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Selective Synthesis of (Benzyl)biphenyls by Successive Suzuki–Miyaura Coupling of Phenylboronic Acids with 4-Bromobenzyl Acetate under Air Atmosphere

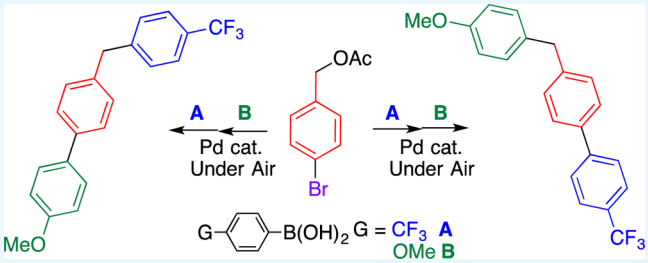
Masato Ohsumi*,† and Nagatoshi Nishiwaki*,‡,§

†Kochi National College of Technology, Nankoku, Kochi 783-8508, Japan

‡School of Environmental Science and Engineering and §Research Center for Material Science and Engineering, Kochi University of Technology, Tosayamada, Kami, Kochi 782-8502, Japan

Supporting Information

ABSTRACT: An efficient Pd-catalyzed cross-coupling reaction of phenylboronic acids and benzyl carbonates was developed, producing diarylmethanes. Benzyl acetates could also be used as coupling partners instead of benzyl carbonates, affording diarylmethanes in comparable yields. This reaction can be conducted under air atmosphere without any care for moisture and oxygen. The ester function showed an intermediate reactivity between chloro and bromo groups. This property facilitated the selective synthesis of diverse (benzyl)biphenyls by successive Suzuki–Miyaura coupling reactions using bromo- and chloro-substituted benzyl esters with two types of boronic acids.



INTRODUCTION

The diphenylmethane framework is often found in polymers,[1] dyes,[2] and bioactive compounds.[3] Although simple diphenylmethane derivatives are easily prepared by acid-catalyzed benzylation,[4] this protocol cannot afford substituted diphenylmethanes because of several limitations of Friedel–Crafts alkylation. This problem is easily solved by using the Suzuki–Miyaura coupling reaction, facilitating the synthesis of substituted unsymmetrical diphenylmethanes. In such cases, benzyl halides are widely used as a coupling partner of an organic boron compound; however, it is necessary to convert the precursor benzyl alcohol to the corresponding benzyl halide beforehand.[5] During the recent developments of synthetic methods for diphenylmethanes, much attention has been paid to other coupling partners: benzyl ethers[6] and benzyl esters such as acetates,[7] pivalates,[8] carbamates,[9] carbonates,[10] sulfonates,[11,12] sulfones,[13] and phosphates.[14] However, these methods require special catalysts and inert gas atmosphere, preventing the practical synthesis of diphenylmethanes. Therefore, we aimed to develop a more convenient approach to diphenylmethane derivatives from easily available boronic acid derivatives and benzyl acetates (or carbonates) under air atmosphere[12,15] using a simple catalyst prepared from a commercially available Pd source and phosphine ligand. Furthermore, the selective synthesis of (benzyl)biphenyls was achieved via the successive Suzuki–Miyaura coupling reactions using bromo- and chloro-substituted benzyl esters with two types of boronic acids.

RESULTS AND DISCUSSION

The cross-coupling reaction of benzyl methyl carbonate (**1a**) with phenylboronic acid (**2a**) to form diphenylmethane (**3a**) under air atmosphere was selected as the model reaction to optimize the reaction conditions, and phosphine ligands, Pd sources, bases, and solvents were screened (Table 1). Among the Pd sources, $PdCl_2$ showed a higher reactivity than $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (entries 1–3); thus, $PdCl_2$ was used for subsequent optimization because of its low-cost and easy-to-use property. A phosphine ligand was crucial for the success of this reaction (entries 3–8). Although the monophosphine coordination Pd complex did not work, the bidentate phosphine ligands exhibited a high catalytic activity and bis[2-(diphenylphosphino)phenyl] ether (DPEPhos) afforded **3a** in the highest yield. $NaHCO_3$ was found to be a more effective base than K_2CO_3 and Na_2CO_3 (entries 8–10). This reaction was also influenced by the solvent (entries 10–14). Polar protic solvents such as *t*-BuOH and EtOH were suitable solvents to increase the yield of **3a** up to 79% (entry 14).

