DOI: 10.1002/adsc.201600299
Advanced Synthesis & Catalysis

Palladium on Carbon-Catalyzed C–H Amination for Synthesis of Carbazoles and its Mechanistic Study

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Received: March 17, 2016; Revised: June 30, 2016; Published online: ■■ ■■, 0000

Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600299.

Abstract: 10% Palladium on carbon (10% Pd/C) successfully catalyzed the intramolecular C–H amination of various *N*-mesylated 2-aminobiphenyls in the presence of a catalytic amount of pyridine *N*-oxide in heated dimethyl sulfoxide (DMSO) under an oxygen atmosphere to afford the corresponding *N*-mesylcarbazoles. The reaction would proceed *via* a single-electron transfer process based on its significant suppression by the addition of a single-electron scavenger, tetracyanoquinodimethane (TCNQ), and the substituents on the aromatic rings of the substrate have an insignificant effect on the reaction progress.

Keywords: C–H amination; heterogeneous catalysis; nitrogen heterocycles; nitrogen oxides; palladium

Introduction

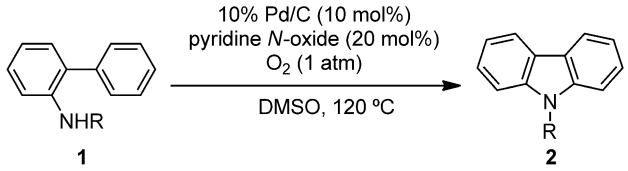
Palladium on carbon (Pd/C) has long been used for the hydrogenation of various reducible functional groups.[1] Recently, the advantages of its properties, such as its stability in air, easy removal of palladium metal from the reaction media by simple filtration, recoverability, reusability, and commercial availability at a relatively low cost, have been reviewed from the perspective of green sustainable chemistry directly linked to practical use. A wide range of Pd/C-catalyzed reactions, including cross-coupling reactions, has been developed,[2,3] while few uses of Pd/C for C–H functionalization reactions have been reported compared to the homogeneous palladium catalysts.[4–7] Recently, the Pd/C-catalyzed C–H functionalization was applied to the synthesis of heterocyclic compounds, e.g., isoquinolines,[5a] benzofurans,[5b] and carbazoles,[5c,d] for their potential biological activities and functionalities.[4e]

We have previously reported the Pd/C-catalyzed oxidations of alkynes to the corresponding 1,2-diketones using oxygen gas (O_2) and dimethyl sulfoxide (DMSO) as the oxidants[8] or pyridine *N*-oxide as an oxidant.[9] For the general palladium-catalyzed C–H functionalization reactions, the Pd(0) species would be generated after each catalytic reaction cycle, and the oxidation step should be required to reproduce the active Pd(II) species from Pd(0).[6] We anticipated that the combined use of these oxidants, O_2, DMSO, and pyridine *N*-oxide, would be effective for the Pd/C-catalyzed C–H functionalization. Very recently, Ying et al. reported an *N*-acetylcarbazole synthesis *via* the intramolecular C–H amination of *N*-acetyl-2-aminobiphenyl catalyzed by their homemade Pd/C, the Pd species of which more largely exists as Pd(II) species rather than Pd(0), in DMSO under O_2 in the presence of molecular sieves as an essential reagent.[5c] In this study, we demonstrate that the use of the commercially available Pd/C, which consists of almost entirely Pd(0) species, could effectively catalyze the cyclization for the *N*-sulfonylcarbazole synthesis without molecular sieves, and the effect being due to the difference in the surface area of the activated carbons of Pd/C and pyridine *N*-oxide as an accelerator. Furthermore, we proposed the involvement of a possible single electron transfer process during the reaction instead of the C–H activation or Heck-type mechanism.[5c,6j]

Results and Discussion

The *N*-tosyl- and *N*-mesyl-2-aminobiphenyls (**1b** and **1c**) in heated DMSO were smoothly cyclized into the corresponding carbazole derivatives in the presence of catalytic amounts of 10% Pd/C (10 mol%) and pyr-

Table 1. Effect of *N*-substituent on the carbazole synthesis.



