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One-step construction of carbazoles by way of the palladium-catalyzed double N-arylation reaction and its application to the total synthesis of murrastifoline-A

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Abstract—The one-step construction of *N*-substituted carbazoles by way of the Pd-catalyzed double N-arylation reaction of primary amines with 2,2′-dibromobiphenyl is described. Aryl and aliphatic amines including *tert*-butylamine and a protected glucopyranosylamine were effectively transformed into the corresponding *N*-substituted carbazoles. The first total synthesis of murrastifoline-A, a biscarbazole alkaloid, based on this methodology is also presented.
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1. Introduction

Carbazole alkaloids are known to show a wide range of biological properties, such as antitumor, antibiotic, psychotropic, antiinflammatory, and antihistaminic activities.[1] Carbazoles are also useful organic materials, as they possess photorefractive, photoconductive, and light-emitting properties. Due to the interesting and important properties of carbazoles, a number of methodologies for the construction of the carbazole ring have been reported.[2] Dehydrogenation of tetrahydrocarbazoles prepared by the Fischer–Borsche synthesis is one of the most classical methods.[3a] Coupling of the metal-coordinated cyclohexadienylium ion with an electron-rich arylamine, followed by metal-mediated oxidative cyclization and aromatization,[3b] the Pd(0) catalyzed intramolecular cyclization of 2-amino-2′-halobiphenyl,[3c] and the Pd(II) mediated oxidative cyclization of a diarylamine[3d] have also been developed. Diels–Alder reaction,[3e] electrocyclic reaction,[3f] and acid catalyzed cyclization of ketosulfoxide[3g] are methods used for the construction from indole derivatives. Cyclization of 2-arylacetanilides by the action of $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of O_2,[3h] and the anionic [4+2] cycloaddition of furoindolones[3i] were reported in 2005. These methods, however, sometimes encounter difficulties in controlling the regioselectivities during the preparation of multi-substituted carbazoles.

Recently, Nozaki and co-workers reported a new synthetic methodology; the Pd-catalyzed double N-arylation of primary amines with biphenyls possessing leaving groups (Br, I, and OTf) at C-2 and 2′.[4] This method is an important extension of the Buchwald–Hartwig N-arylation reaction,[5] and proved to be an excellent protocol for the regioselective construction of unsymmetrical multi-substituted carbazoles in one-step. By this reaction, a variety of primary amines, such as aryl amines and protected amines (*O*-alkyl carbamates) were successfully transformed into the corresponding *N*-substituted carbazoles, however, lower yield has been observed when an aliphatic primary amine (*n*-octylamine) was employed as the substrate under the conditions using $Pd_2(dba)_3$, *t*-Bu_3P, and NaO*t*-Bu in toluene.[4a] The Nozaki group also reported the successful synthesis of mukonine, a carbazole alkaloid, using this novel methodology.[4b]

Our group has an interest in the application of the Buchwald–Hartwig N-arylation reaction to the natural products' synthesis, and reported the first total synthesis of spicamycin,[6] a novel nucleoside antibiotic possessing a unique N-glycoside structure, by way of the Pd-catalyzed coupling of a heptopyranosylamine with a protected 6-chloropurine derivative.[6a,d] To extend the N-arylation methodology to the synthesis of a variety of natural products, we have independently studied the possibility of the Pd-catalyzed double N-arylation reaction of primary amines with 2,2′-dibromobiphenyl. In this paper, we report our results of the Pd-catalyzed double N-arylation reaction, which generated *N*-aryl-, *N*-alkyl-, and *N*-(glucopyranosyl)carbazoles in moderate to high yields in one-pot reactions. The first total synthesis

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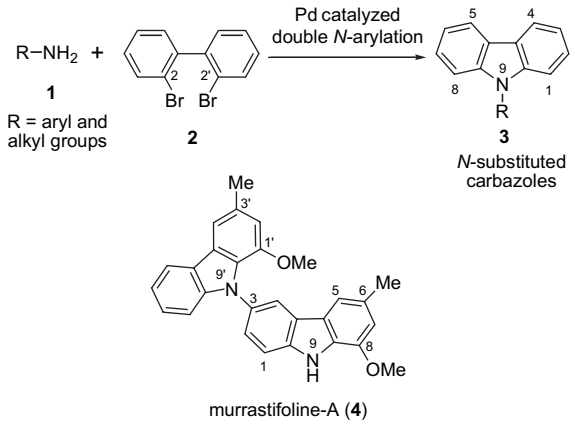


Figure 1.

of murrastifoline-A (**4**), a biscarbazole alkaloid, utilizing this methodology is also disclosed[7] (Fig. 1).

