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Catalytic Carbon–Nitrogen Bond-Forming Cross-Coupling Using *N*-Trimethylsilylamines

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Received: May 25, 2015; Accepted: July 3, 2015; Web Released: July 22, 2015

Carbon–nitrogen bond-forming cross-coupling reaction of haloarenes with *N*-trimethylsilyl (TMS)-substituted secondary and primary arylamines proceeded with the aid of a palladium catalyst and a fluoride activator. Various TMS-N(aryl)$_2$, TMS-NH(aryl), and TMS-N(alkyl)$_2$ reacted to give the corresponding coupled products in high yields. Multi-TMS-amine nucleophiles such as *N*,*N*-(TMS)$_2$-aniline and *N*,*N*′-Ph$_2$-*N*,*N*′-(TMS)$_2$-*p*-phenylenediamine also participated in this C–N coupling to give multiply C–N coupled products in high yields. The novel C–N cross-coupling reaction was successfully applied to C–N bond-forming polymerization. Relative rates of the cross-coupling of *p*-bromotoluene with *N*-TMS-substituted primary and secondary amines showed that *N*-TMS-diphenylamine reacted faster than *N*-TMS-*N*-methylaniline or *N*-TMS-aniline, and *N*-TMS-morpholine was the least reactive, indicating that the low basicity of the nitrogen nucleophile is the key for the smooth coupling.

Introduction

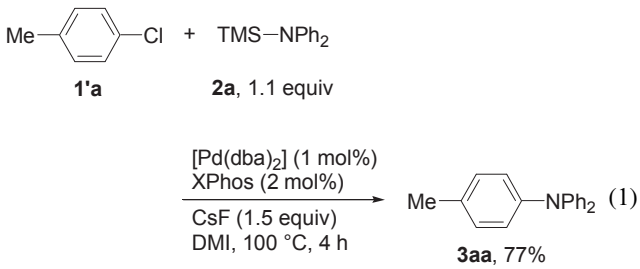
Silicon-based cross-coupling is considered to be a promising carbon–carbon bond-forming strategy toward environmentally-benign organic synthesis.[1] This reaction proceeds under mild conditions, since reactive nucleophilic species are smoothly formed by the interaction of organosilicon reagents with a proper base. Organosilicon reagents are applicable to the carbon–heteroatom coupling strategy in a manner similar to organostannanes.[2] For example, Hartwig attained the cross-coupling of bromoarenes with arylthiosilanes in the presence of Pd(II)/CyPF-*t*-Bu catalyst and cesium fluoride to give unsymmetrical diaryl sulfides.[3] Barluenga reported that *N*-TMS-aldimines cross-couple with haloarenes in the presence of Pd/BINAP catalyst and NaO*t*-Bu to give *N*-arylaldimines.[4] This sort of C–N coupling has been applied by Lautens to the combination of the Catellani reaction using *N*-TMS-imines. Palladium-catalyzed reaction of aryl iodides with *N*-TMS-*ortho*-chlorophenylaldimines gave dibenzopyridine derivatives via C–C and C–N bond formation.[5] Smith and Holmes employed the reaction of *N*-TMS secondary amines with bromoarenes to prepare tertiary amines in the presence of a palladium catalyst and cesium carbonate in supercritical carbon dioxide (scCO_2).[6] Although work disclosed by Smith and Holmes is seminal, the use of scCO_2 limits its scope; scCO_2 reacts with monosilyl primary amines and needs special pressure bottles. Thus, the silicon-based carbon–heteroatom bond formation is obviously of great synthetic significance and expected to be an alternative or complement to the Buchwald–Hartwig reaction[7] and Ullmann coupling reaction.[8] However, the reactivity of the reagents containing a silicon–heteroatom bond remains to be studied. As is the standard C–C cross-coupling, carbon–nitrogen bond-forming polymerization is also an important synthetic issue. For example, Kanbara demonstrated that cross-coupling polymerization of *m*-dibromobenzene with piperazine in the presence of PdCl$_2$[P(*o*-tolyl)$_3$]$_2$ and NaO*t*-Bu gave poly(aryleneimine).[9] In a manner similar to amines, primary and secondary phosphines are also employed for the polymerization with arylene dihalide.[10] Hartwig applied his triarylamine synthesis to the formation of dendrimers, oligo(*m*-aniline)s, and polymers.[11] In this scene, to enhance the efficiency of carbon–heteroatom cross-coupling polymerization, silylamines are apparently attractive due to high solubility and reactivity derived from silyl functionality in a manner similar to organostannanes.[12] With these points of view, we have recently disclosed that the cross-coupling reaction of haloarenes smoothly proceeded with a variety of *N*-TMS-substituted primary and secondary amines under mild conditions in DMI.[13] This reaction involved selective cleavage of N–Si bonds by a fluoride ion with N–H bonds remaining intact. In this article, we report the details of the reaction of haloarenes with *N*-TMS-amines.

Results and Discussion

We first examined the reaction of *p*-bromotoluene (**1a**) with *N*-TMS-diphenylamine (**2a**) and found that the coupling product **3aa** was obtained in a moderate yield in the presence of [Pd(dba)$_2$], XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl),[14] and 5 equiv of TBAT (tetrabutylammonium difluorotriphenylsilicate) as a base in DMI (1,3-dimethyl-2-imidazolidinone) at 100 °C for 24 h (Table 1, Run 1). In contrast, KF, CsF, and CsF in combination with TBAB (tetrabutylammonium bromide) improved the yield of **3aa** (Runs 3–5). On the other hand, TBAF (tetrabutylammonium fluoride) as a popular fluoride reagent had little effect on the reaction (Run 2). Particularly, when CsF alone was employed in excess, **3aa** was obtained in excellent yield (Run 6). Moreover, CsF allowed a low loading of both CsF and the palladium catalyst without loss of efficiency: the best isolated yield of **3aa** was 97% (Run 7).

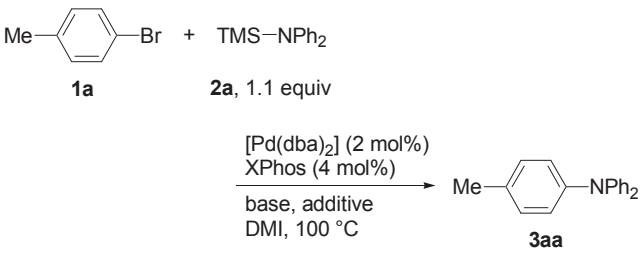
To evaluate the efficiency of XPhos ligand, various phosphine ligands such as PPh_3, PCy_3, and many biaryl phosphines and *N*-heterocyclic carbene ligands were tested in the reaction of *p*-bromoanisole (**1c**) with **2a** for 30 min and the results were summarized in Table 2. These carbene ligands were generated in situ from treatment of corresponding salts with KO*t*Bu for 10 min. Obviously, XPhos only showed effective catalytic activity in this reaction. Of note, the reaction using **1c** was slower than the case of **1a** (Run 3). The reaction for 1 h gave *p*-anisyl diphenylamine **3ca** in 94% isolated yield (Run 4).