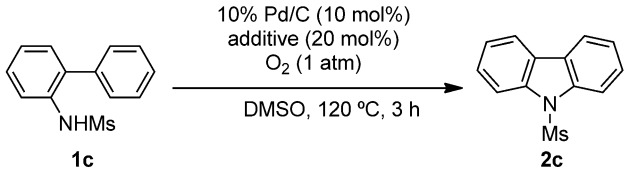
Entry	R	Time [h]	Ratio[a] (**1**:**2**)
1	H (**1a**)	24	**2a** was not obtained.
2	Ts (**1b**)	6	0:100
3	Ms (**1c**)	3	0:100 (98%)[b]
4	Ac (**1d**)	24	72:28[c]
5	Bz (**1e**)	24	100:0
6	Piv (**1f**)	24	100:0

[a] The ratio was determined by ^{1}H NMR.
[b] The isolated yield is indicated in parentheses.
[c] A small amount of deacetylated carbazole was detected in the ^{1}H NMR spectrum (<5%).

idine *N*-oxide (20 mol%) under an O_2 atmosphere (Table 1, entries 2 and 3), although the free 2-aminobiphenyl (**1a**) and *N*-acylated 2-aminobiphenyls (**1d**, **1e**, and **1f**) produced ineffective reactions (entries 1, 4–6). Especially, the *N*-mesylated 2-aminobiphenyl (**1c**) was a good substrate, and the reaction was completed within only 3 h (entry 2).

The addition of pyridine *N*-oxide was found to be very effective for the present cyclization based on the C–H amination (Table 2, entries 1–3), since it was incomplete even after 24 h without pyridine *N*-oxide (entries 1 and 2). 4-Nitroquinoline *N*-oxide and *N*-methylmorpholine *N*-oxide also promoted the reaction (entries 6 and 7), while 3-hydroxypyridine *N*-oxide and 4-nitropyridine *N*-oxide as well as *m*-chloroperoxybenzoic acid (*m*CPBA) showed a negative effect as oxidizing reagents (entries 4, 5, and 8). Interestingly, pyridine dramatically impeded the reaction progress (entry 9), suggesting that pyridine would not be transformed into the active pyridine *N*-oxide under the present oxidative conditions and it would work as a catalyst poison based on the strong coordination ability to the Pd metal.[10]

Table 2. Effect of the additive on carbazole synthesis from *N*-Ms-2-aminobiphenyl.



Entry	Additive	Ratio[a] (**1c**:**2c**)
1	–	25:75
2[b]	–	7:93
3	pyridine *N*-oxide	0:100 (98%)[c]
4	3-hydroxypyridine *N*-oxide	41:59
5	4-nitropyridine *N*-oxide	36:64
6	4-nitroquinoline *N*-oxide	6:94
7	4-methylmorpholine *N*-oxide	12:88
8	*m*CPBA	33:67
9	pyridine	83:17

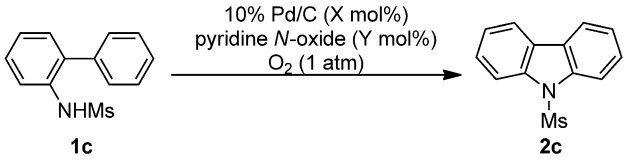
[a] The ratio was determined by ^{1}H NMR.
[b] The reaction was carried out for 24 h.
[c] Isolated yield is indicated in parentheses.

When the reaction was carried out without 10% Pd/C, the C–H amination never proceeded (Table 3, entry 1). The reaction proceeds Pd/C-dose-dependently, and 10 mol% of 10% Pd/C was found to be required to complete the reaction within 3 h (entries 1–4). Increasing the amount of pyridine *N*-oxide up to 20 mol% accelerated the reaction progress (Table 3, entries 4–6 *vs.* Table 2, entry 1), while the addition of an excess amount produced no beneficial effects (Table 3, entry 7). Furthermore, the carbazole was scarcely obtained without either DMSO (Eentries 8–12) or oxygen (Entry 13). The temperature was also found to be an important factor for the present reaction; heating below 120 °C resulted in a drastic decrease in the yield of **2c** (entries 14 and 15). The reaction progress was significantly suppressed by the addition of 10 mol% of tetracyanoquinodimethane (TCNQ) as a single electron scavenger, and the reaction was almost quenched (entry 16). The addition of radical scavengers, such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 1,1-diphenylethene, and 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT), also decelerated the reaction (entries 17–19).