With optimized conditions in hand, coupling reactions of other benzyl carbonates **1b–f** and phenylboronic acids **2a–d** were performed to obtain unsymmetrical diphenylmethanes (Table 2). This reaction was influenced by the electronic nature of the substituent on benzyl carbonate **1** (entries 1–5). When electron-rich benzyl ester **1b** was used, the reaction efficiently

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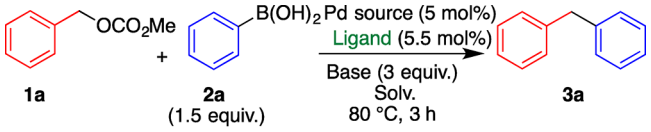
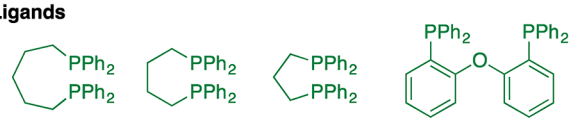
Table 1. Optimization of Reaction Conditions



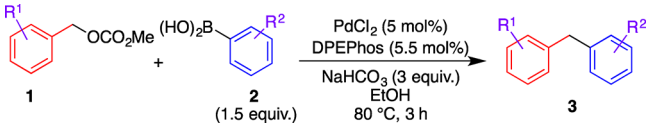
Ligands



entry	Pd source	ligand	base	solvent	yield/%[a]
1	[Pd][b]	DPPPent	K_2CO_3	DMF	27
2	$Pd(OAc)_2$	DPPPent	K_2CO_3	DMF	26
3	$PdCl_2$	DPPPent	K_2CO_3	DMF	32
4	$PdCl_2$		K_2CO_3	DMF	0
5	$PdCl_2$	PPh_3[c]	K_2CO_3	DMF	13
6	$PdCl_2$	DPPB	K_2CO_3	DMF	24
7	$PdCl_2$	DPPP	K_2CO_3	DMF	21
8	$PdCl_2$	DPEPhos	K_2CO_3	DMF	41
9	$PdCl_2$	DPEPhos	Na_2CO_3	DMF	35
10	$PdCl_2$	DPEPhos	$NaHCO_3$	DMF	56
11	$PdCl_2$	DPEPhos	$NaHCO_3$	PhMe	18
12	$PdCl_2$	DPEPhos	$NaHCO_3$	EtOAc	0
13	$PdCl_2$	DPEPhos	$NaHCO_3$	*t*-BuOH	67
14	$PdCl_2$	DPEPhos	$NaHCO_3$	EtOH	79

[a]GC yield (average of two runs). [b]$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %). [c]11 mol %.

Table 2. Cross-Coupling Reactions Using Other Carbonates 1 and Boronic Acids 2

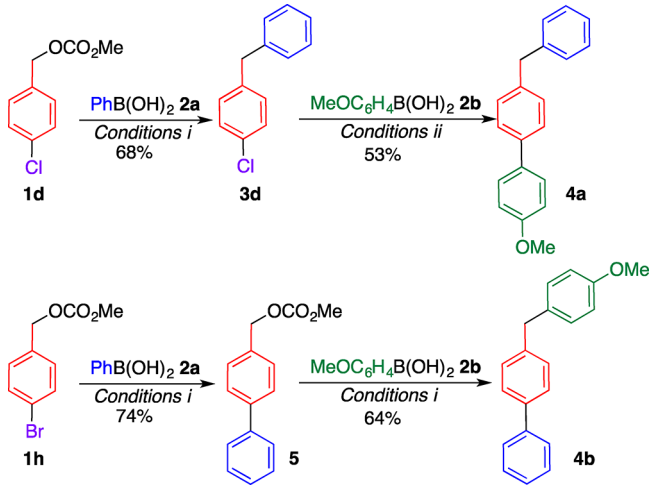


	carbonate		boronic acid		product	
entry	R^1		R^2			yield/%[a]
1	4-MeO	**1b**	H	**2a**	**3b**	97
2	4-Me	**1c**	H	**2a**	**3c**	73
3	4-Cl	**1d**	H	**2a**	**3d**	68
4	$4\text{-}CF_3$	**1e**	H	**2a**	**3e**	55
5	$4\text{-}NO_2$	**1f**	H	**2a**	**3f**	44
6	4-MeO	**1b**	4-MeO	**2b**	**3g**	83
7	4-MeO	**1b**	$4\text{-}CF_3$	**2c**	**3h**	80
8	2-Me	**1g**	H	**2a**	**3i**	41
9	4-MeO	**1b**	2-Me	**2d**	**3j**	72
10	2-Me	**1g**	2-Me	**2d**	**3k**	32