2. Results and discussion

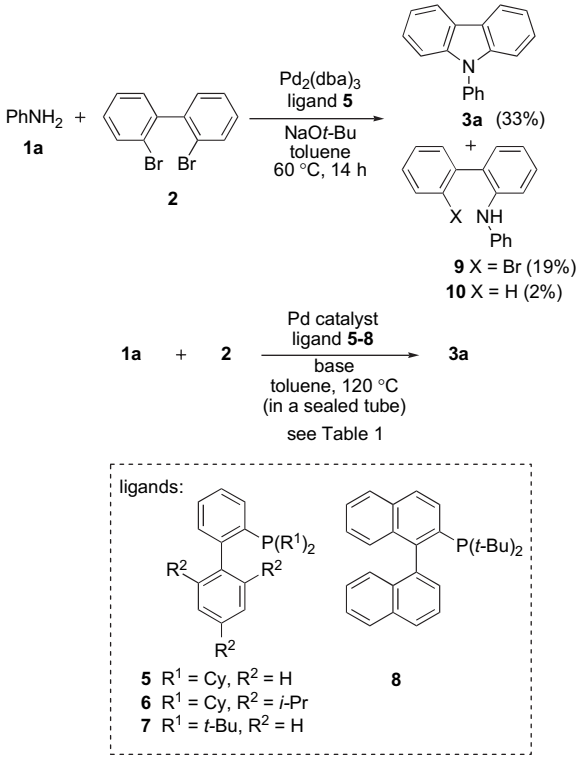
2.1. Double N-arylation of aniline

The double N-arylation of aniline (**1a**) with 2,2′-dibromobiphenyl[8] (**2**) was first attempted under the conditions reported by the Buchwald group for the N-arylation reaction of primary amines[5] with aryl halides after slight modification. When a mixture of **1a** (1 equiv) and **2** (1.1 equiv) in toluene in the presence of $Pd_2(dba)_3$ (10 mol % to **1a**), 2-(dicyclohexylphosphino)biphenyl (**5**)[5c] (30 mol % to **1a**), and NaO*t*-Bu (3 equiv) was heated at 60 °C for 14 h in a sealed tube, the desired product, *N*-phenylcarbazole (**3a**) was isolated in 33% yield (Scheme 1). A mixture of the mono N-arylation products (**9** and **10**) was also obtained in 21% yield (**9**:**10**=10:1, determined by ^{1}H NMR). To our delight, the same reaction at higher temperature (120 °C) significantly improved the yield of the desired product, and carbazole **3a** was obtained in 79% yield. In this case, a small amount of the mono N-arylation products (**9** and **10**) were detected by TLC, but could not be isolated. Although the Buchwald group reported that the mono N-arylation of aniline with 2′-chloroacetophenone proceeded in 81% yield with $Pd_2(dba)_3$ (1 mol %) and ligand **5** (2 mol %),[5c] the double N-arylation of aniline with **2** was found to be very slow with less than 10 mol % Pd catalyst. It was also found that the molar ratio of ligand/$Pd_2(dba)_3$ (2–3:1) was important for higher yields of **3a**. The dependence on the various reaction parameters was then examined. For the ligands, **5** as well as other dialkylphosphinobiaryls (**6**,[5d] **7**,[5c] and **8**[5e]), which have been reported by the Buchwald group being excellent ligands for the N-arylation, were tested. These results are listed in Table 1, which showed that (i) $Pd_2(dba)_3$ was the Pd source of choice (entries 2–4, when $Pd(OAc)_2$ was employed, the formation of Pd metal precipitates was observed during the course of the reaction), (ii) **5** and 2-(dicyclohexylphosphino)-2′,4′,6′-(triisopropyl)biphenyl (**6**) were effective ligands (entries 5–8), and (iii) the use of NaO*t*-Bu as a base gave good results whereas Cs_2CO_3 or K_3PO_4 significantly decreased the yields (entries 5, 9, and 10). As a result, *N*-phenylcarbazole (**3a**) was obtained in 85% yield under the conditions noted in entry 5.