When a mixture of equimolar amounts of non-deuterated substrate (**1c**) and deuterated **1c**-d_5 in DMA was stirred at 120 °C under the optimal conditions for 1.5 h, 39.5% deuterium incorporation into the produced *N*-mesylcarbazole (**2c**) was observed by ^{1}H NMR spectroscopy (Scheme 1).[11] The kinetic isotope effect (KIE, k_H/k_D) is estimated to be 1.53, indicating that the C–H cleavage process would not be the rate-determining step. These results suggest an involvement of a single electron transfer process during the C–H amination, although the oxidative addition of the *ortho*-C–H bond of non-aminated phenyl ring of **1c** to Pd(0) as the rate-determining step could not be thoroughly excluded.

The 10% Pd/C-catalyzed intramolecular ring closing reaction proceeded with little influence of the electronic property and substitution pattern of the substituents on each benzene ring of the *N*-mesyl-2-aminobiphenyl derivatives as the starting materials (Table 4). Carbazole derivatives bearing electron-donating methoxy and methyl substituents (**2g**, **2h**, **2l**, **2m**, **2p**, and **2s**) or electron-withdrawing nitro, trifluoromethyl, ethoxycarbonyl, and chloro substituents (**2i**, **2j**, **2k**, **2n**, **2o**, **2q**, and **2r**) could be synthesized in

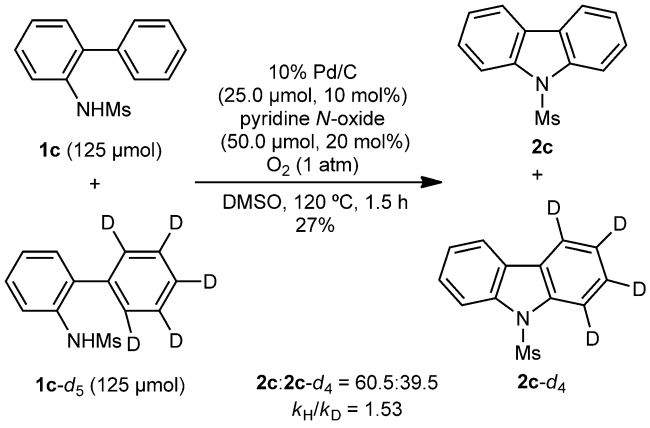
Table 3. Optimization of the reaction conditions for the C–H amination.



Entry	X [mol%]	Y [mol%]	Solvent	*T* [°C]	*t* [h]	Ratio[a] (**1c**:**2c**)
1	0	20	DMSO	120	24	100:0
2	1	20	DMSO	120	3	88:12
3	5	20	DMSO	120	3	56:44
4	10	20	DMSO	120	3	0:100 (98%)[b]
5	10	5	DMSO	120	3	7:93
6	10	10	DMSO	120	3	1:99
7	10	40	DMSO	120	3	22:78
8	10	20	NMP	120	24	94:6
9	10	20	CPME	120	24	98:2
10	10	20	mesitylene	120	24	>99:trace
11	10	20	cyclohexane	120	24	100:0
12	10	20	–	120	3	100:0
13[c]	10	20	DMSO	120	24	100:0
14	10	20	DMSO	100	3	96:4
15	10	20	DMSO	80	3	100:0
16[d]	10	20	DMSO	120	3	95:5
17[e]	10	20	DMSO	120	3	25:75
18[f]	10	20	DMSO	120	3	88:12
19[g]	10	20	DMSO	120	3	80:20

[a] The ratio was determined by ^{1}H NMR.
[b] The isolated yield is indicated in parentheses.
[c] The reaction was carried out under argon.
[d] TCNQ (10 mol%) was added.
[e] TEMPO (10 mol%) was added.
[f] 1,1-Diphenylethene (1 equiv.) was added.
[g] 2,6-Di-*tert*-butyl-4-hydroxytoluene (BHT, 1 equiv.) was added.

good to excellent yields. Furthermore, the intramolecular C–H amination of *N*-mesyl-3′-methoxy-2-aminobiphenyl (**1l**) could proceed in a regioselective manner to give the corresponding 3-substituted carbazoles (**2l**).