[a]Isolated yield.

afforded diphenylmethane **3b** in an excellent yield (entry 1). Benzyl esters **1c** and **1d** showed a reactivity similar to that of **1a** (entries 2 and 3). Notably, chloro-substituted benzyl carbonate **1d** also afforded diarylmethane **3d** in 68% yield without any detectable byproduct caused by an oxidative addition of Pd(0) to the C−**Cl** bond (entry 3). In the cases of **1e** and **1f** bearing an electron-withdrawing trifluoromethyl group, the yields of **3e** and **3f** decreased (entries 4 and 5). By contrast, the electronic nature of boronic acids did not affect this reaction; both the electron-rich and electron-poor boronic acids **2b** and **2c** exhibited almost the same reactivity, affording the corresponding products **3g** and **3h** in high yields (entries 6 and 7). Next, the steric effect of the ortho-substituent was investigated (entries 8−10). Although sterically hindered carbonate **1f** decreased the reaction efficiency, boronic acid **2d** afforded diphenylmethane **3i** without any influence of the ortho-substituent.

Scheme 1. Selective Synthesis of Differently Substituted (Benzyl)biphenyls 4a and 4b[a]



[a]Each reaction was conducted using boronic acid **2** (1.5 equiv), $PdCl_2$ (5 mol %), DPEPhos (5.5 mol %), and $NaHCO_3$ (3 equiv) in ethanol. *Condition i*: 80 °C, 3 h. *Condition ii*: 100 °C, 2 d.

The tolerance of a chloro group of **1d** under the coupling conditions prompted us to study the selective synthesis of (benzyl)biphenyls **4** (Scheme 1). Diphenylmethane **3d** obtained from chlorobenzyl carbonate **1d** and **2a** underwent the coupling reaction with 4-methoxyphenylboronic acid (**2b**), affording (4-benzyl)biphenyl **4a** in a moderate yield. On the other hand, when bromobenzyl carbonate **1h** was reacted with **2a** under the same conditions, the coupling reaction occurred on the benzene ring, affording biphenyl **5**.[16] Different types of (benzyl)biphenyl **4b** were prepared by subsequent coupling reactions with **2b**. Thus, the order of reactivity for the coupling reaction is C−Br > C−O > C−Cl, facilitating the selective C−C bond formation at the desired position.[17] Different reactivities of the C−Br and C−O bonds of **3h** facilitate the one-pot synthesis of several types of (benzyl)biphenyls **4c−g** in moderate to high yields by two sequential coupling reactions by changing the reaction order with boronic acids **2** (Table 3), that is, the first coupling reaction mainly occurs at the C−Br bond, and the second reaction occurs at the C−O bond. These results provide important insights into the molecular design and elaborate synthesis of (benzyl)biphenyls and their analogues.

A plausible reaction mechanism is shown in Scheme 2. The reaction is initiated by the oxidative addition of the Pd species to the C−O bond, accompanied by the elimination of CO_2, affording cationic (η^3-benzyl)Pd(II) **6**.[10] After σ-complex **7** is formed under equilibrium with **6**, intermediate **8** is formed by the transmetalation with arylboronic acid. The subsequent reductive elimination furnishes the cross-coupling product **3** and regenerates the Pd(0) species. When an electron-withdrawing group was introduced on the benzyl group of **1**, the reaction did not proceed efficiently because cationic intermediate **6** is destabilized.

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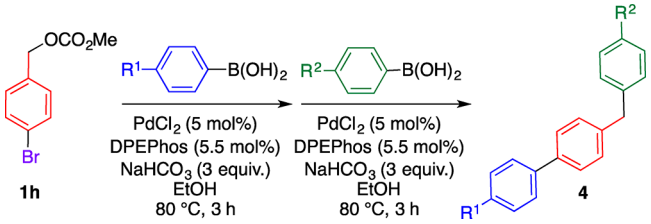
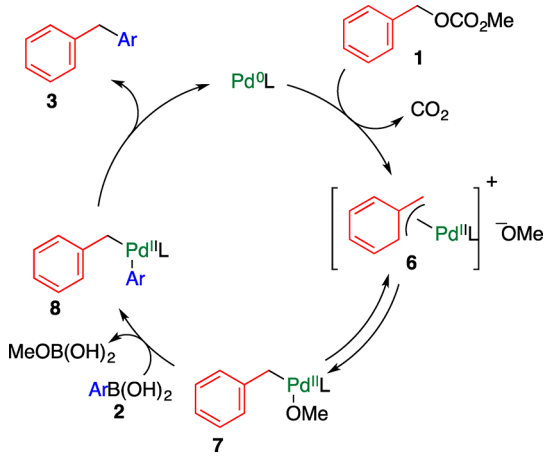
Table 3. One-Pot Synthesis of (Benzyl)biphenyls 4 by Changing the Order of Reaction with Boronic Acids 2



