Development of Chemoselective Suzuki-Miyaura Coupling Reactions

by

Masato Ohsumi

Student ID Number: 1218008

A dissertation submitted to the
Engineering Course, Department of Engineering,
Graduate School of Engineering,
Kochi University of Technology,
Kochi, Japan

in partial fulfillment of the requirements for the degree of
Doctor of Engineering

Assessment Committee:	
Supervisor:	Nagatoshi Nishiwaki
Co-Supervisor:	Ryuichi Sugimoto
Co-Supervisor:	Akitaka Ito
	Yasunori Matsumoto
	Masataka Ohtani

September 2018

This page is originally blank.

Abstract

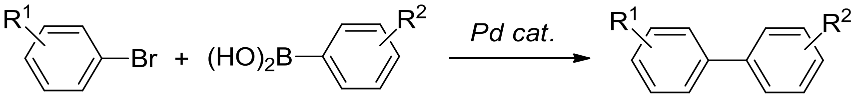
An efficient Pd-catalyzed cross-coupling reaction of phenylboronic acids and benzyl carbonates was developed, producing diarylmethanes. Benzyl acetates could also be used as coupling partners instead of benzyl carbonates, affording diarylmethanes in comparable yields. This reaction can be conducted under 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.

Two reaction conditions were developed to accomplish the substrate switchable Suzuki-Miyaura coupling of benzyl derivatives and arylboronic acid derivatives. Under *Conditions for Esters*, benzyl esters such as carbonates and acetates reacted with arylboronic acids to afford the corresponding diarylmethanes. However, the benzyl halides did not react under the same conditions. On the other hand, benzyl halides such as bromides and chlorides furnished diarylmethanes under *Conditions for Halides*, under which benzyl ester substrates did not react. This switching system was tested using the intermolecular/intramolecular competitive reactions, during which the desired products could be synthesized by selecting the appropriate reaction conditions.

Contents

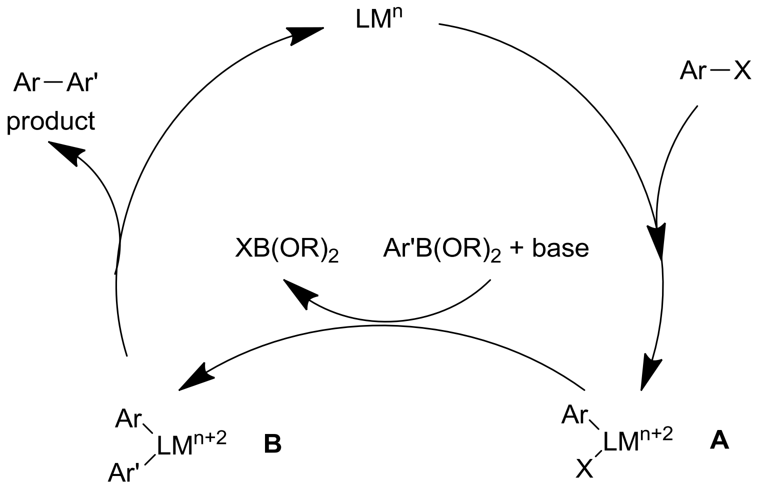
General Introduction

The cross-coupling reaction is very useful as a reaction to form carbon-carbon bonds in many fields such as organic chemistry, pharmaceutical synthesis, materials science. The first report of cross-coupling reaction dates back about 50 years ago. As the world's first cross-coupling reaction, Tsuji succeeded in introducing various nucleophiles in the presence of a palladium catalyst using an allyl compound as a substrate in 1965, and thereafter has been improved by Trost. This reaction is called Tsuji-Trost reaction and has been established.[1] Thereafter, Kumada-Tamao-Corriu coupling using a Grignard reagent,[2] Negishi cross coupling using an organic zinc reagent,[3] Migita-Kosugi-Stille coupling using an organotin reagent,[4] Suzuki-Miyaura coupling using an organic boron compound,[5] Hiyama Cross coupling using organosilicon compounds,[6] have been reported. Of these, Suzuki-Miyaura cross coupling reaction is particularly useful from the viewpoint of functional group acceptability, stability of reagents, and is widely used also in modern organic synthesis field (eq. 1).



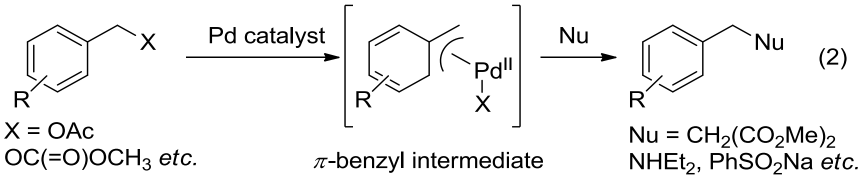
(1)

The Suzuki-Miyaura coupling reaction mechanism is shown in Scheme 1. The reaction is initiated by the oxidative addition of transition metal to the halide to obtain the aryl metal compound (intermediate A). The subsequent transmetallation with the organoboron compound forms intermediate B. Finally, the reductive elimination from the intermediate B furnishes cross-coupling product (Ar-Ar ') and a metal catalyst (LMn).



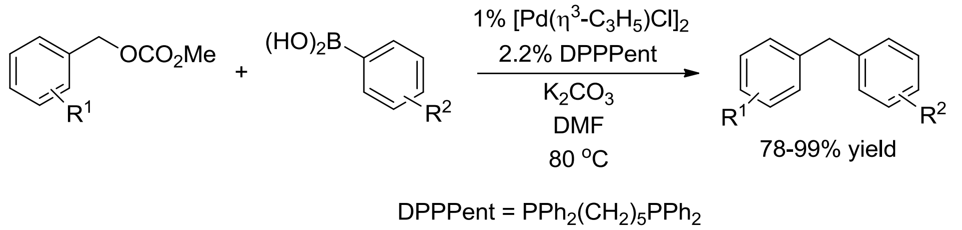
Scheme 1. Suzuki-Miyaura Coupling Reaction Mechanism

Regarding benzylic substrates, palladium-catalyzed nucleophilic substitution of benzyl carbonates or acetates was reported, in which bisphosphine ligands were used. In this reaction, active methylene compounds, amines, sulfones, and phenols can be used as a nucleophile (eq. 2) .[7]

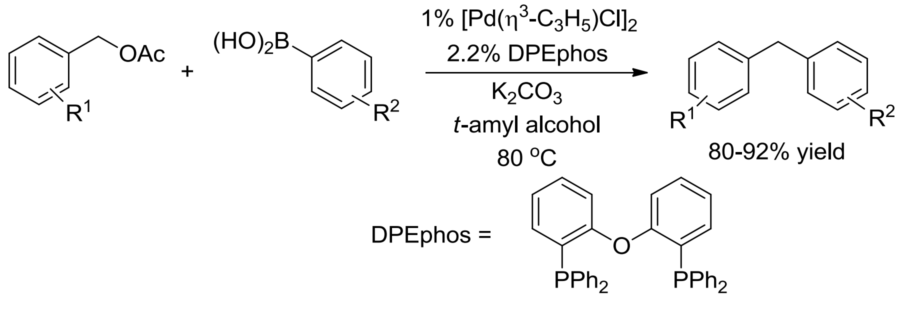


(2)

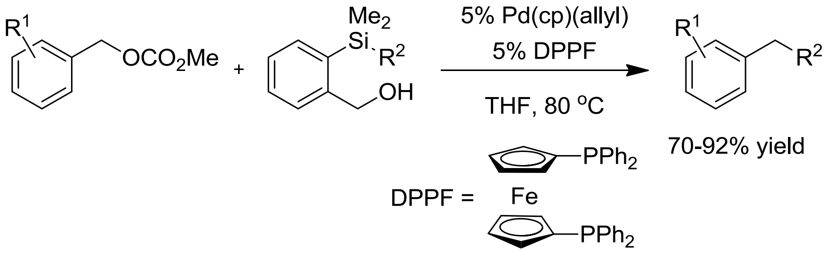
Recently, Suzuki-Miyaura cross-coupling reaction using benzyl carbonate and benzyl acetate as coupling partners was also demonstrated (eq. 3 and 4).[8] It is possible to use organosilicon (eq. 5)[9] and benzyl phosphate (eq. 6)[10] as a coupling partner instead of organoboron compound and benzyl carbonates.