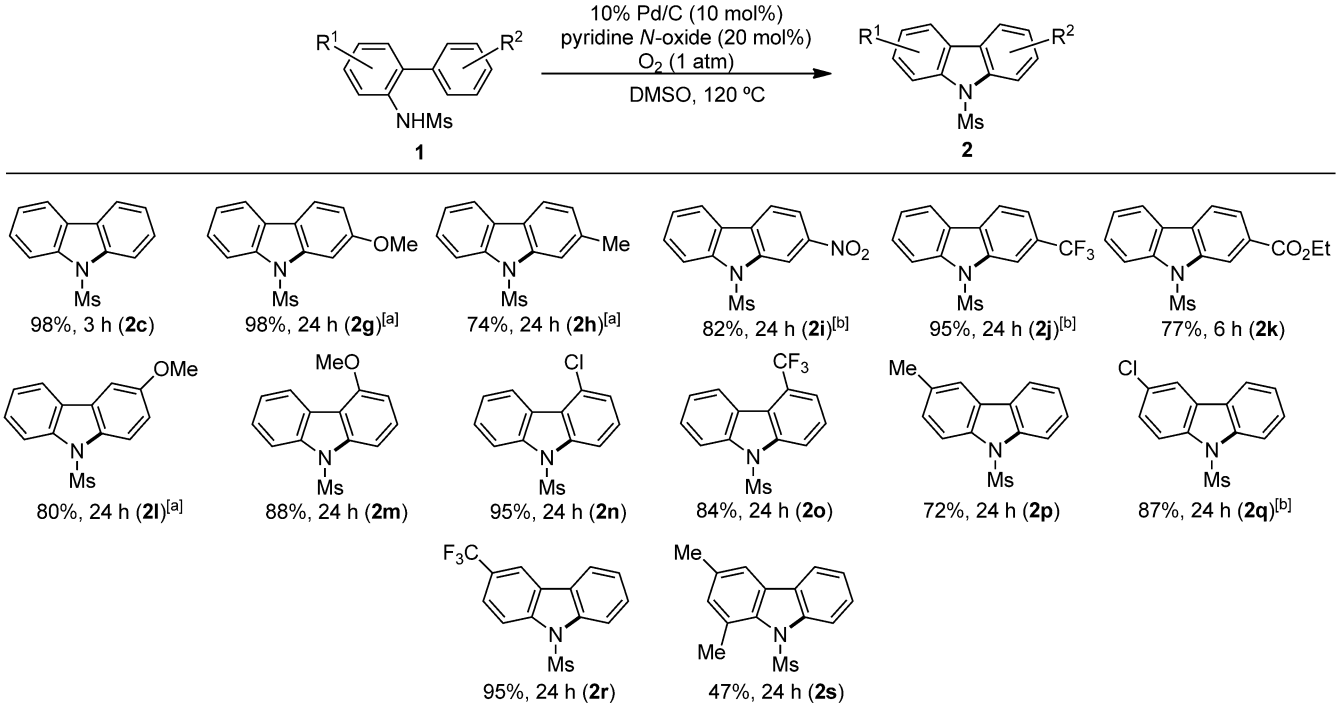


Scheme 1. Competitive reactions of **1c** and **1c**-d_5.

Removal of the *N*-mesyl group from the synthesized carbazole rings (**2c**, **2g**, and **2i**) was readily achieved by the reported method for the detosylation of *N*-tosylated indoles using Cs_2CO_3 in the THF-MeOH combined solvent that produced the corresponding deprotected carbazoles (**3c**, **3g**, and **3i**) in excellent yields (Table 5).[12]

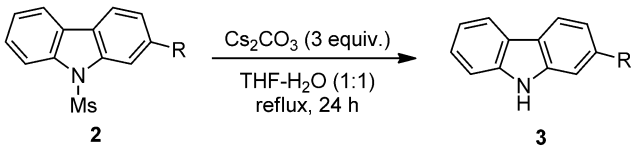
The leaching behavior of palladium species into the filtrate after the removal of the 10% Pd/C from the reaction mixture was measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES) using **1c** as a substrate. Unfortunately, a decent amount of palladium species was detected, and 43% of the Pd from the 10% Pd/C was found to be leached.[13,14] Next, we examined the so-called hot-filtration experiment to clarify if the leached Pd can catalyze the reaction (Scheme 2).[15] A time-course study revealed that the 10% Pd/C time-dependently catalyzed the C–H amination and *N*-Ms-carbazole (**2c**) was generated in 20% yield after 1 h. The reaction was similarly conducted, and the mixture was filtered after 1 h without cooling to remove the 10% Pd/C. The filtrate

Table 4. Substrate scope.