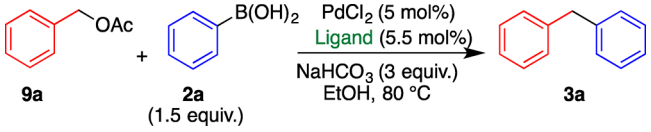
			product	
entry	R^1	R^2		yield/%
1	H	CF_3	**4c**	74
2	CF_3	H	**4d**	80
3	MeO	CF_3	**4e**	54
4	CF_3	MeO	**4f**	47
5	Me	MeO	**4g**	76

Scheme 2. Plausible Mechanism for the Coupling Reaction Using Benzyl Carbonate 1



Considering the above results, the Suzuki–Miyaura coupling reaction was studied using more easily available benzyl acetates **9** instead of carbonates **1**. When acetate **9a** was subjected to the reaction with phenylboronic acid (**2a**) under the optimized conditions determined for carbonate **1a**, the reaction proceeded similarly, affording diphenylmethane (**3a**) in a considerably low yield (Table 4, entry 1). This result indicates that the reactivity of **9a** is lower than that of **1a**. Indeed, the yield increased to 72% by prolonging the reaction time to 24 h. In this reaction, bidentate phosphine ligands were also effective; DPPPent showed the best performance (entries 1–5).

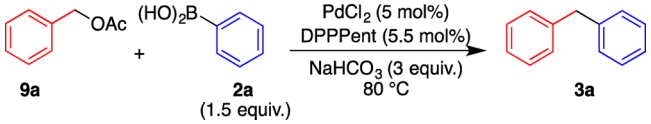
Table 4. Study on the Ligand for the Cross-Coupling of Benzyl Acetate (9a) and Phenylboronic Acid (2a)[a]



		yield/%	
entry	ligand	after 3 h	after 1 d
1	DPEPhos	23	72
2	PPh_3[b]	10	21
3	DPPP	22	53
4	DPPB	26	67
5	DPPPent	34	84

[a]GC yield (average of two runs). [b]11 mol %.

Table 5. Study on the Solvent for the Cross-Coupling Reaction of Benzyl Acetate (9a) and Phenylboronic Acid (2a)



			yield/%[a]	
entry	solv.	temp/°C	after 1 d	after 3 d
1	EtOH	80	72	72
2	DMF	80	3	8
3	1,4-dioxane	80	6	6
4	EtOAc	80	3	12
5	PhMe	80	0	0
6	PhMe[b]	80	11	17
7	EtOH	60	26	75
8	MeOH	60	29	79

[a]GC yield (average of two runs). [b]0.2 mmol EtOH was added.

The reaction rate was significantly influenced by the type of solvent (Table 5). Polar protic solvents such as EtOH and MeOH were effective to complete the reaction within 1 day (entries 1, 7, and 8). Indeed, while the reaction did not proceed in toluene, adding a small amount of EtOH accelerated the reaction (entries 5 and 6). The reaction proceeded in alcoholic media even at 60 °C, even though a longer reaction time was necessary (entries 7 and 8).

The coupling reaction of benzyl acetate **9** proceeds in a manner similar to that of benzyl carbonate **1**, as shown in Scheme 2. In this mechanism, the formation of intermediate complexes **6** and **7** seems to be crucial. In the case of carbonate **1**, the formation of **6** accompanied by decarboxylation is an irreversible process, facilitating the subsequent coupling reaction. Conversely, acetate **9** is regenerated under equilibrium even though cationic (η^3-benzyl)Pd(II) **10** is formed; this is a probable reason for the less reactivity of acetate **9** than that of carbonate **1**. When EtOH was used as a solvent, intermediates **6′** and **7′** were efficiently formed under the biased equilibrium, accelerating the reaction (Scheme 3).

