stirring at room temperature, 8 N KOH aq (143 μL, 1.2 mmol, 6 equiv) and 3-bromothiophene (**2s**) (98.2 mg, 0.62 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane) gave the product **5r** in 0.163 mmol, 82% yield (30.6 mg/37.4 mg); yellow oil: ^{1}H, ^{13}C NMR chemical shifts were literature known; IR (neat, cm^{-1}) 2921, 2856, 1021, 766, 745; HRMS (FAB, positive) *m*/*z* calcd for $C_{12}H_{12}S$ 188.0660, found 188.0652.

Synthesis of 1-Fluoro-4-(4-(trifluoromethyl)benzyl)benzene (5s). To a solution of diborylmethane **1** (104.8 mg, 0.39 mmol, 2 equiv), 1-bromo-4-fluorobenzene (**2d**) (34.2 mg, 0.195 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 4 h stirring at room temperature, 8 N KOH aq (141 μL, 1.2 mmol, 6 equiv) and 1-bromo-4-(trifluoromethyl)benzene (**2m**) (131.9 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and filtered through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane) gave the product **5s** in 0.150 mmol, 77% yield (38.1 mg/49.7 mg); colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J = 8.0 Hz, 2H), 7.29−7.24 (m, 2H), 7.15−7.10 (m, 2H), 7.01−6.95 (m, 2H), 4.00 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7 (J_1 = 244.3 Hz), 145.1, 135.7 (J_4 = 2.4 Hz), 130.4 (J_3 = 8.3 Hz), 129.2, 128.7 (J'_2 = 32.2), 125.6 (J'_4 = 3.6 Hz), 124.3 (J'_1 = 270.5 Hz), 115.6 (J_2 = 21.5 Hz), 40.9; ^{19}F NMR ($CDCl_3$, 466 MHz) δ −62.3; IR (neat, cm^{-1}) 2927, 2856, 1327, 1160, 1124, 817; HRMS (FAB, positive) *m*/*z* calcd for $C_{14}H_{11}F_4$ $[M + H]^+$ 255.0797, found 255.0786.

Synthesis of 1-Methoxy-2-(2-methylbenzyl)benzene (5t). To a solution of diborylmethane **1** (105.7 mg, 0.39 mmol, 2 equiv), 1-bromo-2-methoxybenzene (**2i**) (36.9 mg, 0.197 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 5 h stirring at room temperature, 8 N KOH aq (142 μL, 1.2 mmol, 6 equiv) and 1-bromo-2-methylbenzene (**2h**) (100.3 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 16 h and passed through a pad of silica gel with ether. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **5t** in 0.0867 mmol, 44% yield (18.4 mg/41.9 mg); colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21−7.09 (m, 4H), 7.05−7.02 (m, 1H), 6.88 (m, 1H), 6.84−6.82 (m, 2H), 3.94 (s, 2H), 3.86 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 138.8, 136.9, 130.1, 129.9, 129.8, 128.9, 127.3, 126.2, 126.0, 120.5, 110.2, 55.4, 33.1, 19.6; IR (neat, cm^{-1}) 2933, 2835, 1491, 1462, 1243, 1031, 751; HRMS (FAB, positive) *m*/*z* calcd for $C_{15}H_{16}O$ 212.1201, found 212.1203.

Synthesis of 1-Methoxy-4-phenethylbenzene (7a).[21] To a solution of diborylmethane **1** (106.2 mg, 0.40 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2c**) (37.1 mg, 0.198 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (48 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (143 μL, 1.2 mmol, 6 equiv) and benzyl bromide (**6a**) (100.4 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 24 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 74% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **7a** in 0.133 mmol, 67% yield (28.3 mg/42.1 mg); white solid: mp 56 °C.