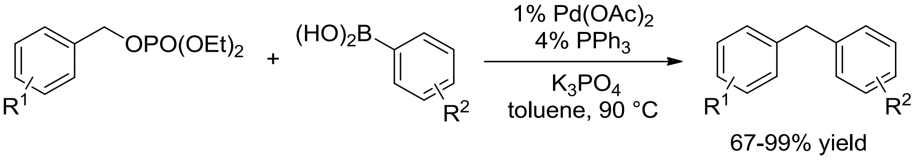
(3)



(4)



(5)



(6)

The benzyl esters can be easily prepared in high yields upon treatment of the corresponding benzyl alcohols with methyl chlorocarbonate or acetic anhydride under the basic conditions. Benzyl esters have been exhibited as excellent coupling partners with organoboron compounds, however, several restrictions should be addressed for the practical use.[11] For example, (1) cross-coupling of benzyl ester and organoboron requires reaction conditions under inert atmosphere. (2) The difference in reactivity between benzyl ester and benzyl halide has not been studied enough.

This paper discusses the expansion and development of cross-coupling between benzyl esters and organoboron compounds under air atmosphere. In the Chapter 2, the synthesis of unsymmetrical benzylbiphenyl is achieved by a successive coupling reactions under mild conditions. In the Chapter 3, it was clarified that the difference in reactivity between benzyl ester and benzyl halide toward organoboron compounds, and the substrate switchable coupling reaction was developed by altering reaction conditions.

References

1. a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron. Lett.* **1965**, 4387–4388; b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292–294; c) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523–1529.

2. a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, *94*, 4374–4376; b) Corriu, R. J. P.; Massse, J. P. J. Chem. Soc., *Chem. Commun*. **1972**, 144–144.

3. King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683–684.

4. a) Kosugi, M. Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301–302; b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc*. **1978**, *100*, 3636–3638.

5. Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.

6. Hatanaka, Y.; Hiyama, T. *J. Org. Chem*. **1988**, *53*, 918–920.

7. a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104–12105. b) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545–3547. c) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973–2975. d) Kuwano, R.; Kusano, H. *Chem. Lett.* **2007**, *36*, 528–529. e) Yokogi, M.; Kuwano, R. *Tetrahedron Lett.* **2007**, *48*, 6109–6112. f) Kuwano, R.; Kusano, H. *Org. Lett.* **2008**, *10*, 1979–1982.

8. a) Kuwano, R.; Yokogi, M. *Chem. Commun.* **2005**, 5899–5901. b) Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945–947.

9. Nakao, Y.; Ebata, S.; Chen, J.; Imanaka, H.; Hiyama, T. *Chem. Lett*. **2007**, *36*, 606–607.

10. McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875–4878.

11. Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235–3246.

Chapter 2.

Practically Usable Synthesis of Diarylmethanes by Pd-catalyzed Cross-Coupling of Phenylboronic Acids with Benzyl Esters under Air Atmosphere

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.

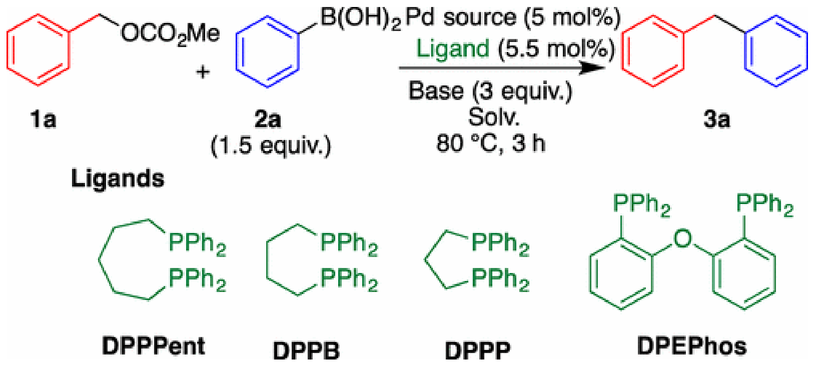
2-1. Introduction

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.

2-2. 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).

Table 1. Optimization of the reaction conditions.

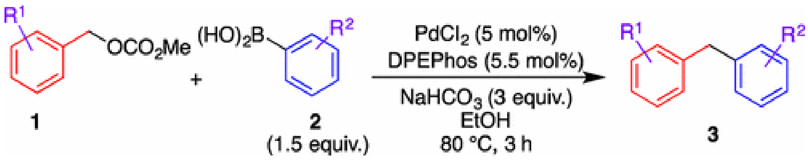


Entry	Pd source	Ligand	Base	Solvent	Yield/%[a]
1	[Pd][b]	DPPPent	K_2CO_3	DMF	27
2	$Pd(OAc)_2$	DPPPent	K_2CO_3	DMF	26
3	$PdCl_2$	DPPPent	K_2CO_3	DMF	32
4	$PdCl_2$		K_2CO_3	DMF	0
5	$PdCl_2$	PPh_3[c]	K_2CO_3	DMF	13
6	$PdCl_2$	DPPB	K_2CO_3	DMF	24
7	$PdCl_2$	DPPP	K_2CO_3	DMF	21
8	$PdCl_2$	DPEPhos	K_2CO_3	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] 11mol%.

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 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.

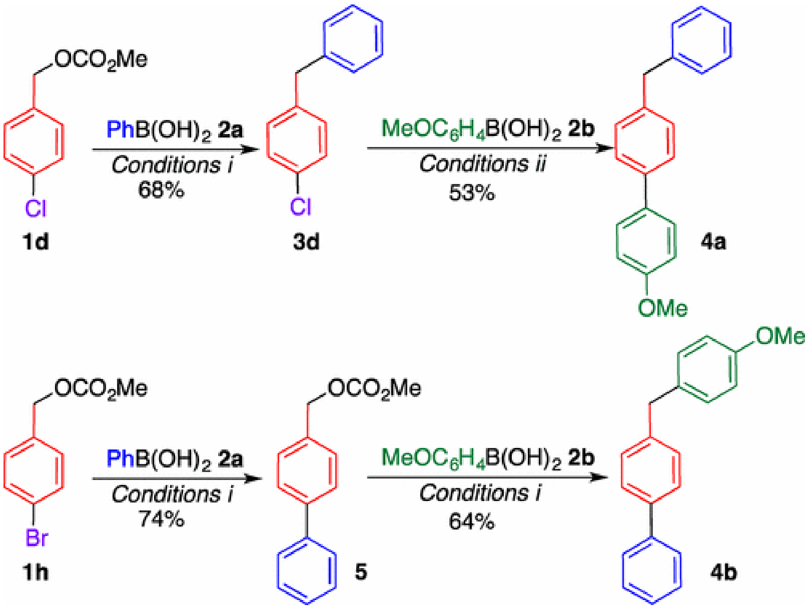
Table 2. Cross-coupling reactions using other carbonates **1** and boronic acids **2**



Entry	Carbonate		Boronic acid		Product	
	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-CF_3	**1e**	H	**2a**	**3e**	55
5	4-NO_2	**1f**	H	**2a**	**3f**	44
6	4-MeO	**1b**	4-MeO	**2b**	**3f**	83
7	4-MeO	**1b**	4-CF_3	**2c**	**3g**	80
8	2-Me	**1f**	H	**2a**	**3h**	41
9	4-MeO	**1b**	2-Me	**2d**	**3i**	72
10	2-Me	**1f**	2-Me	**2d**	**3j**	32

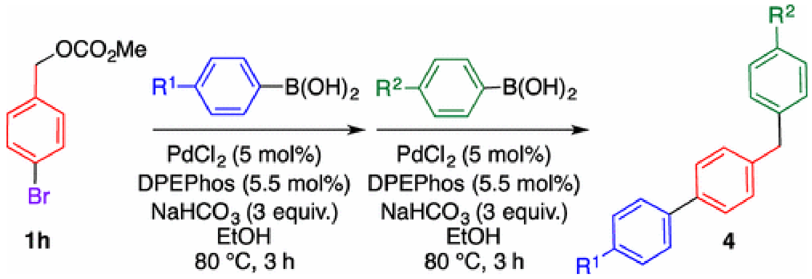
[a] Isolated yield.

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.