Other benzyl acetates **9b–e** were subjected to the coupling reaction with arylboronic acids **2a–d** under the optimized conditions (Table 6). The reactions showed substituent effect similar to that observed in the reactions of benzyl carbonates **1**

Scheme 3. Plausible Mechanism for Forming Intermediate 7′ from Benzyl Acetate 9

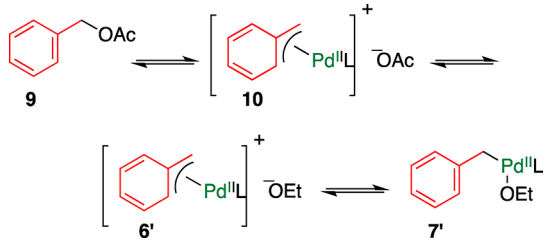


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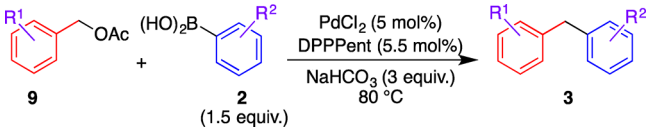
Table 6. Cross-Coupling of Other Acetates 9 with Boronic Acids 2

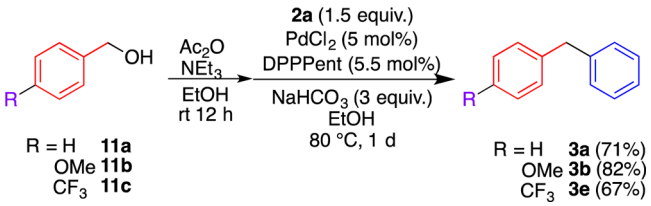


	acetate		boronic acid		product	
entry	R^1		R^2			yield/%[a]
1	4-MeO	**9b**	H	**2a**	**3b**	93
2	4-Cl	**9c**	H	**2a**	**3d**	77
3	4-CF_3	**9d**	H	**2a**	**3e**	56
4	2-Me	**9e**	H	**2a**	**3i**	32
5	4-MeO	**9b**	4-MeO	**2b**	**3g**	87
6	4-MeO	**9b**	4-CF_3	**2c**	**3h**	91
7	4-MeO	**9b**	2-Me	**2d**	**3j**	81

[a]Isolated yield.

shown in Table 2, that is, although the electron-rich acetates efficiently underwent the coupling reaction, the yield of **3** decreased in the case of electron-poor acetates (entries 1−3). Furthermore, the use of an ortho-substituent decreased the yield of the reaction (entry 4). On the other hand, this reaction was not influenced by the electronic nature of boronic acid **2** (entries 5−7).

Scheme 4. Direct One-Pot Conversion from Benzyl Alcohols 11 to Diarylmethanes 3



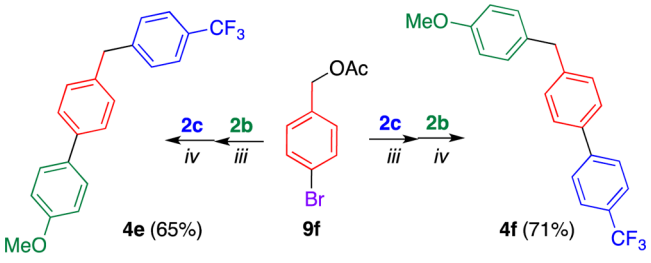
Easy access to benzyl acetates enabled the direct transformation of benzyl alcohols **11** to diphenylmethanes **3** in one pot (Scheme 4). Benzyl alcohol **11a** afforded **3a** in a comparable yield upon the sequential treatment with acetic anhydride in the presence of triethylamine followed by the Pd-catalyzed coupling reaction with boronic acid **2a**; the precursor benzyl acetate **9a** was not isolated. This protocol was applicable to both electron-rich and electron-poor benzyl alcohols **11b** and **11c**, furnishing the corresponding diphenylmethanes **3b** and **3e**, respectively, without a significant decrease in the yields.

4-Bromobenzyl acetate **9f** also served as the precursor of (benzyl)biphenyls **4e** and **4f** (Scheme 5). The less reactivity of **9f** than **1h** facilitated a more selective coupling reaction at the C−Br bond than that at the C−O bond, thus affording **4e** and **4f** in higher yields, respectively. Because (benzyl)biphenyls bearing both electron-donating and electron-withdrawing groups have not been synthesized except for several examples,[18] this protocol is a new synthetic tool for such compounds.