[a] 20 mol% of 10% Pd/C were used.
[b] 15 mol% of 10% Pd/C were used.

Table 5. Removal of *N*-Ms group from *N*-Ms-carbazoles.

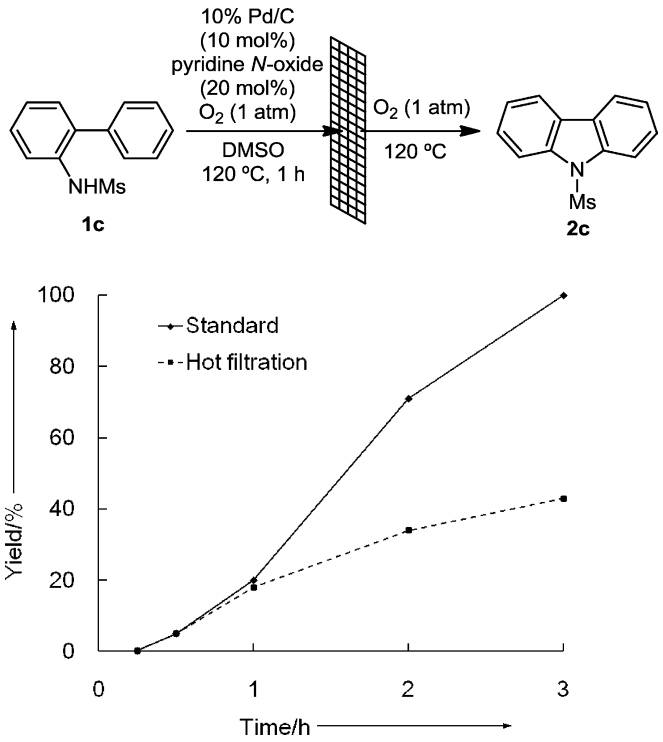


Entry	R	Yield [%][a]
1	H (**2c**)	100 (**3c**)
2	MeO (**2g**)	99 (**3g**)
3[b]	NO_2 (**2i**)	89 (**3i**)

[a] Isolated yield.
[b] The reaction was carried out in THF-MeOH (2:1) at room temperature for 5 h.

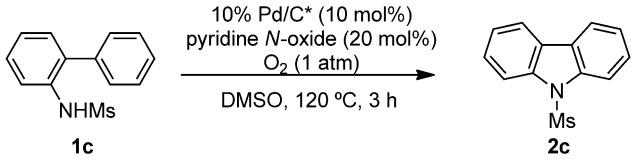
without 10% Pd/C was then heated again at 120 °C under an O_2 atmosphere and the time course was followed. As a result, the C–H amination also proceeded after the removal of the 10% Pd/C, although the reaction rate was significantly lower. These results indicated that the palladium species were leached from the Pd/C into the reaction media and they could function as the real catalyst species.

The progress of the present C–H amination was also found to be dependent on the surface area of the activated carbon used as the catalyst support (Table 6). When the surface area of the activated carbon support of 10% Pd/C is greater than



Scheme 2. Time-course study of the reaction in the filtrate after the removal of 10% Pd/C. Standard run (◆): The reaction of *N*-Ms-2-aminobiphenyl (**1c**) was carried out without filtration. Hot-filtration (■): 10% Pd/C was removed by filtration without cooling after a 1-h reaction at 120 °C and the filtrate was heated again at 120 °C.

Table 6. Effect of activated carbon of 10% Pd/C on the carbazole synthesis from *N*-Ms-2-aminobiphenyl.