Synthesis of (*E*)-1-Methoxy-4-(4-phenylbut-3-en-1-yl)-benzene (7b). To a solution of diborylmethane **1** (105.6 mg, 0.39 mmol, 2 equiv), 1-bromo-4-methoxybenzene (**2d**) (36.9 mg, 0.197 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (10.2 mg, 20 μmol, 10 mol %) in dioxane (2.0 mL) was added 8 N KOH aq (47 μL, 0.4 mmol, 2 equiv) at room temperature. After 3 h stirring at room temperature, 8 N KOH aq (142 μL, 1.2 mmol, 6 equiv) and cinnamyl bromide (**6b**) (116.0 mg, 0.59 mmol, 3 equiv) were added. The mixture was stirred at 60 °C for 24 h and passed through a pad of silica gel with ether. Concentration gave the residue, the NMR yield of which was determined to be 49% by the integration ratio of the crude NMR with 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (hexane/ether = 30/1) gave the product **7b** in 0.093 mmol, 47% yield (22.1 mg/47.0 mg); yellow solid: mp 69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.25 (m, 4H), 7.21−7.11 (m, 3H), 6.84 (d, J = 8.5 Hz, 2H), 6.41 (d, J = 15.6 Hz, 1H), 6.25 (dt, J = 15.6, 6.8 Hz, 1H), 3.79 (s, 3H), 2.73 (t, J = 7.2 Hz, 2H), 2.49 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8, 137.7, 133.8, 130.3, 130.1, 129.3, 128.5, 126.9, 126.0, 113.8, 55.2, 35.1, 34.9; IR (neat, cm^{-1}) 2928, 2885, 2835, 1448, 1246, 1037, 816, 748; HRMS (FAB, positive) *m*/*z* calcd for $C_{17}H_{18}O$ 238.1350, found 238.1358.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of products. 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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■ REFERENCES

(1) (a) Hsin, L. W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321. (b) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P., Jr.; Zhuang, L.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923. (c) Boyd, R. E.; Rasmussen, C. R.; Press, J. B.; Raffa, R. B.; Codd, E. E.; Connelly, C. D.; Li, Q. S.; Martinez, R. P.; Lewis, M. A.; Almond, H. R.; Reitz, A. B. *J. Med. Chem.* **2001**, *44*, 863.

(2) Review, see: Liégault, B.; Renaud, J. L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290.

(3) Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, *4*, 3635.

(4) (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, *13*, 3368. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826.

(5) Flaherty, A.; Trunkfield, A.; Barton, W. *Org. Lett.* **2005**, *7*, 4975.

(6) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024.

(7) Although aryl iodides gave the comparable yield of products, arylchloride, aryltriflate, arylphosphate, arylacetate, and arylcarbonate typically gave poor yield of products. The arylbromides bearing NO_2, carboxylate, thiophenyl, furanyl, or pyridyl group did not give the products at all. The use of a 1,1-diborylalkane typically gave low yield of the corresponding diarylated product along with the corresponding monoarylated product.
(8) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600.
(9) Peña-López, M.; Ayán-Varela, M.; Sarandeses, L. A.; Sestelo, J. P. *Chem.—Eur. J.* **2010**, *16*, 9905.
(10) Sun, G.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 4929.
(11) Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S.; Ghigo, G. *Eur. J. Org. Chem.* **2009**, 4346.
(12) Qian, X.; Kozak, C. M. *Synlett* **2011**, 852.
(13) Bank, S.; Schepartz, A.; Giammatteo, P.; Zubieta, J. *J. Org. Chem.* **1983**, *48*, 3458.
(14) Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 4121.
(15) Srimani, D.; Bej, A.; Sarkar, A. *J. Org. Chem.* **2010**, *75*, 4296.
(16) Niwa, A.; Iwamura, H.; Nakagawa, Y.; Fujita, T. *J. Agric. Food Chem.* **1990**, *38*, 514.
(17) Li, M.-B.; Tang, X.-L.; Tian, S.-K. *Adv. Synth. Catal.* **2011**, *353*, 1980.
(18) Shang, R.; Huang, Z.; Chu, L.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 4240.
(19) Henry, N.; Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A. *Eur. J. Org. Chem.* **2008**, 4824.
(20) Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686.
(21) Kantam, M. L.; Chakravarti, R.; Chintareddy, V. R.; Sreedhar, B.; Bhargava, S. *Adv. Synth. Catal.* **2008**, *350*, 2544.