CONCLUSIONS

Two synthetic methods were developed for diphenylmethanes **3** by Suzuki−Miyaura coupling using benzyl esters such as benzyl carbonates **1** and benzyl acetates **9**. In both the cases, the Pd catalyst was generated from commercially available $PdCl_2$ and bidentate bis(phosphine)s, and the reaction was

Scheme 5. One-Pot Synthesis of Two Kinds of (Benzyl)biphenyls 4e and 4f by Changing the Order of Reaction with Boronic Acids 2b and 2c[a]



[a]Each reaction was conducted using boronic acid **2** (1.5 equiv), $PdCl_2$ (5 mol %), DPPPent (5.5 mol %), and $NaHCO_3$ (3 equiv) with heating at 80 °C in ethanol. *Condition iii*: for 3 h. *Condition iv*: for 1 d.

conducted in air atmosphere. This is advantageous from practical viewpoints compared to the conventional methods. It is also possible to synthesize diphenylmethanes **3** in one pot from benzyl alcohols **11** by sequential acetylation and coupling reactions. Furthermore, diverse (benzyl)biphenyls **4** were successfully synthesized by utilizing different reactivities of the C−Br and C−O bonds.

EXPERIMENTAL SECTION

General Procedure of the Suzuki−Miyaura Coupling Reaction. To a solution of $PdCl_2$ (1.8 mg, 10 μmol), DPEPhos (5.9 mg, 11 μmol), $NaHCO_3$ (50.2 mg, 0.6 mmol), and phenylboronic acid **2a** (36.6 mg, 0.3 mmol) in ethanol (1.0 mL), benzyl carbonate **1a** (33.2 mg, 0.2 mmol) was added, and the resultant mixture was heated in a screw-capped sealed tube at 80 °C for 3 h. After filtration using a Celite pad, the filtrate was extracted with hexane (10 mL × 3). The combined organic layer was washed with brine (10 mL × 1), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was treated with flash column chromatography (EtOAc/hexane = 90/10) to afford the coupling product **3a** (26.5 mg, 0.158 mmol, 79%).

When other conditions and substrates were employed, the experiments were conducted in a similar way.

4′-Phenyl-4-[(4-trifluoromethylphenyl)methyl]-1,1′-biphenyl (4c). White solid; mp 87−88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67−7.23 (m, 13H), 4.07 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.1, 140.9, 139.5, 139.2, 129.6, 129.4, 128.9, 127.5, 127.2, 127.1, 125.6, 125.5, 41.4; IR (neat) 2359, 2253, 1793, 1617, 1487, 1382, 1325, 1129, 908, 740 cm^{-1}; HRMS (EI, magnetic field) calcd for $C_{20}H_{15}F_3$, 312.1126; found, 312.1123.

4′-(4-Methoxyphenyl)-4-[(4-trifluoromethylphenyl)-methyl]-1,1′-biphenyl (4e). White solid; mp 127−128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56−7.47 (m, 6H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.05 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 145.3, 139.1, 138.5, 133.4, 129.3, 128.7, 128.4, 128.1, 127.1, 125.5, 123.0, 114.3, 55.4, 41.4; IR (neat) 3446, 2360, 2341, 1610, 1041, 907, 732 cm^{-1}; HRMS (EI, magnetic field) calcd for $C_{21}H_{17}F_3O$, 342.1231; found, 342.1231.

4-(4-Methoxyphenyl)-4′-[(4-trifluoromethylphenyl)-methyl]-1,1′-biphenyl (4f). White solid; mp 88−90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66−7.25 (m, 10H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.97 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 144.6, 141.9,

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137.5, 132.9, 130.0, 130.0, 129.6, 129.5, 127.3, 125.8, 123.1, 114.1, 55.4, 40.8; IR (neat) 3446, 2359, 2342, 1576, 1042, 907, 733 cm^{-1}; HRMS (EI, magnetic field) calcd for $C_{21}H_{17}F_3O$, 342.1231; found, 342.1230.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b01450.

^1H and ^{13}C NMR spectra for benzyl(biphenyl)s **4c**, **4e**, and **4f** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ohsumi@ms.kochi-ct.ac.jp (M.O.).

*E-mail: nishiwaki.nagatoshi@kochi-tech.ac.jp. Phone: +81-887-57-2517. Fax: +81-887-57-2520 (N.N.).

ORCID

Nagatoshi Nishiwaki: 0000-0002-6052-8697

Notes

The authors declare no competing financial interest.

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