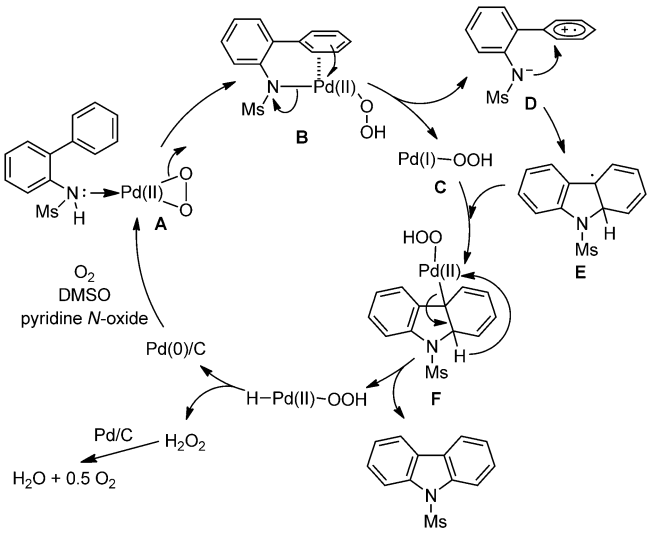


Entry	Surface area of activated carbon of 10% Pd/C (m^2/g)	Ratio[a] (**1c**:**2c**)
1	1000	0:100
2	1150	0:100
3	1550	19:81

[a] Ratio was determined by ^{1}H NMR.

1000 $m^2 g^{-1}$, the reaction was effectively catalyzed (entries 1 and 2), while a part of *N*-mesyl-aminobiphenyl (**1c**) remained unreacted using the 10% Pd/C possessing an excessively high surface area of the activated carbon (>1500 $m^2 g^{-1}$) (entry 3). The large surface area of the catalyst support is generally considered to be a crucial factor for the smooth reaction progress because of the facilitation of the easy contact of the substrate with palladium metal on the catalyst surface. The decrease in the catalyst efficiency for the present reaction would be caused by the delayed elimination of the substrate or/and product from the reactive sites on the catalyst surface based on the increased interaction or intermolecular force between the carbon support and substrate/product. The palladium leaching would also be hampered by the coverage of the substrate and/or product on the carbon support based on the interaction.

Scheme 3 shows our proposed reaction mechanism. Some of the Pd(0) species would be oxidized to Pd(II) oxide (**A**)[16] by the oxidative cooperation of O_2, DMSO, and pyridine *N*-oxide, and leached from 10% Pd/C. Although the function of DMSO as a ligand might not be omitted, it should work as an oxidizing reagent, since the present reaction gives off the strong odor of dimethyl sulfide. The nucleophilic attack of the sulfonamide moiety of *N*-Ms-2-aminobiphenyl to the palladium would afford a Pd(II) amide complex (**B**), where Pd(II) would be on the aromatic ring to form a charge-transfer complex. A single electron could be transferred from the aromatic ring to Pd(II) to generate a short-lived Pd(I)-OOH (**C**) and radical cation bearing an amide anion within the molecule (**D**), the latter of which would be converted to the benzyl radical (**E**) *via* intramolecular cyclization. The radical (**E**) and Pd(I)-OOH (**C**) would be quickly coupled to afford the Pd(II)-OOH species (**F**), and the β-hydrogen elimination would afford the desired carbazole and H-Pd(II)-OOH. The subsequent reductive elimination would give the Pd(0) species and



Scheme 3. Proposed reaction mechanism.

H_2O_2. H_2O_2 can be readily decomposed to water and O_2 in the presence of 10% Pd/C.[14]

Conclusions

We have developed an efficient method for the synthesis of a wide variety of carbazole derivatives *via* the Pd/C-catalyzed intramolecular cyclization by the combined use of commercially available 10% Pd/C, DMSO, oxygen, and pyridine *N*-oxide. The pyridine *N*-oxide was revealed to significantly enhance the carbazole generation. The reaction progress was completely suppressed by the addition of a catalytic amount of TCNQ, which acts as a single-electron scavenger. The kinetic study using the deuterated substrate **2c**-d_5 suggested that the C–D cleavage is not a rate-determining step of this reaction. Therefore, we newly proposed the reaction mechanism, which involved a single electron transfer process as a key step. Furthermore, the surface area of the activated carbon of 10% Pd/C was found to be an important factor for the catalyst activity, and the absorption and desorption of the substrate and/or product onto/from the catalyst support affected the reaction progress.