Less reactive aryl chloride can be used in this C–N coupling reaction. Cross-coupling of 4-chlorotoluene (**1′a**) with **2a** under the same conditions took place with a longer reaction time than the case of 4-bromotoluene (**1a**), and gave **3aa** in 77% yield (eq 1).



(1)

Table 1. Effect of bases on the reaction of 4-bromotoluene (**1a**) with TMS–NPh$_2$ (**2a**)

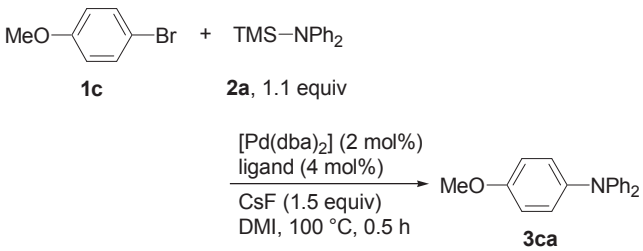


Run	Base, Additive	Time /h	NMR yield of **3aa** /%
1	TBAT (1.1 equiv)	24	55
2[b]	TBAF (1.5 equiv)	14	6
3	KF (5.0 equiv)	8	78
4	KF (3.0 equiv), TBAB (10 mol %)	22	68
5	CsF (3.0 equiv), TBAB (10 mol %)	22	72
6	CsF (5.0 equiv)	2	97
7[c]	CsF (1.5 equiv)	0.5	>99 (97)[d]

a) Unless otherwise noted, a mixture of **1a** (0.50 mmol), **2a** (0.55 mmol), [Pd(dba)$_2$] (10 µmol), XPhos (20 µmol), base, and additive in DMI (0.50 mL) was heated at 100 °C. b) THF was used instead of DMI. c) [Pd(dba)$_2$] (5.0 µmol) and XPhos (10 µmol) were used. d) Isolated yield.

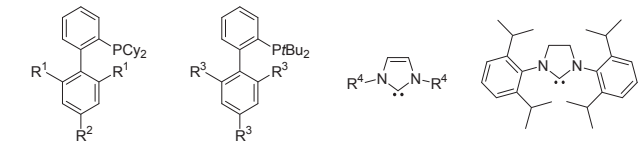
The optimized conditions were applied to the reaction of various bromoarenes **1** with **2a** and the results are summarized in Table 3. Bromobenzene (**1b**) underwent the reaction without any problem (Run 1). Electron-donating and -withdrawing substituents such as OMe, NMe_2, NPh_2, CF_3, and NO_2 at a *para* position did not hamper the reaction to give coupling products in excellent yields (Runs 2–6). Of note, electron-withdrawing groups on the aryl group in **1** accelerated the reaction rate. Base-sensitive carbonyl groups (**1h** and **1i**)[15] did not interfere with the

Table 2. Effect of ligands on the reaction of 4-bromoanisole (**1c**) with TMS–NPh$_2$ (**2a**)



Run	Ligand	NMR yield of **3ca**/%
1	PPh_3	0
2	PCy_3	0
3	XPhos	86
4[b]	XPhos	94[c]
5	SPhos	14
6	RuPhos	11
7	CyJohnPhos	6
8	*t*BuXPhos	15
9	JohnPhos	2
10	IMes·HCl, KO*t*Bu (4 mol %)	9
11	IPr·HCl, KO*t*Bu (4 mol %)	0
12	IAd·HBF$_4$, KO*t*Bu (4 mol %)	6
13	SIPr·HCl, KO*t*Bu (4 mol %)	0

a) Unless otherwise noted, a mixture of **1c** (0.2 mmol), **2a** (0.22 mmol), [Pd(dba)$_2$] (4 µmol), ligand (8 µmol), and CsF (0.3 mmol) in DMI (0.20 mL) was heated at 100 °C for 0.5 h. b) 1 h. c) Isolated yield. PCy_3: tricyclohexylphosphine.



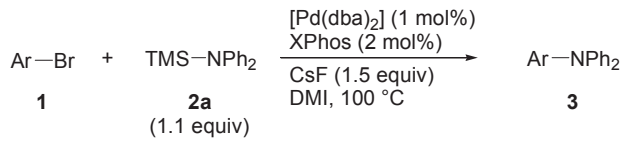
XPhos: $R^1 = R^2 = i$Pr
SPhos: R^1 = OMe, R^2 = H
RuPhos: $R^1 = O i$Pr, R^2 = H
CyJohnPhos: $R^1 = R^2$ = H

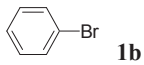
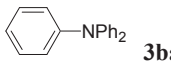
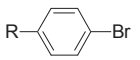
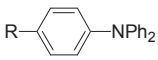
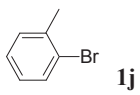
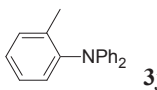
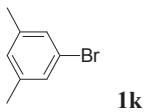
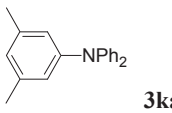
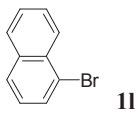
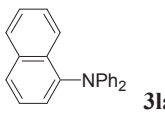
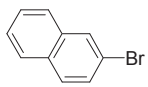
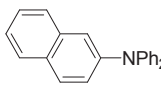
*t*BuXPhos: $R^3 = i$Pr
JohnPhos: R^3 = H

IMes: R^4 = mesityl
IPr: R^4 = 2,6-*i*Pr$_2$-C$_6$H$_3$
IAd: R^4 = 1-adamantyl

SIPr

Table 3. Cross-coupling reaction of bromoarenes **1** with *N*-TMS-diphenylamine **2a**



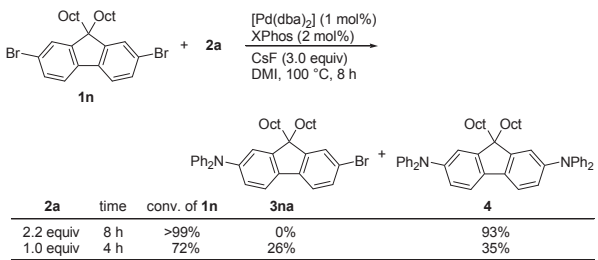
Run	1	Time /h	3	Yield /%[b)]
1	 **1b**	1	 **3ba**	97
				
2	**1c**, R = MeO	1	**3ca**	94
3	**1d**, R = NMe_2	1	**3da**	89
4	**1e**, R = NPh_2	3	**3ea**	99
5	**1f**, R = CF_3	0.5	**3fa**	98
6	**1g**, R = NO_2	0.5	**3ga**	97
7	**1h**, R = CO_2Me	0.5	**3ha**	99
8	**1i**, R = PhCO	0.5	**3ia**	99
9	 **1j**	12	 **3ja**	99
10	 **1k**	1	 **3ka**	98
11	 **1l**	3	 **3la**	94
12	 **1m**	1	 **3ma**	99

a) Unless otherwise noted, a mixture of **1** (0.50 mmol), **2a** (0.55 mmol), [Pd(dba)$_2$] (5.0 µmol), XPhos (10 µmol), CsF (0.75 mmol), and DMI (0.50 mL) was heated at 100 °C. b) Isolated yield.

reaction (Runs 7 and 8). Sterically hindered bromide, 2-bromotoluene (**1j**) successfully reacted to form coupling product **3ja** in 99% yield, albeit in longer reaction time (Run 9). 1-Bromo-3,5-dimethylbenzene (**1k**) and 1- and 2-bromonaphthalenes (**1l** and **1m**) gave **3ka**, **3la**, and **3ma** in excellent yields (Runs 10–12).