Table 1. The double N-arylation of aniline (**1a**) with 2,2′-dibromobiphenyl (**2**)[a]

Entry	Pd Source	Ligand	Base	Time (h)	Yield of **3a** (%)[b]
1	$Pd_2(dba)_3$	**5**	NaO*t*-Bu	14	79
2[c]	$Pd_2(dba)_3$	**5**	NaO*t*-Bu	24	84
3	$Pd(PPh_3)_4$	**5**	NaO*t*-Bu	24	69
4[d]	$Pd(OAc)_2$	**5**	NaO*t*-Bu	24	62
5	$Pd_2(dba)_3$	**5**	NaO*t*-Bu	24	85
6	$Pd_2(dba)_3$	**6**	NaO*t*-Bu	24	82
7	$Pd_2(dba)_3$	**7**	NaO*t*-Bu	24	51
8	$Pd_2(dba)_3$	**8**	NaO*t*-Bu	13	22
9	$Pd_2(dba)_3$	**5**	Cs_2CO_3	24	42
10	$Pd_2(dba)_3$	**5**	K_3PO_4	24	32

[a] Reaction conditions: A mixture of **1a** (1.0 equiv), **2** (1.1 equiv), Pd catalyst (10 mol %), ligand (30 mol %), and base (3.0 equiv) in toluene was heated at 120 °C in a sealed tube.
[b] Isolated yield after chromatographic purification.
[c] $Pd_2(dba)_3$ (5 mol %), **5** (15 mol %).
[d] $Pd(OAc)_2$ (20 mol %), **5** (50 mol %).

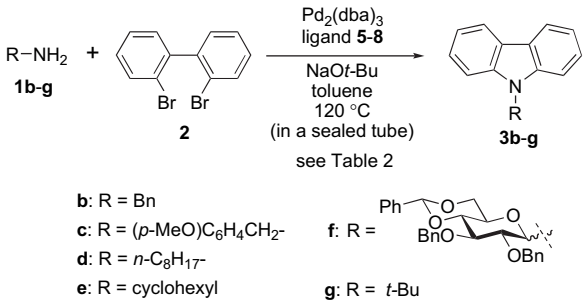


Scheme 1. dba=Dibenzylideneacetone, Cy=cyclohexyl.

2.2. Double N-arylation of aliphatic amines

The successful preparation of *N*-phenylcarbazole (**3a**) by the double N-arylation reaction led us to explore the reaction of aliphatic primary amines with dibromobiphenyl **2** (Scheme 2 and Table 2).

Although ligands **5** and **6**, which were found to be effective for the reaction of aniline, gave less satisfactory results when benzylamine was employed (entries 1 and 2), the use of 2-(di-*tert*-butylphosphino)binaphthyl (**8**) brought about a significant improvement, giving the desired product, *N*-benzylcarbazole (**3b**), in 60% yield (entry 4). The phosphine group in **8** is more electron-rich and sterically bulky than that in **5** and **6**. These electronic and steric factors play an important role in suppressing any undesired side reactions, such as



Scheme 2. Bn=–CH_2Ph.

Table 2. The double N-arylation of aliphatic amines with 2,2′-dibromobiphenyl (**2**)[a]

Entry	Amine	Ligand	Product	Time (h)	Yield (%)[b]
1	**1b**	**5**	**3b**	13	20
2	**1b**	**6**	**3b**	13	9
3	**1b**	**7**	**3b**	13	42
4	**1b**	**8**	**3b**	13	60
5	**1c**	**8**	**3c**	13	71
6	**1d**	**8**	**3d**	24	67
7	**1e**	**8**	**3e**	24	80
8[c]	**1f**[d]	**8**	**3f**[e]	24	52
9	**1g**	**8**	**3g**	13	17
10	**1g**	**6**	**3g**	13	42

[a] Reaction conditions: A mixture of **1** (1.0 equiv), **2** (1.1 equiv), $Pd_2(dba)_3$ (10 mol %), ligand (30 mol %), and NaO*t*-Bu (3.0 equiv) in toluene was heated at 120 °C in a sealed tube.
[b] Isolated yield after chromatographic purification.
[c] **2** (300 mol % to **1f**), $Pd_2(dba)_3$ (100 mol %), and **8** (300 mol %) at 60 °C.
[d] β-Anomer.
[e] Obtained as an anomeric mixture (α/β=1:1.7).