Experimental Section

Typical Procedure for the Synthesis of *N*-Ms-Carbazole Derivatives (Table 4)

A mixture of the *N*-Ms-2-aminobiphenyl derivative (250 μmol), pyridine *N*-oxide (4.8 mg, 50.0 μmol), and 10% Pd/C (26.6 mg, 25.0 μmol) in DMSO (1 mL) was stirred at 120 °C under an O_2 atmosphere. After a specific time, the mixture was cooled to room temperature and passed through a celite pad. The pad was washed with EtOAc

(10 mL) and H_2O (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (10 mL × 2), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane-EtOAc or CH_2Cl_2-MeOH).

Demesylation of *N*-Ms-Carbazoles (Table 5)

A mixture of the *N*-Ms-carbazole derivative (250 μmol) and Cs_2CO_3 (244 mg, 750 μmol) in THF-MeOH [1 mL (1:1 or 2:1)] was stirred at room temperature or refluxed. After a specific time, the mixture was cooled to room temperature, and partitioned between CH_2Cl_2 (20 mL) and H_2O (10 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc).

Assay of Leached Palladium in the Reaction Media

A mixture of *N*-mesyl-2-aminobiphenyl (**1c**) (618 mg, 2.50 mmol), pyridine *N*-oxide (47.5 mg, 500 μmol), and 10% Pd/C (266 mg, 250 μmol) in DMSO (10 mL) was stirred at 120 °C under an O_2 atmosphere. After 3 h, the mixture was cooled to room temperature, then passed through a membrane filter (0.20 μm, Milipore Corporation). The filter was washed with EtOAc (50 mL), and the filtrate was concentrated to *ca.* 10 mL under vacuum. EtOAc was added to the residue, and the solution was transferred to a 50-mL volumetric flask. EtOAc was added up to a 50 mL total volume, and the residual palladium was measured by inductively coupled plasma atomic emission spectrometry (ICP-AES) using a Shimadzu ICP8000. The palladium concentration was determined to be 227 mg L^{-1} [11.35 mg, 43% of the used 10% Pd/C ($11.35 \div 26.6 \times 100$)].

Time-Course Study of Carbazole Synthesis in the Filtrate after Removal of the 10% Pd/C by Hot Filtration (Scheme 2)

Standard run: Five test tubes were prepared, and the intramolecular cyclization of *N*-mesyl-2-aminobiphenyl (**1c**) (61.8 mg, 250 μmol) under an O_2 atmosphere was carried out using pyridine *N*-oxide (4.8 mg, 50.0 μmol) and 10% Pd/C (26.6 mg, 25.0 μmol) in DMSO (1 mL) at 120 °C in each test tube. The reaction was treated after 15 min, 0.5 h, 1 h, 2 h, and 3 h according to the typical procedure for the synthesis of the *N*-Ms-carbazole derivatives. The EtOAc extracts of each reaction mixture were concentrated under vacuum. The residue was weighed, and the ^{1}H NMR spectra were measured. The yield of *N*-mesyl-carbazole (**2c**) was determined by the ^{1}H NMR ratio and weight of the residue, which contained only **1c** and **2c** (0.3%, 5%, 20%, 71%, and 100% after 15 min, 0.5 h, 1 h, 2 h, and 3 h, respectively).

Hot filtration: Three test tubes were prepared, and the intramolecular cyclization of *N*-mesyl-2-aminobiphenyl (**1c**) (124 mg, 500 μmol) under an O_2 atmosphere was carried out using pyridine *N*-oxide (9.5 mg, 100 μmol) and 10% Pd/C (53.2 mg, 50.0 μmol) in DMSO (2 mL) at 120 °C in each test tube. After 1 h, 1 mL from each reaction mixture in the three test tubes was filtered using a 0.45-μm Millipore membrane filter without cooling. Each filtrate, except for one filtrate, was heated again at 120 °C for 1 h or 2 h. EtOAc (10 mL) and H_2O (10 mL) were then added to each test tube, and the layers were separated. The aqueous layer was extracted with EtOAc (10 mL × 2), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The yields of **2c** after reheating for 0 h, 1 h, and 2 h were determined using the same procedure for the standard run (18%, 34%, and 43%, respectively).

Acknowledgements

We thank the N.E. Chemcat Corporation for the kind gift of the Pd/Cs and the ICP-AES measurements.

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8 Palladium on Carbon-Catalyzed C–H Amination for Synthesis of Carbazoles and its Mechanistic Study

Adv. Synth. Catal. **2016**, *358*, 1 – 8

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