Scope of silylamines was next examined, and the results are summarized in Table 4. *N*-TMS-Methylphenylamine (**2b**) smoothly cross-coupled with **1a** to form coupled product **3ab** in 75% yield (Run 1). One of the major side reactions in Buchwald–Hartwig coupling is the formation of imine, by the β-hydride elimination from the amidopalladium(II) intermediate. In this case, imine and its hydrolyzed form, aniline, were not detected. The only side product observed was *N*-methylaniline. *N*-TMS-aniline (**2c**) gave selectively mono arylated product **3ac** in 96% yield without double arylation (Run 2). *N*-TMS-morpholine (**2d**) was successfully converted to arylated amine **3ad** (Run 3). *N*-TMS-diarylamines **2e** (R^2 = Ph, R^3 = *m*-tolyl) and **2f** (R^2 = Ph, R^3 = 1-naphthyl) smoothly gave triarylamines **3ae** and **3af** (Runs 4 and 5). *N*-TMS-azole derivatives were also applicable to this reaction using 4-bromobenzotrifluoride (**1f**). For example, the coupling of *N*-TMS-indole (**2g**) gave *N*-arylated indole **3fg** in 76% yield (Run 6). As *N*-arylcarbazoles have received much attention as electronic materials,[16] the present C–N coupling reaction using *N*-TMS-carbazole (**2h**) was examined in the presence of double amounts of the palladium catalyst and KF and produced *N*-(4-trifluoromethylphenyl)carbazole (**3fh**) in excellent yield (Run 7). When 1 mol % of the palladium catalyst or CsF was used, the yield of **3fh** was decreased. Thus, this example clearly shows that the present C–N coupling reaction should be a facile entry for preparation of *N*-arylcarbazoles.[8,17]

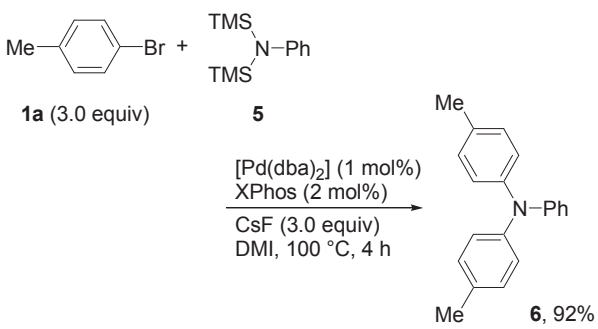
Double C–N bond-forming reaction readily took place as was seen with 2,7-dibromo-9,9-dioctylfluorene (**1n**). The reaction of **1n** with 2.2 equiv of **2a** smoothly underwent sequential double amination to give bis(diphenylamino) derivative **4** in 93% yield without formation of a mono-amination product **3na** (eq 2). When 1 equiv of **2a** was used, a mixture of **3na** and **4** resulted in 26% and 35% yield, respectively, with 28% recovery of **1n**. These results suggest that mono-amination product **3na** has a higher reactivity than **1n** toward the Pd(0) complex.



2a	time	conv. of **1n**	**3na**	**4**
2.2 equiv	8 h	>99%	0%	93%
1.0 equiv	4 h	72%	26%	35%

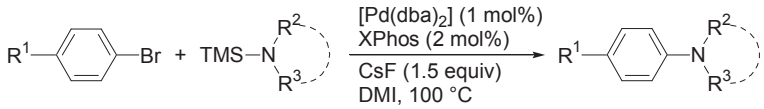
(2)

Multiple *N*-arylation is also possible. *N*,*N*-Bis(TMS)-aniline (**5**) smoothly reacted with excess 4-bromotoluene (**1a**) in freshly distilled DMI using rigorously dried CsF to give triarylamine **6** in 92% yield (eq 3). In this reaction, when slightly wet DMI and CsF or commercially available "dry" DMI and CsF were directly used without drying, yield of **6** was significantly inferior because of the extremely moisture-sensitive nature of **5**. *N*,*N*′-Diphenyl-*N*,*N*′-bis(TMS)-*p*-phenylenediamine (**7**) cross-coupled with excess bromobenzene (**1b**) to give *N*,*N*,*N*′,*N*′-tetraphenyl-*p*-phenylenediamine (**3ea**) in 98% yield (eq 4). Tris(TMS)amine (**8**) was applied to the synthesis of triarylamines, i.e. the reaction of 4.5 equiv of **1a** with **8** gave triarylated product **9** in 44% yield accompanied by a double arylated product, bis(4-tolyl)amine (**10**) in 7% yield (eq 5). This is the first example of triarylamine synthesis starting with tris(TMS)-amine.

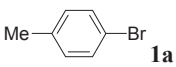
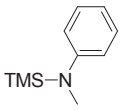
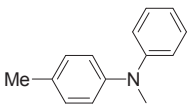
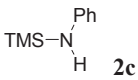
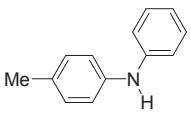
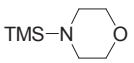
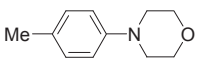
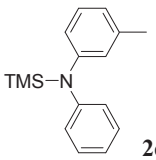
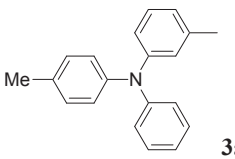
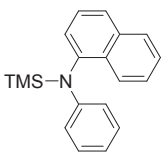
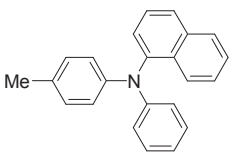
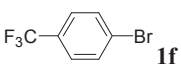
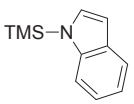
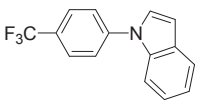
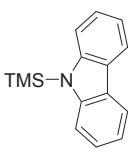
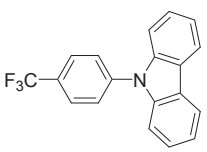


(3)

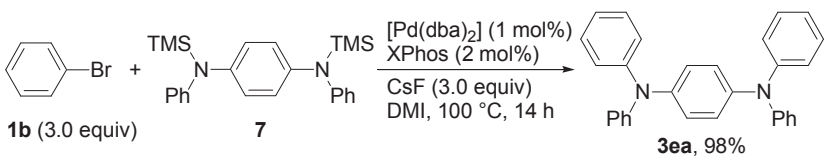
Table 4. Cross-coupling reaction of **1** with various *N*-silylamines **2**