the formation of unreactive Pd bis-amine complexes and/or β-hydride elimination of the Pd-amido intermediates,[5a,g] in the double N-arylation process. Compound **8** was also found to work well for other aliphatic primary amines (entries 5–7). It is important to note that the *N*-alkylcarbazoles, which were prepared in poor yields under Nozaki's conditions,[4a] were obtained in moderate to good yields by the double N-arylation reactions when **8** was employed as the ligand. Under similar conditions, glucopyranosylamine derivative **1f**, a structurally complex and chemically unstable amine, could be converted into *N*-(glucopyranosyl)carbazole derivative **3f**[9] in 52% yield, although excess amounts of the Pd catalyst and ligand **8** were required (entry 8). The reaction of *tert*-butylamine (**1g**) with ligand **8** (entry 9), however, resulted in a low yield of the desired product. It was found that the use of ligand **6** instead of **8** produced a better result by generating *N*-(*tert*-butyl)carbazole (**3g**) in moderate (42%) yield (entry 10). The steric bulk of ligand **8** would prevent the sterically hindered *tert*-butylamine from approaching the catalyst. While the reasons for the better yield by the double N-arylation of *tert*-butylamine with ligand **6** are not clear, the effectual combination of the electronic (**6** should be electron richer than **5**, but electron poorer than **8**) and steric (**6** is smaller than **8**) factors in **6** would contribute to its effectiveness.

Based on these experiments, it was shown that the double N-arylation methodology is effective for the one-step synthesis of various *N*-substituted carbazoles. For aniline, the combination of $Pd_2(dba)_3$, NaO*t*-Bu, and ligand **5** provided the product in good yield. For aliphatic primary amines with sterically unencumbered structures, the use of ligand **8** gave favorable results, whereas the use of ligand **6** proved to be effective for the sterically hindered *tert*-butylamine (**1g**).

2.3. Total synthesis of murrastifoline-A

We next tried to extend this methodology to the synthesis of the structurally more complicated carbazole alkaloid, murrastifoline-A (**4**). Murrastifoline-A was isolated by Furukawa and co-workers from the root bark of *Murraya euchrestifolia* (Rutaceae) collected in Taiwan.[10] The structure elucidation study by spectral analyses revealed that murrastifoline-A is a new biscarbazole possessing the dimeric structure of 1′-methoxy-3′-methylcarbazole (murrayafoline-A, murrastifoline-A numbering), where the nitrogen in one carbazole unit (at the 9′-position) is connected to a carbon atom at the 3-position of another carbazole unit. While many monomeric carbazoles have been isolated from higher plants,[2] much attention has been recently focused on such biarylic biscarbazole alkaloids[11,12] due to their interesting structures and expected biological activities. The *C*,*N*-bonded biaryl biscarbazole structure found in **4** is very unique among the biscarbazole alkaloids,[11] however, reports on the synthetic approach to the *C*,*N*-bonded biaryl biscarbazoles are limited.[11d,12] In 2001, Bringmann disclosed the total synthesis of murrastifoline-F, an isomer of murrastifoline-A (**4**) in which the nitrogen in a carbazole unit at the 9′-position is bonded to another carbazole at C-5 (murrastifoline-A numbering), by the lead tetraacetate-mediated oxidative coupling of 1′-methoxy-3′-methylcarbazole.[12b]

Our retrosynthetic analysis of murrastifoline-A (**4**) is shown in Figure 2. The biscarbazole structure of murrastifoline-A (**4**) could be constructed by the key double N-arylation of the bottom-half segment, carbazolamine **12**, with the top-half segment, dibromobiphenyl derivative **11**. For preparation of both the top and bottom segments (**11** and **12**), we chose 2-amino-5-methylphenol (**13**) as the common starting material.