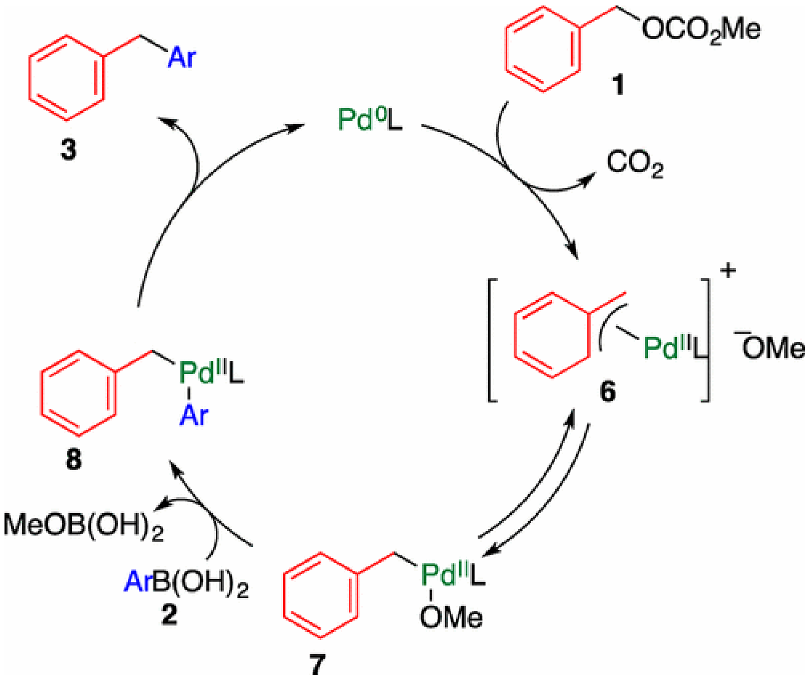
Scheme 1. Selective synthesis of differently substituted (benzyl)biphenyls **4** and **6**. Each reaction was conducted using boronic acid **2** (1.5 equiv.), $PdCl_2$ (5 mol%), DPEPhos (5.5 mol%), $NaHCO_3$ (3equiv.) in ethanol. *Conditions i*; 80 °C, 3 h. *Conditions ii*; 100 °C, 2 d.

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



Entry	R^1	R^2	product	
				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

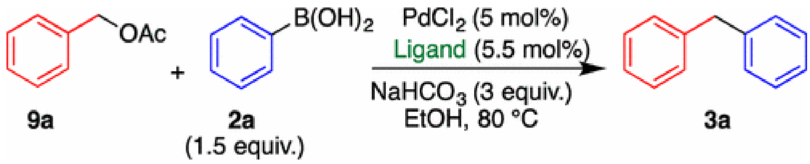
A plausible reaction mechanism is shown in Scheme 2. The reaction is initiated by the oxidative addition of the Pd species to the C–O bond, accompanied by the elimination of CO_2, affording cationic (η^3-benzyl)Pd(II) **6**.[10] After σ-complex **7** is formed under equilibrium with **6**, intermediate **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.



Scheme 2. A plausible mechanism for the coupling reaction using benzyl carbonate

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 (**12a**) and phenylboronic acid (**2a**).

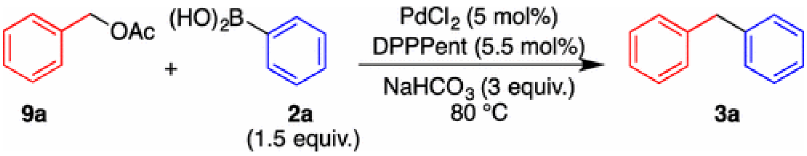


Entry	Ligand	Yield/%[a] After 3 h	Yield/%[a] After 1 d
1	DPEPhos	23	72
2[c]	PPh$_3$[b]	10	21
3	DPPP	22	53
4	DPPB	26	67
5	DPPPent	34	84

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

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).

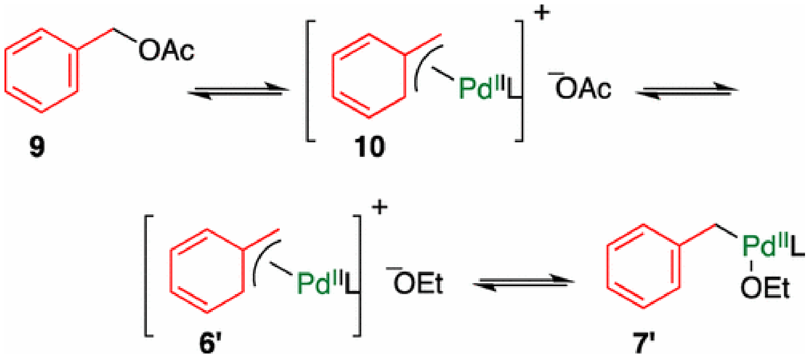
Table 5. Study on the solvent for the cross-coupling reaction of benzyl acetate **(12a)** and phenylboronic acid **(2a)**[a]



Entry	Solv.	Temp/°C	Yield/%[a]	
			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.

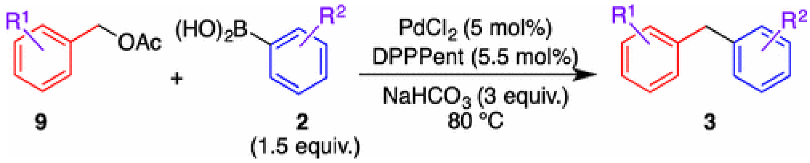
The coupling reaction of benzyl acetate **9** proceeds in a manner similar to that of benzyl carbonate **1**, as shown in Scheme 2. In this mechanism, the formation of intermediate complexes **6** and **7**seems to be crucial. In the case of carbonate **1**, the formation of **6** accompanied by decarboxylation 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).



Scheme 3. A plausible mechanism for forming intermediate **10’** from benzyl acetate **12**

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** 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).

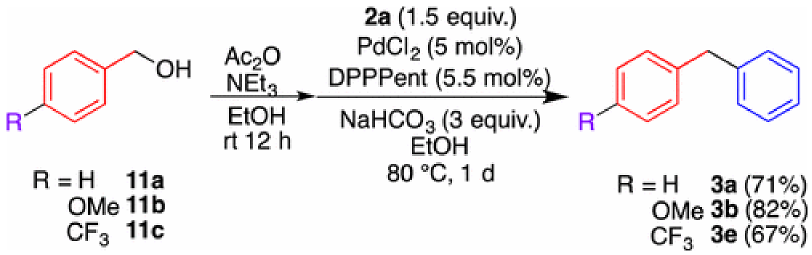
Table 6. Cross-coupling of Other acetates **12** with boronic acids **2**



Entry	Acetate		Boronic acid		Product	
	R^1		R^2			Yield/%[a]
1	4-MeO	**12b**	H	**2a**	**3b**	93
2	4-Cl	**12c**	H	**2a**	**3d**	77
3	4-CF_3	**12d**	H	**2a**	**3e**	56
4	2-Me	**12e**	H	**2a**	**3h**	32
5	4-MeO	**12b**	4-MeO	**2b**	**3f**	87
6	4-MeO	**12b**	4-CF_3	**2c**	**3g**	91
7	4-MeO	**12b**	2-Me	**2d**	**3i**	81

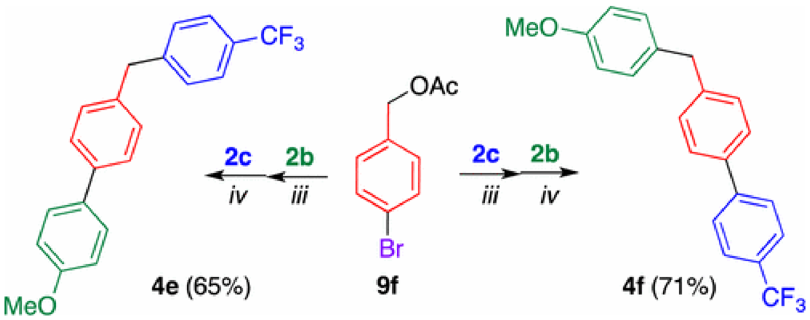
[a] Isolated yield.

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.



Scheme 4. Direct one-pot conversion from benzyl alcohols **13** to diarylmethanes **3**.

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.



Scheme 5. One-pot synthesis of two kinds of (benzyl)biphenyls **7** and **8** by changing the order of reaction with boronic acids **2b** and **2c**. Each reaction was conducted using boronic acid **2** (1.5 equiv.), $PdCl_2$ (5 mol%), DPPPent (5.5 mol%), $NaHCO_3$ (3equiv.) with heating at 80 °C in ethanol. *Conditions iii*; for 3 h. *Conditions iv*; for 1 d.

2-3. Conclusion

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 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.

2-4. Experimental

General information

All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a JEOL 400 spectrometer at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a JEOL 400 spectrometer at 100 MHz. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The melting points were determined on an As-one melting-points apparatus ATM-02, and were uncorrected. High-resolution mass spectra were obtained on an AB SCEIX Triplet TOF 4600 mass spectrometer. Gas chromatography (GC) was performed with Shimadzu GC 8A. Flash column chromatography was performed with Wako-gel C-200 (100–200 mesh, Wako).