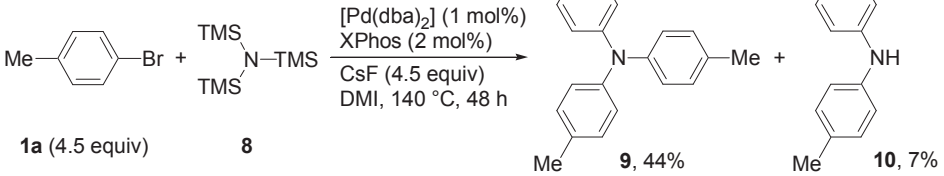
1 **2** (1.1 equiv) **3**

Run	**1**	**2**	Time /h	**3**	Yield /%[b]
1	 **1a**	 **2b**	1	 **3ab**	75
2	**1a**	 **2c**	5.5	 **3ac**	96
3	**1a**	 **2d**	12	 **3ad**	70
4	**1a**	 **2e**	0.5	 **3ae**	90
5	**1a**	 **2f**	0.5	 **3af**	99
6	 **1f**	 **2g**	13	 **3fg**	76
7[c]	**1f**	 **2h**	24	 **3fh**	99

a) Unless otherwise noted, a mixture of **1** (0.50 mmol), **2** (0.55 mmol), [Pd(dba)$_2$] (5.0 µmol), XPhos (10 µmol), CsF (0.75 mmol), and DMI (0.50 mL) was heated at 100 °C. b) Isolated yield. c) [Pd(dba)$_2$] (10 µmol), XPhos (20 µmol), and KF (2.50 mmol) were used.

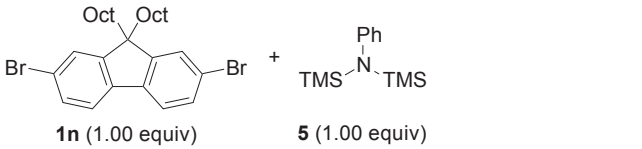


1b (3.0 equiv) **7** **3ea**, 98% (4)

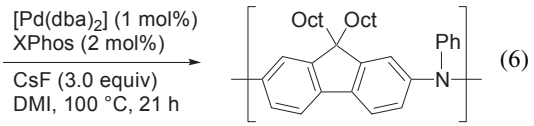


1a (4.5 equiv) **8** **9**, 44% **10**, 7% (5)

The successful examples of double *N*-arylation described above showed that the present reaction had potential for C–N bond-forming polymerization to give polymers consisting of carbon–nitrogen bonds in the main chain, potential organic materials as electron carriers.[18] Thus, we applied the double *N*-arylation to the cross-coupling polymerization in order to synthesize poly(aryleneimine)s. Coupling of **1n** with *N*,*N*-bis(TMS)aniline (**5**) smoothly took place to give copolymer **11** with $M_n = 4400$, $M_w = 9900$, and $M_w/M_n = 2.2$ in 85% yield (eq 6). Using *p*-phenylenediamine-based bis(TMS)amine **7** and **1n**, copolymer **12** with $M_n = 6000$, $M_w = 12000$, and $M_w/M_n = 2.0$ was obtained in 90% yield (eq 7).

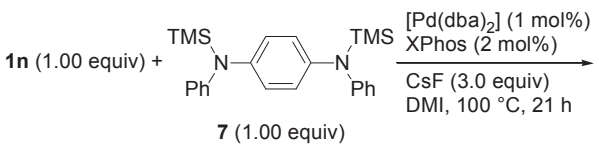


1n (1.00 equiv) **5** (1.00 equiv)

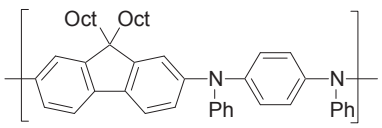


(6)

11
85%, M_n = 4400, M_w = 9900
M_w/M_n = 2.2



7 (1.00 equiv)



(7)

12
90%, M_n = 6000, M_w = 12000
M_w/M_n = 2.0

In order to get insights into the reactivity difference in various *N*-TMS-amines containing one or two phenyl, methyl, and alkyl groups, we carefully monitored the reaction of **1a** with **2a**, **2b**, **2c**, or **2d**, respectively, under the optimized conditions. A graph of the time courses of the formation of **3** is shown in Figure 1. As a result, we observed that the reaction with *N*-TMS-diphenylamine (**2a**) was completed in 10 min and gave **3aa** in more than 90% yield, whereas the reaction with *N*-TMS-morpholine (**2d**) was the slowest (4% yield in 1 h; 25% yield in 3 h). Obviously, the reaction rate order was: TMS-NPh$_2$ (**2a**) > TMS-NMePh (**2b**) ≅ TMS-NHPh (**2c**)[19] > *N*-TMS-morpholine (**2d**), as is the case in Table 3. The result contrasts sharply to the C–N coupling rates of 3-bromothiophene with various free amines.[20]

Next, we treated *N*-TMS-diphenylamine (**2a**) with CsF in the absence of a haloarene and the palladium catalyst at 100 °C for 30 min and observed the formation of diphenylamine (**13a**) in 30% yield (eq 8) after hydrolysis of probable intermediates, five-coordinated fluoroaminosilicate (**i**)[21] and/or cesium amide (**ii**) (R = R′ = Ph) (Figure 2). *N*-TMS-amines **2b** and **2c** were also desilylated but slightly slower than **2a**. In any case, these

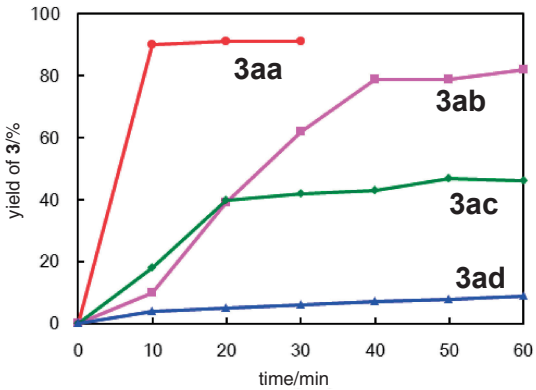
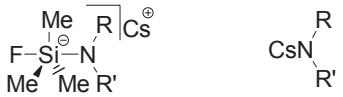


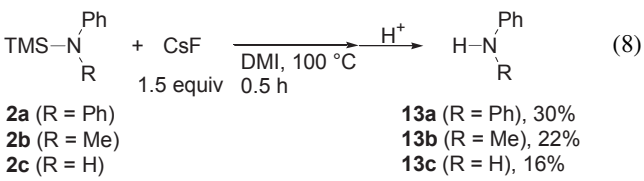
Figure 1. Comparison of rates for the reaction of **1a** with various *N*-TMS-amines. Yields of **3aa** (red), **3ab** (purple), **3ac** (green), and **3ad** (blue) were assayed by NMR.



i **ii**

Figure 2. Possible intermediates of the reaction of **2** with CsF.