The synthesis of top-half segment (**11**) commenced from the known *O*-tosylate (**14**),[13] prepared from commercially available **13** in 89% yield (Scheme 3). The conventional iodination with *N*-iodosuccinimide (NIS) of **14** afforded **15** (69%), whose Suzuki–Miyaura cross-coupling reaction[14] with 2-bromophenylboronic acid in the presence of $Pd(PPh_3)_4$

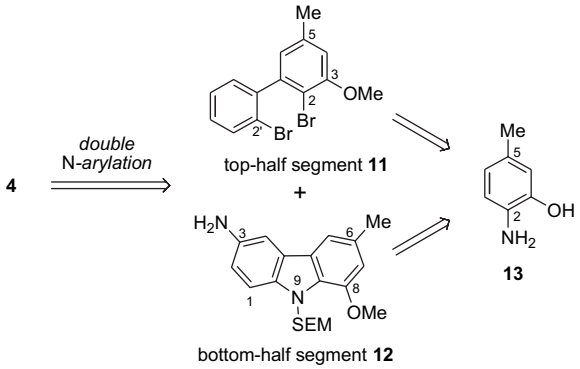
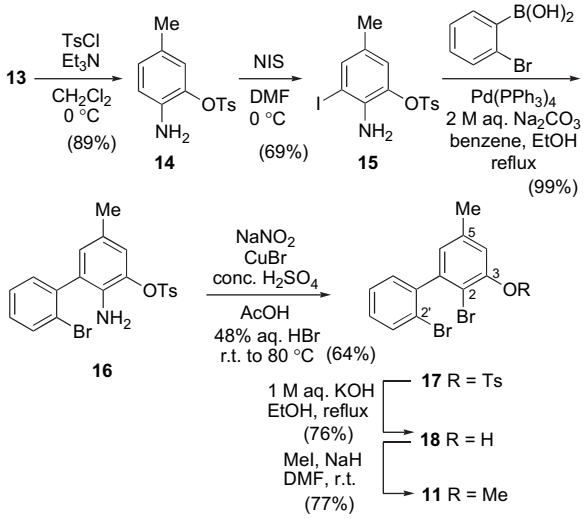


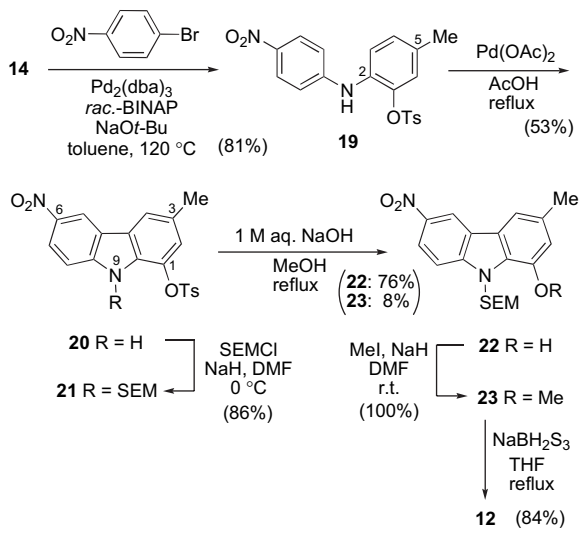
Figure 2. SEM=–$CH_2OCH_2CH_2SiMe_3$.

in EtOH–benzene–2 M aqueous Na_2CO_3 cleanly afforded **16** in 99% yield. Sandmeyer reaction of **16** gave dibromobiphenyl **17** in 64% yield. In this reaction, the use of AcOH as a co-solvent was essential for the effective diazotization. The *O*-Ts protecting group in **17** was removed by basic hydrolysis to give **18**, whose O-methylation furnished the top-half segment **11** in 59% yield from **17**.



Scheme 3. Ts=–$SO_2C_6H_4$(*p*-Me).

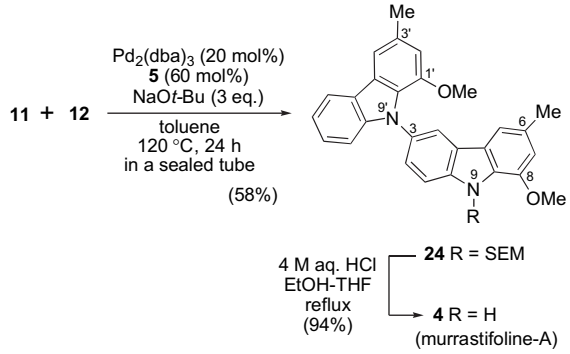
The bottom-half segment **12** was synthesized as shown in Scheme 4. Thus, the Buchwald–Hartwig N-arylation[5f] of **14** with 4-bromonitrobenzene afforded diarylamine **19** in 81% yield. The treatment of **19** with excess $Pd(OAc)_2$ in AcOH induced the cyclization[3d,13b] to provide carbazole **20** in 53% yield. After protection of the nitrogen function in **20** with the 2-trimethylsilylethoxymethyl (SEM) group (86% yield), the product **21** was treated with NaOH in MeOH-H_2O to provide de-*O*-tosyl derivative **22** along with its methyl ether **23** in 76 and 8% isolated yields, respectively. Methyl ether **23** would be formed by the nucleophilic aromatic substitution reaction of compound **21** with the methoxide ion.[15] The O-methylation of **22** quantitatively