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, 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.

2-5. References and notes

1. a) Li, W.; Liu, F.; Wei, L.; Zhao, T. *J. Appl. Polym. Sci.* **2007**, *104*, 3903– 3908; b) Akiike, T.; Kakutani, K. Jpn. Kokai Tokkyo Koho, JP 2006143765, **2006**; c)Nikitenko, S. I.; Koltypin, Y.; Pickup, D. M.; Van-Eck, E. R. H.; Gedanken, A. *Ultrason. Sonochem.* **2003**, *10*,11– 15.

2. a) Xie, B.-B.; Xia, S.-H.; Chang, X.-P.; Cui, G. *Phys. Chem. Chem. Phys.* **2016**, *18*, 403– 413; b) Prosposito, P.; Zhang, H.; Glasbeek, M. *J. Sol-Gel Sci. Technol.* **2011**, *60*, 347– 351.

3. a) Nambo, M.; Kurihara, D.; Yamada, T.; Nishiwaki-Ohkawa, T.; Kadofusa, N.; Kimata, Y.; Kuwata, K.;Umeda, M.; Ueda, M. *Plant Cell Physiol.* **2016**, 57, 2255–2268; b) Chiellini, G.; Nesi, G.; Sestito, S.; Chiarugi, S.; Runfola, M.; Espinoza, S.; Sabatini, M.;Bellusci, L.; Laurino, A.; Cichero, E.; Gainetdinov, R. R.; Fossa, P.; Raimondi, L.; Zucchi, R.; Rapposelli, S. *J. Med. Chem.* **2016**, *59*, 9825– 9836; c)Pham, T. T. M.; Sylvestre, M. *J. Bacteriol.* **2013**, *195*, 3563– 3574; d) Eisenreich,

W.; Ladyzhynsky, N. S.; Li, D.; Schultz, L.; Wang, Z.; Macha, S.; Barta, A.PCT Int. Appl., WO 2010092126, **2010**.

4. a) Taylor, S. F. R.; Sá, J.; Hardacre, C. *ChemCatChem* **2011**, *3*, 119– 121; b) Li, J.-H.; Liu, W.-J.; Yin, D.-L. *Synth. Commun*. **2004**, *34*, 3161– 3165; c) Mukaiyama, T.; Kamiyama, H.; Yamanaka, H. *Chem. Lett.* **2003**, *32*, 814– 815; d) Zhou, D.-Q.; Wang, C.-M.; Yang, J.-H.;Huang, M.-Y.; Jiang, Y.-Y. *Polym. Adv. Technol.* **2002**, *13*, 169–172.

5. a) Bedford, R. B.; Brenner, P. B.; Carter, E.; Carvell, T. W.; Cogswell, P. M.; Gallagher, T.; Harvey, J. N.;Murphy, D. M.; Neeve, E. C.; Nunn, J.; Pye, D. R. *Chem.—Eur. J*. **2014**, *20*, 7935– 7938; b) Sun, Y.-Y.; Yi, J.; Lu, X.; Zhang, Z.-Q.; Xiao, B.;Fu, Y. *Chem. Commun*. **2014**, *50*, 11060– 11062; c)Zhang, Y.-Q. *J. Chem. Res*. **2013**, *37*, 375– 376; d) Norbe, S. M.; Monterio, A. L. *Tetrahedron Lett*. **2004**, *45*, 8225– 8228; e) Doucet, H.; Santelli, M.; Chahen, L. *Synlett* **2003**, 1668– 1672.

6. a) Tobisu, M.; Zhao, J.; Kinuta, H.; Furukawa, T.; Igarashi, T.; Chatani, N. *Adv. Synth. Catal.* **2016**, 358,2417– 2421; b) Tobisu, M.; Yasutome, A.; Kinuta, H.;Nakamura, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5572– 5575.

7. a) Stewart, G. W.; Maligres, P. E.; Baxter, C. A.; Junker, E. M.; Krska, S. W.; Scott, J. P. *Tetrahedron* **2016**, *72*, 3701– 3706; b) Kuwano, R.; Yokogi, M. *Chem. Commun.*

2005, 5899– 5901.

8. Chen, Q.; Fan, X.-H.; Zhang, L.-P.; Yang, L.-M. *RSC Adv.* **2015**, *5*, 15338– 15340.

9. Wang, X.-X.; Luo, M.-J.; Lu, J.-M. *Org. Biomol. Chem.* **2015**, *13*, 11438– 11444.

10. a) Ohtake, Y.; Emura, T.; Nishimoto, M.; Takano, K.; Yamamoto, K.; Tsuchiya, S.; Yeu, S.-Y.; Kito, Y.;Kimura, N.; Takeda, S.; Tsukazaki, M.; Murakata, M.; Sato, T. *J. Org. Chem.* **2016**, 81, 2148– 2153; b) Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945– 947.

11. Wu, G.; Xu, S.; Deng, Y.; Wu, C.; Zhao, X.; Ji, W.; Zhang, Y.; Wang, J. *Tetrahedron* **2016**, *72*, 8022– 8030.

12. Wang, X.-X.; Xu, B.-B.; Song, W.-T.; Sun, K.-X.; Lu, J.-M. *Org. Biomol. Chem.* **2015**, *13*, 4925– 4930.

13. Nambo, M.; Keske, E. C.; Rygus, J. P. G.; Yim, J. C.-H.; Crudden, C. M. *ACS Catal.* **2017**, *7*, 1108– 1112.

14. a) Liu, K.; Rao, W.; Parikh, H.; Li, Q.; Guo, T. L.; Grant, S.; Kellogg, G. E.; Zhang, S. *Eur. J. Med. Chem.***2012**, *47*, 125– 137; b) McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875– 4878.

15. Synthesis of diphenylmethanes under air is also reported by other groups: Endo, K.; Ishioka, T.; Ohkubo, T.;Shibata, T. *J. Org. Chem.* **2012**, *77*, 7223– 7231.

16. Ohsumi, M.; Kuwano, R. *Chem. Lett.* **2008**, *37*, 796– 797.

17. A (benzyl)biphenyl derivative was prepared using the different reactivity between C–Cl and C–F bonds: Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2014**, *53*,13835– 13839.

18. a) Vernekar, S. K. V.; Liu, Z.; Nagy, E.; Miller, L.; Kirby, K. A.; Wilson, D. J.; Kankanala, J.;Sarafianos, S. G.; Parniak, M. A.; Wang, Z. *J. Med. Chem*. **2015**, *58*, 651– 664; b) Li, Y.; Zhao, Y.; Liu, Z.; Wang, R. *J. Chem. Inf. Model.* **2011**, *51*, 1474–1491; c) Rottländer, M.; Knochel, P. *Synlett* **1997**, 1084– 1086.

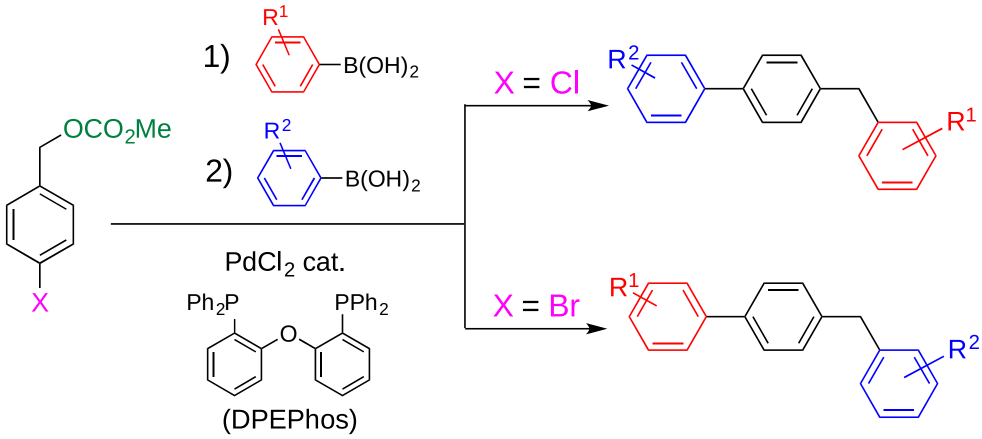
Chapter 3.