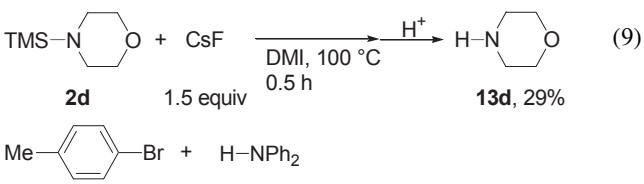
hydrolysis rates of **2a**, **2b**, and **2c** are slower than the reaction of **1a**, suggesting that the C–N coupling rate is clearly independent of the reactivity of **2a**, **2b**, and **2c** toward CsF and **i** and **ii** may be not involved in transmetalation step.[22] On the other hand, *N*-TMS-morpholine (**2d**) was desilylated at a rate similar to **2a** and faster than the reaction of **1a** (eq 9), indicating that, in the case of **2d**, transmetalation proceeds via the formation of **i** or **ii**. Of note, a mixture of **1a** with diphenylamine (**13a**) was heated at 100 °C in the presence of [Pd(dba)$_2$] (1 mol %), XPhos (2 mol %), and CsF (1.5 equiv) in DMI for 30 min to give **3aa** only in 7% yield,[23] suggesting that free arylamines, if present, may also be activated by CsF to form cesium amide (**ii**) as active species for cross-coupling,[24] albeit more slowly than *N*-TMS-arylamines (eq 10).



(8)

2a (R = Ph)
2b (R = Me)
2c (R = H)

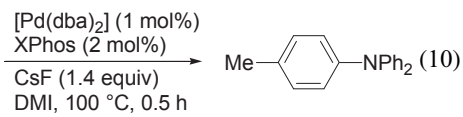
13a (R = Ph), 30%
13b (R = Me), 22%
13c (R = H), 16%



(9)

2d **13d**, 29%

1a **13a** (1.1 equiv)



(10)

3aa, 7%

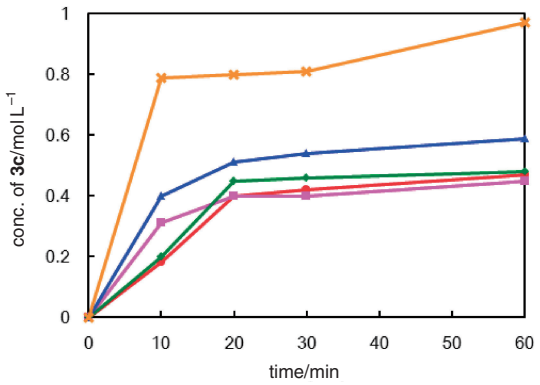


Figure 3. Comparison of rates for the reaction of **1a** with **2c**. Standard conditions (red), 2 mol % of [Pd(dba)$_2$]/2XPhos (purple), 2 equiv of **1a** (green), 2.2 equiv of **2c** (blue), and 3.0 equiv of CsF (yellow).

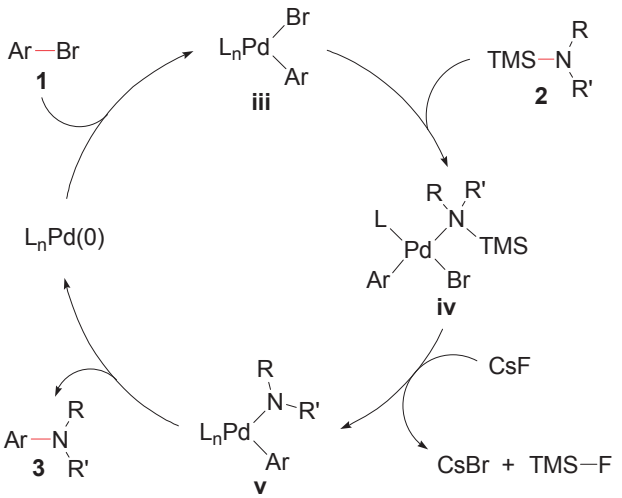
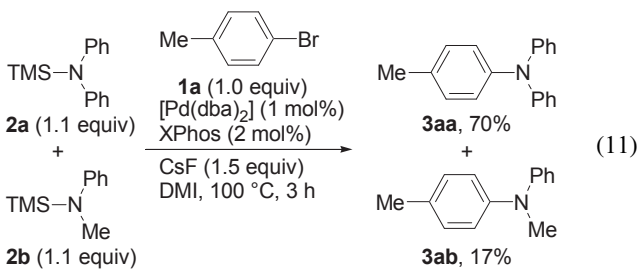


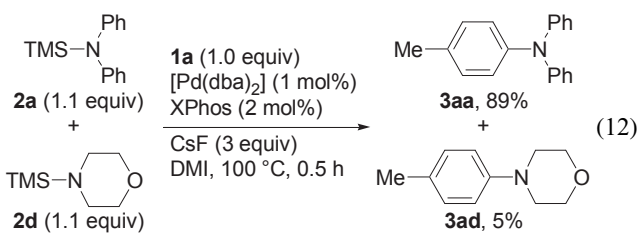
Figure 4. A proposed reaction mechanism.

We also examined the concentration effect of the palladium catalyst, CsF, and **1a**, employing **2c** as a representative substrate. The amount of one of the reagents was doubled as compared with the standard conditions, and the product formation was monitored by NMR, as described in Figure 3. It is noteworthy that use of CsF in a double amount enhanced the reaction rate, whereas other reagents and the palladium catalyst apparently failed to accelerate or decelerate the reaction though a slight acceleration was observed with a double amount of **2c**. It should be noted that the acceleration was not observed with **1a** even in a double amount, indicating that the oxidative addition step is not the rate-limiting step[25,26] and that CsF participates in a step strongly relating to the reaction rate.

According to the above experimental results and the mechanisms discussed in the Buchwald–Hartwig coupling[7,25] and the silicon-based cross-coupling,[24] a catalytic cycle of the silicon-based C–N coupling may be proposed as drawn in Figure 4. Oxidative addition of bromoarene **1** to a palladium(0) complex triggers the reaction to give Ar–Pd–Br complex (**iii**),[27] followed by coordination of silylamine **2** to **iii** to form **iv**. Then, fluoride anion attacks the silicon center of **iv** to give Ar–Pd–NRR′ complex (**v**) with the generation of cesium bromide and fluorotrimethylsilane.[28] Finally, reductive elimination from complex **v** gives rise to release of C–N coupled product **3** and the palladium(0) complex. The high performance of **2** in the cross-coupling may be attributed to the rate of the transmetalation step: the reaction of **iv** with cesium fluoride, which is affected by the basicity of parent amines HNRR′.[29] Thus, the transmetalation step is presumably the rate-limiting. This view is in accord with the rate acceleration by use of double amount of CsF. The fact that electron-withdrawing aryl groups accelerate the C–N coupling can be explained by assuming that these aryl groups enhance the electrophilic nature of silicon center in **iv** toward fluoride anion.

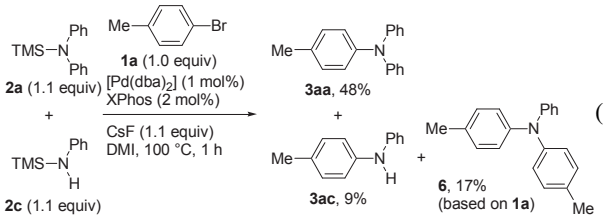
TMS-Amine-Selective Coupling. With these observations in hand, we further examined reactivity difference of *N*-TMS-diarylamines for selective cross-coupling. An equimolar mixture of **2a** and **2b** reacted with **1a** to give **3aa** in 70% yield in preference over **3ab** (17%) (eq 11). When **2d** was used instead of **2b**, triarylamine **3ad** was selectively formed in 89% yield (**3aa**:**3ad** = 18:1), although 3 equiv of CsF was needed for completion of the reaction (eq 12). These results show that the reactivity difference is attributed to the structure of *N*-TMS-amines; the basicity of parent amines. Namely, the reaction order of TMS-NRR′ in the cross-coupling is TMS-N(aryl)$_2$ > TMS-N(alkyl)(aryl) > TMS-N(alkyl)$_2$. It is obvious that the present coupling reaction is the most convenient approach for the synthesis of functionalized triarylamines.



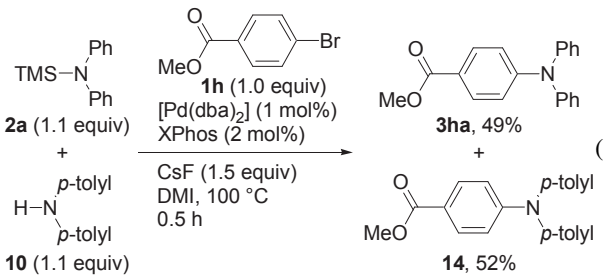


Competition reaction between **2a** and **2c** was next performed to see whether free N–H bonds remain intact. Upon use of CsF (1.1 equiv), **2a**-derived product **3aa** was isolated as a major product in 48% yield along with **3ac** and double arylation product **6** in 9% and 17% (based on the amount of **1a** used) yields, respectively (eq 13). The results definitely suggest that *N*-TMS–NPh$_2$ (**2a**) was selectively activated by CsF in preference to *N*-TMS-aniline **2c**. This reactivity difference contrasts sharply to the coupling reaction of bromoarenes with *N*-phenyl-1,4-phenylenediamine, where free H–NHAr bonds are preferentially activated to give *N*-phenyl-*N*′-aryl-1,4-phenylenediamine.[30] Formation of doubly coupled product **6**

may be attributed to the reaction of **1a** with initially coupled product **3ac** through presumable amide ion exchange of **3ac** with $CsNPh_2$ derived from **2a** and CsF. To compare the performance of $HN(aryl)_2$ and $TMSN(aryl)_2$ for the cross-coupling with a bromoarene, a competition reaction of **2a** and bis(*p*-tolyl)amine (**10**) toward *p*-bromoacetophenone (**1h**) was carried out and gave a mixture of 4-MeOC(O)-C_6H_4-NPh_2 (**3ha**) and 4-MeOC(O)C_6H_4-N(*p*-tolyl)$_2$ (**14**) (from **10**) in 49% and 52% yields, respectively (eq 14). The non-selective coupling demonstrates that diarylamines should be activated through a proton abstraction by a species generated from *N*-TMS-diarylamines and CsF before rate-limiting transmetalation.

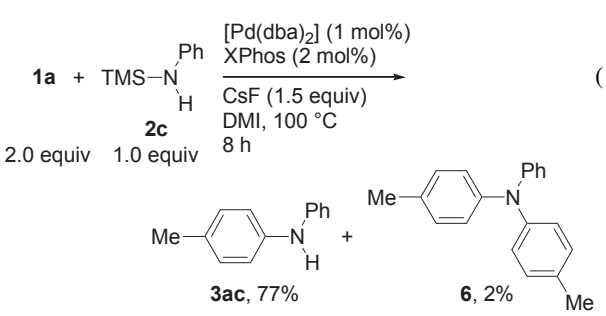


(13)

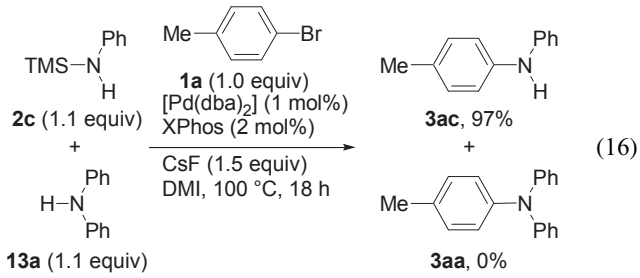


(14)

Selective reaction of **1a** with **2c** to give **3ac** (Table 3, Run 2) is remarkable in understanding the activation of a Si–N bond. Formation of **6** in eq 13 suggests that the product **3ac** may react with **1a** under the reaction conditions. In fact, as shown in Run 2 of Table 3, initial coupled product **3ac** was solely formed in 96% yield without formation of **6**. This is retained even if excess **1a** is applied to the reaction (eq 15), and **3ac** is obtained as a major product, suppressing formation of **6**. These results suggest that possible active species like **i**, or **ii** (R = Ph, R′ = H) undergo transmetalation in preference to activation of diarylamine **3ac**. It appears that a TMS-amide of a more basic amine apparently is activated more selectively by a fluoride ion than that with a less basic amine. To test this hypothesis, a competition experiment between **2c** and diphenylamine (**13a**) with **1a** was performed (eq 16). As expected, **3ac** was obtained in 97% yield without generation of **13a**-derived product, **3aa**.



(15)



(16)

Conclusion

Silylamine-based carbon–nitrogen bond-forming cross-coupling with haloarenes was achieved in the presence of a palladium catalyst and cesium fluoride in a common solvent. Variously functionalized substrates are widely applied to this transformation, which might lead to invention of novel functionalized organic materials by double and multiple C–N bond-forming cross-couplings. The feature of the present C–N coupling is attributed to a high reactivity of nitrogen nucleophiles. Basicity of parent amines may appear to affect the reaction rate and selectivity: *N*-TMS-diarylamines are the fastest, whereas *N*-TMS-dialkylamines are the slowest. Moreover, the fact that high loading of CsF raised the reaction rate indicates that formation of N-ligated aryl–Pd–halide complexes or amido-palladium complexes through transmetalation is rate limiting. Competition experiments also show the selectivity difference. TMS-NPh_2 reacts with bromoarenes rather than TMS-NMePh and further faster than *N*-TMS-morpholine. Moreover, TMS-NHPh undergoes C–N coupling bearing the free N–H bond intact. In view of the importance of triarylamines in medicinal chemistry and functional organic materials, the reported method should be useful to rapidly construct such structures.