Substrate Switchable Suzuki-Miyaura Coupling for Benzyl Ester vs. Benzyl Halide

ABSTRACT: Two reaction conditions were developed to accomplish the substrate switchable Suzuki-Miyaura coupling of benzyl derivatives and arylboronic acid derivatives. Under *Conditions for Esters*, benzyl esters such as carbonates and acetates reacted with arylboronic acids to afford the corresponding diarylmethanes. However, the benzyl halides did not react under the same conditions. On the other hand, benzyl halides such as bromides and chlorides furnished diarylmethanes under *Conditions for Halides*, under which benzyl ester substrates did not react. This switching system was tested using the intermolecular/intramolecular competitive reactions, during which the desired products could be synthesized by selecting the appropriate reaction conditions.

3-1. Introduction

Diarylmethanes are an important class of compounds because they are widely used as a framework for functional materials including polymers,[1] dyes,[2] and biologically active compounds.[3] Various methods have been reported for their synthesis, including the Suzuki-Miyaura coupling reaction, which has become our focus.[4-6] In a typical Suzuki-Miyaura coupling, benzyl esters (carbonates or acetates) are reacted with arylboronic acids in the presence of a Pd catalyst under air atmosphere to efficiently afford the corresponding diarylmethanes.[5] In our protocol, the Pd catalyst is prepared from inexpensive and commercially available $PdCl_2$ and bidentate bis(phosphine) ligands. The ability to use an accessible catalyst improved the practicality of the reaction. Moreover, the reactivity of the benzyl esters was found to be between that of chloro- and bromobenzenes. This property facilitated the selective synthesis of benzyl(biphenyl)s by successive Suzuki-Miyaura coupling reactions (Scheme 1). These results prompted us to investigate a more challenging project; controlling chemoselectivity for benzyl esters and benzyl halides. In this study, we managed to successfully switch the substrate favored for coupling by changing the reaction conditions.

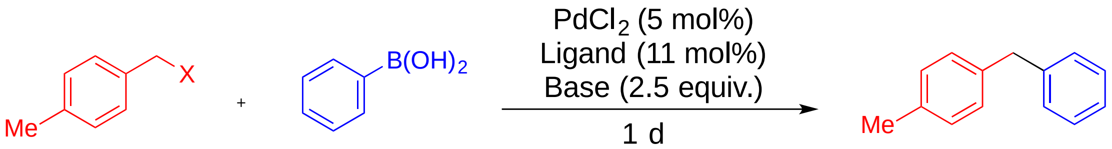


Scheme 1. Chemoselective Synthesis of Benzyl(biphenyl)s.

3-2. Results and Discussion

When benzyl carbonate **1A** was reacted with phenylboronic acid (**5a**) (1.25 equiv.) in the presence of the Pd catalyst derived from $PdCl_2$ (5 mol%) and DPEPhos (5.5 mol%) in ethanol, the coupling reaction proceeded to afford diarylmethane **6Aa**[4f] in a 76% yield after heating at 80 °C for 1 d (Table 1, Entry 1). These conditions are referred to as *Conditions for Esters*, in which lack of any reagent did not undergo the reaction at all. Although benzyl acetate **2A** reacted similarly, its reactivity was lower than that of carbonate **1A** (Entry 2). On the other hand, benzyl halides **3A** and **4A** did not react under the same conditions (Entries 3 and 4). After surveying several reaction condition options, the choice of ligand, base, and solvent was found to be crucial to switching the reactivity. A combination of triphenylphosphine and Na_2CO_3 facilitated the reaction of benzyl chloride **4A** (Entry 5). A complete switch was made to afford **6Aa** efficiently while **1A** did not react (Entries 6–10; successful reactions were performed in a mixed THF/water (v/v = 1/1) solvent at 40 °C, referred to *Conditions for Halides*). Benzyl bromide **3A** showed similar behavior to **4A** to undergo the coupling reaction efficiently only under *Conditions for Halides* (Entry 8). Usually, THF and water is miscible; however, a mixed solvent (*v*/*v* = 1/1) was separated into two layers in this reaction. On the other hand, the yields of **6Aa** were considerably lower in reactions performed using a homogeneous mixed solvent of THF and water (*v*/*v* = 4/1), THF and ethanol (*v*/*v* = 1/1) or THF alone (Entries 11–16). In addition, triethylamine was not an effective base for this reaction (Entry 17). To the contrary, the reaction proceeded more efficiently when a mixed solvent of toluene and water (*v*/*v* = 1/1) was employed (Entries 18 and 19). Based on these results, the presence of water was found to be crucial for this reaction. Although there is a report that aqueous conditions are effective for the reaction using DPEPhos,[7] exact role of water is not clarified yet.

Table 1 Assessment of Switchable Reaction Conditions Depending on the Substrate.



Substrate

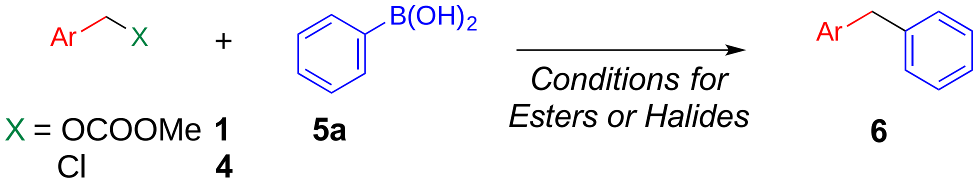
5a
(1.25 equiv.)

6Aa

Entry	Substrate		Ligand	Base	Solv.	Temp.	Conversion	Yield
	X					/°C	of Substrate	/%[a]
1	OCOOMe	**1A**	DPEPhos	$NaHCO_3$	EtOH	80	89	76
2	OAc	**2A**	DPEPhos	$NaHCO_3$	EtOH	80	65	59
3	Br	**3A**	DPEPhos	$NaHCO_3$	EtOH	80	6	0
4	Cl	**4A**	DPEPhos	$NaHCO_3$	EtOH	80	4	0
5	Cl	**4A**	PPh_3	Na_2CO_3	EtOH	80	13	10
6	OCOOMe	**1A**	PPh_3	Na_2CO_3	THF/H_2O[b]	80	100	23
7	Cl	**4A**	PPh_3	Na_2CO_3	THF/H_2O[b]	80	100	92
8	Br	**3A**	PPh_3	Na_2CO_3	THF/H_2O[b]	80	100	89
9	OCOOMe	**1A**	PPh_3	Na_2CO_3	THF/H_2O[b]	40	4	0
10	Cl	**4A**	PPh_3	Na_2CO_3	THF/H_2O[b]	40	85	81
11	OCOOMe	**1A**	PPh_3	Na_2CO_3	THF/H_2O[c]	40	0	0
12	Cl	**4A**	PPh_3	Na_2CO_3	THF/H_2O[c]	40	78	74
13	OCOOMe	**1A**	PPh_3	Na_2CO_3	THF/EtOH[b]	40	8	4
14	Cl	**4A**	PPh_3	Na_2CO_3	THF/EtOH[b]	40	16	12
15	OCOOMe	**1A**	PPh_3	Na_2CO_3	THF	40	0	0
16	Cl	**4A**	PPh_3	Na_2CO_3	THF	40	9	4
17	Cl	**4A**	PPh_3	Et_3N	THF	40	30	14
18	OCOOMe	**1A**	PPh_3	Na_2CO_3	PhMe/H_2O[b]	40	0	0
19	Cl	**4A**	PPh_3	Na_2CO_3	PhMe/H_2O[b]	40	67	62

[a] Determined by ^{1}H NMR. [b] *v*/*v* = 1/1 (heterogeneous). [c] *v*/*v* = 4/1 (homogeneous).

Table 2. Chemoselective Coupling Reactions Using Benzyl Carbonates **1** and Benzyl Chlorides **4**.