Experimental

General. All manipulations of oxygen- and moisture-sensitive materials were conducted with standard Schlenk technique or in a dry box under an argon atmosphere. Preparative TLC was performed using Wakogel® B-5F. Analytical TLC was performed on Merck Kieselgel 60 F254 (0.25 mm) plates. HPLC was performed by JAI LC-9210NEXT. Visualization was accomplished with UV light (254 nm). ^1H and ^{13}C NMR spectra in $CDCl_3$ solution were recorded with a Varian Mercury 400 spectrometer. All reactions were carried out under an argon atmosphere. Unless otherwise noted, commercially available reagents were used without further purification. CsF was used before drying under reduced pressure with heating. Anhydrous DMI was purchased from Aldrich and used after distillation over CaH_2. Silylamines were prepared according to a reported procedure.[6b,15,31] Silylamines are so sensitive to hydrolysis that all reaction flasks for preparation and cross-coupling, round-bottom flasks, and distillation apparatus for isolation were all adequately flame-dried.

Cross-Coupling Reaction of Aryl Halide with *N*-Trimethylsilylamine. *A general procedure for the synthesis of arylamines*. To a mixture of haloarene **1** (0.50 mmol), CsF (0.75 mmol), $[Pd(dba)_2]$ (5.0 μmol), XPhos (10 μmol), and DMI (0.50 mL) in a well flame-dried screw vial was added *N*-trimethylsilylamine **2** (0.55 mmol), and the mixture was stirred at 100 °C for the time specified in Tables 1 and 2. The resultant mixture

was quenched with H_2O. The aqueous layer was extracted with Et_2O, and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$. After concentration in vacuo, the residue was purified by flash chromatography on silica gel or preparative TLC to afford arylamine **3**.

Reaction of *p*-Bromotoluene with Tris(trimethylsilyl)-amine (eq 5). To a mixture of *p*-bromotoluene (387 mg, 2.3 mmol), CsF (343 mg, 2.3 mmol), [Pd(dba)$_2$] (3.0 mg, 5.2 µmol), XPhos (4.9 mg, 10 µmol), and DMI (0.50 mL) in a screw vial were added tris(trimethylsilyl)amine (116 mg, 0.49 mmol) and decane as an internal standard, and the mixture was stirred at 140 °C for 48 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with Et_2O, and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$. After concentration in vacuo, the residue was purified by flash chromatography on silica gel or preparative TLC to afford arylamine tri(*p*-tolyl)amine (63 mg, 0.22 mmol) in 44% yield.

Time Course Experiment: The Reaction of *p*-Bromotoluene (1a) with *N*-Trimethylsilylamine 2 (Figure 1). *General procedure*: To a mixture of *p*-bromotoluene (**1a**, 0.20 mmol), CsF (0.30 mmol), [Pd(dba)$_2$] (2.0 µmol), XPhos (4.0 µmol), DMF (20 µL, an internal standard) and DMI (0.20 mL) in a screw vial was added *N*-trimethylsilylamine **2** (0.22 mmol). The vial was closed with a screw cap and taken outside the dry box. The reaction was monitored by ^{1}H NMR at 90 °C. **The reaction with 2a:** Average yields (3 times) of **3aa** after 10, 20, and 30 min were 90%, 91%, and 91%. **The reaction with 2b:** Average yields (3 times) of **3ab** after 10, 20, 30, 40, 50, and 60 min were 10%, 39%, 62%, 79%, 79%, and 82%. **The reaction with 2c:** Average yields (3 times) of **3ac** after 10, 20, 30, 40, 50, and 60 min were 18%, 40%, 42%, 43%, 47%, and 47%. **The reaction with 2d:** Average yields (3 times) of **3ad** after 10, 20, 30, 40, 50, and 60 min were 4%, 5%, 6%, 7%, 8%, and 9%.

Treatment of *N*-TMS-Diphenylamine (2a) with CsF (eq 8). *General procedure*: (*N*-Trimethylsilyl)diphenylamine (24 mg, 0.098 mmol) was added to a mixture of CsF (23 mg, 0.15 mmol) in DMI (0.10 mL) prepared in a 3 mL-vial in a dry box. The vial was closed with a screw cap and taken outside the dry box. The mixture was heated at 100 °C for 30 min and subjected to hydrolysis by $CDCl_3$. The crude product was analyzed by ^{1}H NMR to determine the yield of diphenylamine (30%).

Reaction of *p*-Bromotoluene (1a) with Diphenylamine (13a) (eq 10). To a mixture of *p*-bromotoluene (**1a**, 38 mg, 0.22 mmol), CsF (45 mg, 0.30 mmol), [Pd(dba)$_2$] (1.2 mg, 2.1 µmol), XPhos (1.9 mg, 4.0 µmol), and DMI (0.20 mL) in a screw vial was added diphenylamine (40 mg, 0.24 mmol). The vial was closed with a screw cap and taken outside the dry box. The mixture was heated at 100 °C for 30 min and analyzed by ^{1}H NMR to determine the yield of diphenyl(*p*-tolyl)amine (7% yield). When the mixture was heated for 18 h, the yield was about 30%.

Concentration Effect of Palladium Catalysts, CsF, 1a, or 2c (Figure 3). Conditions A: *Normal conditions (same data as shown in Figure 1)*: 1a (1.0 mmol), **2c** (1.1 mmol), [Pd(dba)$_2$] (10 µmol), XPhos (20 µmol), CsF (1.5 mmol), DMF (20 µL, an internal standard), and DMI (1.0 mL). Average concentrations (3 times) of **3ac** after 10, 20, 30, and 60 min were 0.18, 0.40, 0.42, and 0.47 (mol L^{-1}). **Conditions B: *twice amounts of [Pd(dba)$_2$]//2XPhos*: 1a** (0.50 mmol), **2c** (0.55 mmol), [Pd(dba)$_2$] (10 µmol), XPhos (20 µmol), CsF (0.75 mmol), and DMI (0.50 mL). Average concentrations (3 times) of **3ac** after 10, 20, 30, and 60 min were 0.31, 0.40, 0.40, and 0.45 (mol L^{-1}). **Conditions C: *twice amounts of 1a*: 1a** (1.0 mmol), **2c** (0.55 mmol), [Pd(dba)$_2$] (5.0 µmol), XPhos (10 µmol), CsF (0.75 mmol), and DMI (0.50 mL). Average concentrations (3 times) of **3ac** after 10, 20, 30, and 60 min were 0.20, 0.45, 0.46, and 0.48. **Conditions D: *twice amounts of 2c*: 1a** (0.30 mmol), **2c** (0.66 mmol), [Pd(dba)$_2$] (3.0 µmol), XPhos (6.0 µmol), CsF (0.45 mmol), and DMI (0.30 mL). Average concentrations (3 times) of **3ac** after 10, 20, 30, and 60 min were 0.40, 0.51, 0.54, and 0.59. **Conditions E: *twice amounts of CsF*: 1a** (0.30 mmol), **2c** (0.33 mmol), [Pd(dba)$_2$] (3.0 µmol), XPhos (6.0 µmol), CsF (0.90 mmol), and DMI (0.30 mL). Average concentrations (3 times) of **3ac** after 10, 20, 30, and 60 min were 0.79, 0.80, 0.81, and 0.89.