*Reactions of Esters **1***[a]

Entry	Benzyl Carbonate		Conversion	Product	
	Ar		of **1**		Yield/%
1	4-MeOC$_6$H$_4$	**1B**	100	**6Ba**[4c]	92
2	4-CF$_3$C$_6$H$_4$	**1C**	70	**6Ca**[4i]	58
3	4-NO$_2$C$_6$H$_4$	**1D**	49	**6Da**[4f]	41
4	2-MeC$_6$H$_4$	**1E**	40	**6Ea**[4i]	34
5	2-pyridyl	**1F**	81	**6Fa**[8]	60
6	2-furyl	**1G**	68	**6Ga**[4c]	51
7	2-thienyl	**1H**	77	**6Ha**[4c]	64

*Reactions of Halides **4***[b]

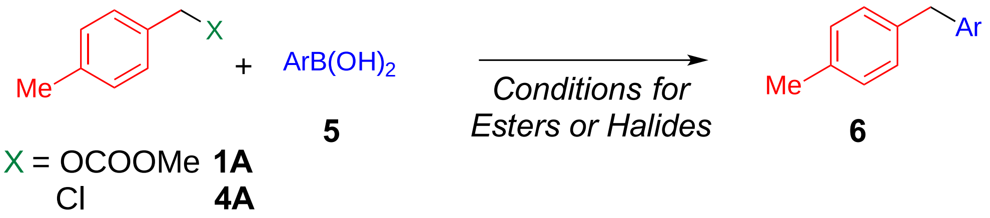
Entry	Benzyl Chloride		Conversion	Product	
	Ar		of **4**		Yield/%
8	4-MeOC$_6$H$_4$	**4B**	90	**6Ba**	87
9	4-CF$_3$C$_6$H$_4$	**4C**	74	**6Ca**	70
10	4-NO$_2$C$_6$H$_4$	**4D**	62	**6Da**	54
11	2-MeC$_6$H$_4$	**4E**	48	**6Ea**	45
12	2-pyridyl	**4F**	73	**6Fa**	67
13	2-furyl	**4G**	64	**6Ga**	52
14	2-thienyl	**4H**	69	**6Ha**	64

Each reaction was conducted using boronic acid (1.25 equiv.), PdCl$_2$ (5 mol%).
[a] *Conditions for Esters*: DPEPhos (5.5 mol%), NaHCO$_3$ (2.5 equiv.) in ethanol, at 80 °C for 1 d. [b] *Conditions for Halides*: Ph$_3$P (11 mol%), Na$_2$CO$_3$ (2.5 equiv.) in THF/H$_2$O (*v*/*v* = 1/1), at 40 °C for 1 d.

Other benzyl derivatives **1**–**4** were coupled under the conditions optimized for 4-methylbenzyl carbonate **1A** (*Conditions for Esters*) or 4-methylbenzyl chloride **4A** (*Conditions for Halides*), and each reaction proceeded in high conversion yield (Table 2). Under *Conditions for Esters*, benzyl carbonates **1** and benzyl acetates **2** exhibited similar reactivity to afford the corresponding diarylmethanes **6** in comparable yields; however, benzyl halides **3** and **4** did not react except for highly reactive methoxy derivatives **3B** and **4B**. To the contrary, only benzyl halides **3** and **4** coupled under *Conditions for Halides*, and no reaction was observed when benzyl esters **1** and **2** were employed. In cases of the less reactive, electron-deficient benzyl chlorides **4C**–**F**, yields of diarylmethanes **6Ca**–**Fa** were higher than those obtained in the reactions using **1C**–**F** under *Conditions for Esters*.

When other boronic acids, **5b**–**d**, were reacted under *Conditions for Esters*, carbonate **1A** and acetate **2A** afforded diarylmethanes **6Ab**–**Ad** while halides **3A** and **4A** did not afford **6**. The coupling reactions were not influenced by the electronic properties of the substituents on the boronic acids **5**. On the other hand, **1A** and **2A** were unreactive under *Conditions for Halides*. Instead, bromide **3A** and chloride **4A** furnished **6Ab**–**Ad** in higher yields. The substrates (benzyl esters or benzyl halides) were successfully switched by changing reaction conditions. Furthermore, the switching mode was not influenced by substituents on the benzene ring of either coupling partner.

Table 3. Switchable Coupling Reaction Using Other Boronic Acid.



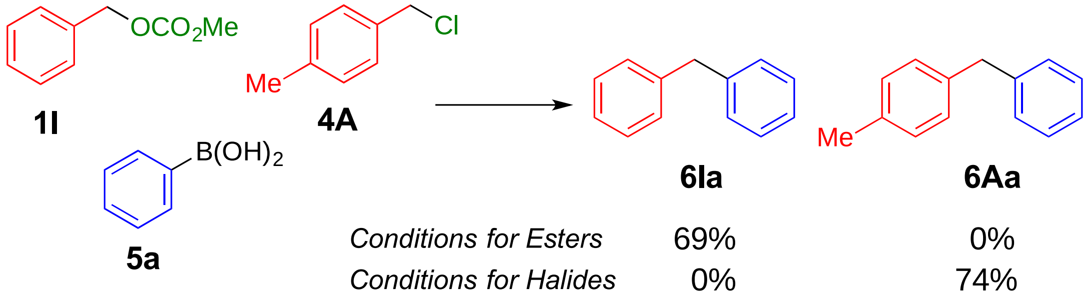
*Reactions of Ester **1A***[a]

Entry	Boronic Acid		Conversion of **1**/%	Product	Yield/%
1	4-$MeOC_6H_4$	**5b**	87	**6Ab**[6d]	79
2	4-$CF_3C_6H_4$	**5c**	86	**6Ac**[9]	75
3	2-MeC_6H_4	**5d**	85	**6Ad**[10]	70

*Reactions of Halide **4A***[b]

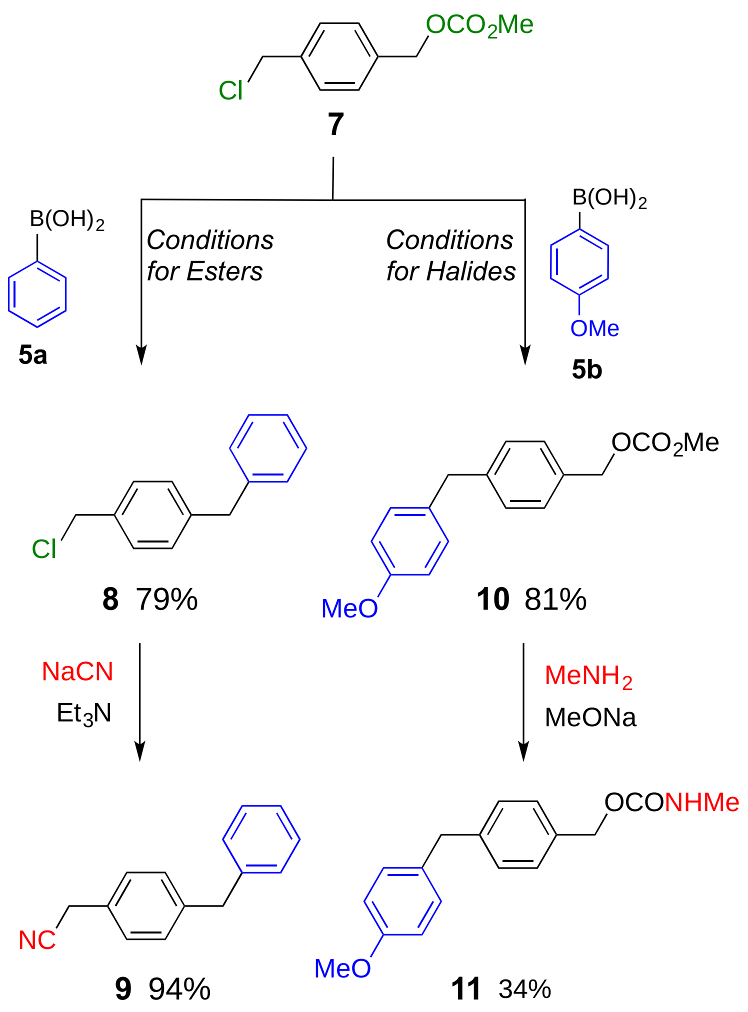
Entry	Benzyl Chloride		Conversion of **4**/%	Product	Yield/%
4	4-$MeOC_6H_4$	**5b**	70	**6Ab**	62
5	4-$CF_3C_6H_4$	**5c**	67	**6Ac**	60
6	2-MeC_6H_4	**5d**	66	**6Ad**	52

Each reaction was conducted using boronic acid (1.25 equiv.), $PdCl_2$ (5 mol%). [a] *Conditions for Esters*: DPEPhos (5.5 mol%), $NaHCO_3$ (2.5 equiv.) in ethanol, at 80 °C for 1 d. [b] *Conditions for Halides*: Ph_3P (11 mol%), Na_2CO_3 (2.5 equiv.) in THF/H_2O (*v*/*v* = 1/1), at 40 °C for 1 d.



Scheme 2. Competitive Reactions Using **1I** and **4A**.

Next, we conducted directly competitive reactions of the two substrates. A mixture of equimolar of benzyl carbonate **1I** and benzyl chloride **4A** was reacted with phenylboronic acid **5a**. When the reaction was conducted under *Conditions for Esters*, only carbonate **1I** was consumed to form **6Ia**;[9] **4A** remained unreacted. To the contrary, only chloride **4A** was consumed under *Conditions for Halides*. Hence, this switching system was useful even when the reaction mixture contains both benzyl esters and halides.



Scheme 3. Intramolecular Chemoselective Coupling Reactions of Differently Substituted Compound **7**.

Compound **7**, which possesses both a benzyl ester and benzyl halide moiety was subjected to each of the two reaction conditions. Compound **8**[11] was selectively obtained under *Conditions for Esters*. On the other hand, compound **10** was the product when the reaction was carried out under *Conditions for Halides*. Product **8** was further converted to benzyl cyanide **9**[12] upon treatment with sodium cyanide, and product **10** was transformed to benzyl carbamate **11** by nucleophilic substitution with methylamine.[13] As a result, two different classes of compound were synthesized from common starting material **7**.

3-3. Conclusion

A chemoselective Suzuki-Miyaura coupling reaction was achieved by switching reaction conditions. Benzyl carbonates **1** and benzyl acetates **2** underwent the coupling reaction with arylboronic acids **5** to afford the corresponding diarylmethanes **6** using a Pd catalyst derived from $PdCl_2$ and DPEPhos in ethanol in the presence of $NaHCO_3$ (*Conditions for Esters*). Benzyl halides **3** and **4** did not react under the same conditions. On the other hand, when benzyl halides **3** and **4** were reacted using a Pd catalyst derived from $PdCl_2$ and Ph_3P in THF/water in the presence of Na_2CO_3 (*Conditions for Halides*), the coupling reaction efficiently proceeded to afford diarylmethanes **6** while benzyl esters **1** and **2** did not react. These switchable conditions facilitated the chemoselectivity even when benzyl esters and benzyl halides coexist in a reaction mixture or molecule. The present system will be a useful tool in elaborate syntheses.

3-4. Experimental

General information

All the reagents and solvents were commercially available and used as received. The ^1H NMR spectra were measured on a JEOL 400 spectrometer at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a JEOL 400 spectrometer at 100 MHz. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The melting points were determined on an As-one melting-points apparatus ATM-02, and were uncorrected. High-resolution mass spectra were obtained on an AB SCEIX Triplet TOF 4600 mass spectrometer. Gas chromatography (GC) was performed with Shimadzu GC 8A. Flash column chromatography was performed with Wako-gel C-200 (100–200 mesh, Wako).

All diarylmethanes **6**, **8** and **9** are commercially available. Hence, the structures of these products were confirmed by comparison of spectral data with those of authentic samples.

General Procedure of the Suzuki−Miyaura Coupling Reaction under *Conditions for Esters*

To a solution of $PdCl_2$ (1.8 mg, 10 μmol), DPEPhos (5.9 mg, 11 μmol), $NaHCO_3$ (42.0 mg, 0.5 mmol), and phenylboronic acid **5a** (30.5 mg, 0.25 mmol) in EtOH (1.0 mL), 4-methylbenzyl carbonate **1A** (36.0 mg, 0.2 mmol) was added, and the resultant mixture was heated in a screw-capped sealed tube at 80 °C for 1 d. After treatment with flash column chromatography using hexane to afford **6Aa** (26.6 mg, 0.146 mmol, yield 73%), which is confirmed to be not so different from the yield (76%) determined by ^1H NMR. When other conditions and substrates were employed, the experiments were conducted in a similar way.

General Procedure of the Suzuki−Miyaura Coupling Reaction under *Conditions for Halides*

To a solution of $PdCl_2$ (1.8 mg, 10 μmol), PPh_3 (5.8 mg, 22 μmol), Na_2CO_3 (53.0 mg, 0.5 mmol), and phenylboronic acid **5a** (30.5 mg, 0.25 mmol) in THF and water (*v*/*v* = 1/1) (1.0 mL), 4-methylbenzyl chloride **4A** (28.1 mg, 0.2 mmol) was added, and the resultant mixture was heated in a screw-capped sealed tube at 40 °C for 1 d. After treatment with flash column chromatography using hexane to afford **6Aa** (28.8 mg, 0.158 mmol, yield 79%), which is confirmed to be not so different from the yield (81%) determined by ^{1}H NMR. When other conditions and substrates were employed, the experiments were conducted in a similar way.

Intermolecular Competitive Reaction

4.4.1. Under Conditions for Esters

To a solution of $PdCl_2$ (1.8 mg, 10 μmol), DPEPhos (5.9 mg, 11 μmol), $NaHCO_3$ (42.0 mg, 0.5 mmol), and phenylboronic acid **5a** (30.5 mg, 0.25 mmol) in EtOH (0.5 mL), a solution of benzyl carbonate **1I** (30.0 mg, 0.2 mmol) and 4-methylbenzyl chloride **4A** (28.1 mg, 0.2 mmol) in EtOH (0.5 mL) was added, and the resultant mixture was heated in a screw-capped sealed tube at 80 °C for 1 d. After treatment with flash column chromatography using hexane to afford **6Ia** (23.2 mg, 0.138 mmol, yield 69%) without any detectable **6Aa**.

4.4.2. Under Conditions for Halides

To a solution of $PdCl_2$ (1.8 mg, 10 μmol), PPh_3 (5.8 mg, 22 μmol), Na_2CO_3 (53.0 mg, 0.5 mmol), and phenylboronic acid **5a** (30.5 mg, 0.25 mmol) in THF and water (*v*/*v* = 1/1) (0.5 mL), a solution of benzyl carbonate **1I** (30.0 mg, 0.2 mmol) and 4-methylbenzyl chloride **4A** (28.1 mg, 0.2 mmol) in THF and water (*v*/*v* = 1/1) (0.5 mL) was added, and the resultant mixture was heated in a screw-capped sealed tube at 40 °C for 1 d. After treatment with flash column chromatography using hexane to afford **6Aa** (26.9 mg, 0.148 mmol, yield 74%) without any detectable **6Ia**.

Chemical Conversion of Diphenylmethanes

*4.5.1. 4-[(4-Methoxyphenyl)methyl]phenylmethyl Methyl Carbonate (**10**).*

White solid; mp 176–177 °C. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 2H), 4.21 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 159.9, 156.0, 137.2, 130.4, 129.2, 127.5, 127.2, 114.0, 113.7, 69.6, 55.3, 54.9, 40.6; IR (neat) 3473, 2958, 1747, 1613, 1515, 1442, 1377, 1247 cm^{-1}; HRMS (ESI–TOF) *m/z* [M+Na]$^+$ Calcd for $C_{17}H_{18}O4Na$ 309.1097; found 309.1099.

*4.5.2.Cyanation of Benzyl Chloride **8**.*

To a solution of benzyl chloride **8** (216 mg, 1.0 mmol) in DMSO (2 mL), were added sodium cyanide (147 mg, 3.0 mmol) and triethylamine (304 mg, 3.0 mmol), and the resultant mixture was heated at 80 °C for 1 d. After filtration using a Celite pad, the filtrate was extracted with ethyl acetate (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 = 20/80) to afford benzyl cyanide **9** (194 mg, 0.94 mmol, yield 94%).

*4.5.3. 4-[(4-Methoxyphenyl)methyl]phenylmethyl Methyl Carbamate (**11**).*

To a solution of carbonate **10** (286 mg, 1.0 mmol) in toluene (2 mL), were added methylamine (31.1 mg, 1.0 mmol) and sodium methoxide (54 mg, 1.0 mmol), and the resultant mixture was heated at 80 °C for 1 d. After filtration using a Celite pad, the filtrate was extracted with ethyl acetate (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 = 50/50) to afford carbamate **11** (96 mg, 0.34 mmol, yield 34%). White solid; mp 94–95 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.1–6.3(br, 1H), 5.04 (s, 2H), 4.19 (s, 2H), 3.72 (s, 3H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 155.9, 137.1, 130.4, 129.2, 127.5, 127.2, 114.3, 113.7, 68.4 ,54.9, 40.8, 21.2; IR (neat) 3319, 2957, 1747, 1657, 1515, 1443, 1273 cm^{-1}; HRMS (ESI–TOF) *m/z* $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_3Na$ 308.1257, found 308.1258.