Competition Experiment between (*N*-Trimethylsilyl)-diphenylamine (2a) and *N*-Trimethylsilyl-*N*-methylaniline (2b) toward *p*-Bromotoluene (1a) (eq 11). To a mixture of **1a** (34 mg, 0.20 mmol), CsF (45 mg, 0.30 mmol), [Pd(dba)$_2$] (1.1 mg, 1.9 µmol), XPhos (1.9 mg, 4.0 µmol), and DMI (0.20 mL) in a screw vial were added **2a** (54 mg, 0.22 mmol) and **2b** (39 mg, 0.22 mmol), and the resulting mixture was stirred at 100 °C for 3 h. The reaction mixture was analyzed by ^{1}H NMR to determine the formation of **3aa** and to estimate yields of **3ab** (17%). Finally, the reaction mixture was diluted with Et_2O, and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative TLC to afford **3aa** (36 mg, 0.14 mmol, 70%).

Competition Experiment between (*N*-Trimethylsilyl)-diphenylamine (2a) and (*N*-Trimethylsilyl)morpholine (2d) toward *p*-Bromotoluene (1a) (eq 12). To a mixture of **1a** (34 mg, 0.20 mmol), CsF (90 mg, 0.59 mmol), [Pd(dba)$_2$] (1.5 mg, 2.6 µmol), XPhos (2.4 mg, 5.0 µmol), and DMI (0.20 mL) in a screw vial were added **2a** (55 mg, 0.23 mmol) and **2d** (37 mg, 0.23 mmol) and the mixture was stirred at 100 °C for 0.5 h. Assay of the reaction mixture by ^{1}H NMR confirmed the formation of **3aa** and showed that the yield of **3ad** was 5%. The reaction mixture was diluted with Et_2O, and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. This crude was purified by preparative TLC to afford **3aa** (46 mg, 0.18 mmol, 89% yield).

Competition Experiment between (*N*-Trimethylsilyl)-diphenylamine (2a) and (*N*-Trimethylsilyl)aniline (2c) toward *p*-Bromotoluene (1a) (eq 13). To a mixture of **1a** (86 mg, 0.50 mmol), CsF (85 mg, 0.56 mmol), [Pd(dba)$_2$] (3.7 mg, 6.4 µmol), XPhos (5.0 mg, 11 µmol), decane (an internal standard, 5.0 µL, 0.051 mmol), and DMI (0.50 mL) in a screw vial were added **2a** (14 mg, 0.56 mmol) and **2c** (110 mg, 0.56 mmol), and the mixture was stirred at 100 °C for 1 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with Et_2O (three times), and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$. After concentration in vacuo, the residue was analyzed by ^{1}H NMR to confirm the formation of **3aa**, **3ac**, and **6**, and separated by HPLC to afford **3aa** (63 mg, 0.24 mmol, 48%),

3ac (8.3 mg, 0.045 mmol, 9%), and **6** (15 mg, 0.084 mmol, 17% based on the amount of **1a**).

Competition Experiment between (*N*-Trimethylsilyl)-diphenylamine (2a) and Bis(*p*-tolyl)amine (10) toward Methyl *p*-Bromobenzoate (1h) (eq 14). To a mixture of **1h** (110 mg, 0.51 mmol), CsF (113 mg, 0.75 mmol), [$Pd(dba)_2$] (3.3 mg, 5.7 µmol), XPhos (5.3 mg, 10 µmol), decane (an internal standard, 5.0 µL, 0.051 mmol), and DMI (0.50 mL) in a screw vial were added **2a** (130 mg, 0.539 mmol) and **10** (109 mg, 0.552 mmol) and the mixture was stirred at 100 °C for 30 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with Et_2O, and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was analyzed by ^{1}H NMR to determine the yields of **3ha** and **14** (49% and 52%, respectively). These products were separated by preparative TLC to afford a mixture of **3ha** and **14**.

The Reaction of *p*-Bromotoluene (1a, 2 equiv) with (*N*-Trimethylsilyl)aniline (2c) (eq 15). To a mixture of *p*-bromotoluene (**1a**, 180 mg, 1.05 mmol), CsF (116 mg, 0.77 mmol), [$Pd(dba)_2$] (2.9 mg, 5.0 µmol), XPhos (4.8 mg, 10 µmol), decane (an internal standard, 5.0 µL, 0.051 mmol), and DMI (0.5 mL) in a screw vial were added **2c** (83 mg, 0.50 mmol). The vial was closed with a screw cap and taken out from the dry box. The mixture was heated at 100 °C for 8 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with Et_2O (three times), and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was subjected to preparative TLC to afford **3ac** (71 mg, 0.39 mmol, 77%) and **6** (3.0 mg, 0.011 mmol, 2%).

Competition Experiment between (*N*-Trimethylsilyl)-aniline (2c) and Diphenylamine (13a) toward *p*-Bromotoluene (1a) (eq 16). To a mixture of **1a** (36 mg, 0.21 mmol), CsF (48 mg, 0.32 mmol), [$Pd(dba)_2$] (1.3 mg, 2.3 µmol), XPhos (1.9 mg, 4.0 µmol), and DMI (0.50 mL) in a screw vial were added **2c** (41 mg, 0.25 mmol) and **13a** (41 mg, 0.24 mmol) and the mixture was stirred at 100 °C for 18 h. The mixture was analyzed by ^{1}H NMR and GC to determine **3ac** (97% yield) and none of **3aa**.

This work has been supported financially by a Grant in-Aids for Scientific Research (S) (No. 21225005 to T.H.) and Young Scientists (B) (No. 25870747 to Y.M.) from JSPS. T.H. and Y.M. also acknowledges Sumitomo Chemical (T.H. and Y.M.) and Asahi Glass Foundation (Y.M.).

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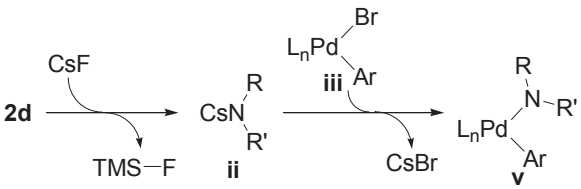
27 Substitution of a bromide ion bound to an arylpalladium with a fluoride forms an Ar–Pd–F complex. This is suggested to be an alternative potential pathway for the cross-coupling. See ref 24.

28 The reaction with **2d** can be considered to proceed via transmetalation of complex **iii** with **i** and/or **ii**, as is based on the results from eq 9.



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