3-5. References and notes

1. a) Li, W.; Liu, F.; Wei, L.; Zhao, T. *J. Appl. Polym. Sci.* **2007**, *104*, 3903–3908; b) Akiike, T.; Kakutani, K. *Jpn. Kokai Tokkyo Koho* JP 2006143765, **2006**; c) Nikitenko, S. I.; Koltypin, Y.; Pickup, D. M.; Van-Eck, E. R. H.; Gedanken, A. *Ultrason. Sonochem*. **2003**, *10*, 11–15.
2. a) Xie, B.-B.; Xia, S.-H.; Chang, X.-P.; Cui, G. *Phys. Chem. Chem. Phys.* **2016**, *18*, 403–413; b) Prosposito, P.; Zhang, H.; Glasbeek, M. *J. Sol-Gel Sci. Technol*. **2011**, *60*, 347–351.
3. a) Nambo, M.; Kurihara, D.; Yamada, T.; Nishiwaki-Ohkawa, T.; Kadofusa, N.; Kimata, Y.; Kuwata, K.; Umeda, M.; Ueda, M. *Plant Cell Physiol.* **2016**, *57*, 2255–2268; b) Chiellini, G.; Nesi, G.; Sestito, S.; Chiarugi, S.; Runfola, M.;

Espinoza, S.; Sabatini, M.; Bellusci, L.; Laurino, A.; Cichero, E.; Gainetdinov, R. R.; Fossa, P.; Raimondi, L.; Zucchi, R.; Rapposelli, S. *J. Med. Chem*. **2016**, *59*, 9825–9836; c) Pham, T. T. M.; Sylvestre, M.; *J. Bacteriol.* **2013**, *195*, 3563– 3574; d) Eisenreich, W.; Ladyzhynsky, N. S.; Li, D.; Schultz, L.; Wang, Z.; Macha, S.; Barta, A. *PCT Int. Appl.* WO 2010092126, **2010**.

4. **From benzyl halides** a) Bedford, R. B.; Brenner, P. B.; Carter, E.; Carvell, T. W.; Cogswell, P. M.; Gallagher, T.; Harvey, J. N.; Murphy, D. M.; Neeve, E. C.; Nunn, J.; Pye, D. R. *Chem. – Eur. J.* **2014**, *20,* 7935–7938; b) Sun, Y.-Y.; Yi, J.; Lu, X.; Zhang, Z.-Q.; Xiao, B.; Fu, Y. *Chem. Commun.* **2014**, *50*, 11060–11062; c) Zhang, Y.-Q. J. *Chem. Res.* **2013**, *37*, 375–376; d) Henry, N.; Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A. *Eur. J. Org. Chem.* **2008**, 4824–4827; e) Burns, M. J.; Fairlamb, I. J. S.; Kapdi, A. R.; Sehnal, P.; Taylor, R. J. K. *Org. Lett.* **2007**, *9*, 5397–5400; f) Norbe, S. M.; Monterio, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225–8228; g) Doucet, H.; Santelli, M.; Chahen, L. *Synlett* **2003**, 1668–1672. **From benzyl carbonates** h) Ohtake, Y.; Emura, T.; Nishimoto, M.; Takano, K.; Yamamoto, K.; Tsuchiya, S.; Yeu, S.-Y.; Kito, Y.; Kimura, N.; Takeda, S.; Tsukazaki, M.; Murakata, M.; Sato, T. *J. Org. Chem*. **2016**, *81*, 2148–2153; i) Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945–947. **From benzyl acetates** j) Stewart, G. W.; Maligres, P. E.; Baxter, C. A.; Junker, E. M.; Krska, S. W.; Scott, J. P. *Tetrahedron* **2016**,*72*, 3701–3706; k) Kuwano, R.; Yokogi, M. *Chem. Commun*. **2005**, 5899–5901.
5. Ohsumi, M.; Nishiwaki, N. *ACS Omega* **2017**, *2*, 7767–7771.

6. Suzuki-Miyaura coupling using other benzylic systems were also reported; however, selective coupling reaction using different reactivity has not been studied. **From benzyl pivalates** a) Chen, Q.; Fan, X.-H.; Zhang, L. P.; Yang, L.-M. *RSC Adv.* **2015**, *5*, 15338−15340; **From benzyl carbamates** b) Wang, X.-X.; Luo, M.-J.; Lu, J.-M. *Org. Biomol. Chem.* **2015**, *13*, 11438−11444; **From benzyl ethers** c) Tobisu, M.; Zhao, J.; Kinuta, H.; Furukawa, T.; Igarashi, T.; Chatani, N. *Adv. Synth. Catal.* **2016**, *358*, 2417−2421; d) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5572−5575; **From benzyl sulfonates** e) Wu, G.; Xu, S.; Deng, Y.; Wu, C.; Zhao, X.; Ji, W.; Zhang, Y.; Wang, J. *Tetrahedron* **2016**, *72*, 8022−8030; f) Wang, X.-X.; Xu, B.-B.; Song, W.-T.; Sun, K.-X.; Lu, J.-M. *Org. Biomol. Chem.* **2015**, *13*, 4925−4930; **From benzyl sulfones** g) Nambo, M.; Keske, E. C.; Rygus, J. P. G.; Yim, J. C.-H.; Crudden, C. M. *ACS Catal.* **2017**, *7*, 1108−1112; **From benzyl phosphates** h) Liu, K.; Rao, W.; Parikh, H.; Li, Q.; Guo, T. L.; Grant, S.; Kellogg, G. E.; Zhang, S. *Eur. J. Med. Chem.* **2012**, *47*, 125−137; i) McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875−4878; From phenylacetate j) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508.
7. Das, K.; Shibuya, R.; Nakahara, Y.; Germain, N.; Ohshima, T.; Mashima, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 150–154.
8. Reddy, B. R. P.; Chowdhury, S.; Auffrant, A.; Gosmini, C. *Adv. Synth. Catal.* **2018**, *360*, 3026−3029.

9. Procter, R. J.; Dunsford, J. J.; Rushworth, P. J.; Hulcoop, D. G.; Layfield, R. A.; Ingleson, M. J. *Chem. – Eur. J.* **2017**, *23*, 15889–15893.

10. Forster, F.; Metsänen, T. T.; Irran, E.; Hrobárik, P.; Oestreich, M. *J. Am. Chem. Soc.* **2017**, *139*, 16334–16342.

11. Schäfer, G.; Bode, J. W. *Angew. Chem. Int. Ed.* **2011**, *50*, 10913–10916.

12. Sabnis, Y.; Rosenthal, P. J.; Desai, P.; Avery, M. A. *J. Biomol. Struct. Dyn.* **2002**, *19*, 765–774.

13. Tundo, P.; McElroy, C. R.; Aricò, F. *Synlett* **2010**, *10*, 1567–1571.

Acknowledgement

This study has been carried out under the direction of Professor Nagatoshi Nishiwaki at the Kochi University of Technology and I would like to deeply appreciate for a lot of comments, instructions and the approval.

Also I am grateful to everyone in the Nishiwaki laboratory of Kochi University of Technology for measuring many samples.

I appreciate follow up of work by all staff of Kochi National College of Technology. Finally, I would lile to express my thanks to my parents, Akihiko Ohsumi and Reiko Ohsumi, my wife, Miki Ohsumi, my son, Keita Ohsumi.

Kochi University of Technology
September 2018

Masato Ohsumi

List of Publications

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

Masato Ohsumi and Nagatoshi Nishiwaki

ACS Omega, **2017**. 3, 7767–7771.

Substrate Switchable Suzuki-Miyaura Coupling for Benzyl Ester vs. Benzyl Halide

Masato Ohsumi and Nagatoshi Nishiwaki

Tetrahedron Under Submission.

Supplementary List of Publications

Development of Thermal Insulation Material Using Coconut Fiber to Reuse Agricultural Industrial Waste
Ryushi Kimura, Masato Ohsumi and Lusi Susanti
ICEE2017 Paper ID53.

Catalytic Asymmetric Hydrogenation of 2,3,5-Trisubstituted Pyrroles Masato Ohsumi, Hiroki Kusano, and Ryoichi Kuwano
J. Am. Chem. Soc., **2008**,130, 808–809.

Palladium-catalyzed Cross-coupling of Benzylic Carbonates with Organostannanes Masato Ohsumi and Ryoichi Kuwano
Chem. Lett., **2008**, 27, 769–797.

Photocyclization Reaction of a Diarylmaleimide Derivative in Polar Solvents
Masato Ohsumi, Tuyoshi Fukaminato, and Masahiro Irie
Chem. Commun., **2008**, 3281–3283.

Chemical Control of the Photochromic Reactivity of Diarylethene Derivatives
Masato Ohsumi, Tuyoshi Fukaminato, and Masahiro Irie
Chem. Commun., **2005**, 3921–3923.