Scheme 4. BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

afforded **23**. Although the attempted reduction of the nitro function in **23** by catalytic hydrogenation (H_2 in the presence of 5% Pd on carbon) resulted in the formation of many unidentified products, the treatment of **23** with $NaBH_2S_3$[16] cleanly provided the bottom-half segment **12** in 84% yield.

With both the top- and bottom-half segments in hand, the crucial double N-arylation reaction was explored (Scheme 5). From the observations of the coupling reactions of aniline with 2,2′-dibromobiphenyl (Table 1), it was expected that the use of **5** as the ligand would be the most effective for the reaction. Indeed, when a mixture of segments **11** and **12** in toluene was heated at 120 °C in the presence of $Pd_2(dba)_3$, NaO*t*-Bu, and **5**, the double N-arylation successfully took place to provide the desired *N*-protected biscarbazole **24** in 58% yield. It was found, as anticipated, the use of ligands **6** and **8** gave less satisfactory results (28% yield with **6** and 23% yield with **8**). Finally, the *N*-SEM group was removed under acidic conditions to furnish murrastifoline-A (**4**) in 94% yield. The spectral data of synthetic **4** were fully identical with those of the natural product.[10]



Scheme 5.

3. Conclusion

In summary, we described the Pd-catalyzed double N-arylation reaction of primary amines with 2,2′-dibromobiphenyls, which provided *N*-substituted carbazoles in a one-step reaction. By the choice of ligands, both the aryl and aliphatic amines including *tert*-butylamine and an *O*-protected glucopyranosylamine could be transformed into the corresponding carbazoles. Based on this methodology, the first total synthesis of murrastifoline-A (**4**) has been accomplished. This synthesis fully confirmed the proposed structure of the natural product and revealed that the double N-arylation methodology is highly effective for the one-step construction of the structurally complex, unsymmetrical multisubstituted carbazole derivatives.

4. Experimental

4.1. General

Melting points (mp) were determined on a Mitamura-riken micro hot stage and are uncorrected. ^{1}H NMR spectra were measured with a JEOL JNM-*Lambda* 300 (300 MHz) or a Varian MVX-300 (300 MHz) spectrometer, with

tetramethylsilane as the internal standard for solutions in $CDCl_3$ at rt, unless otherwise noted. Chemical shifts are reported as δ values in ppm. ^{13}C NMR spectra were taken on a 75 MHz spectrometer. Mass spectra were measured by a JEOL GC-Mate spectrometer with EI mode (70 eV), unless otherwise noted. Optical rotations were measured with a JASCO DIP-370 instrument with 1-dm tube and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a JASCO FTIR-200 spectrometer. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Solvents were dried over 3 Å molecular sieves after distillation. Benzene, toluene, and DMF were distilled from CaH_2. MeOH was distilled from $CaSO_4$ (DRIERITE®). AcOH was distilled from Ac_2O and $KMnO_4$. EtOH (95%, dried over 3 Å molecular sieves), Et_2O (dehydrated), THF (dehydrated, stabilizer free), and CH_2Cl_2 (dehydrated) were purchased from Kanto Chemical Co., INC. For column chromatography, Merck silica gel 60 (230–400 mesh) was used, unless otherwise noted. For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} on glass plates, 0.25 mm) were used. For preparative TLC, Merck precoated TLC plates (silica gel 60 F_{254} on glass plates, 0.5 mm) were used.

4.2. General procedure for the double N-arylation reaction (Tables 1 and 2)

Ar was bubbled into a mixture of amine (**1**) (0.250 mmol), dibromobiphenyl (**2**) (85.8 mg, 0.275 mmol), $Pd_2(dba)_3$ (22.9 mg, 0.0250 mmol), ligand (**5**, **6**, **7** or **8**) (0.0750 mmol), and NaO*t*-Bu (72.1 mg, 0.750 mmol) in toluene (1 mL) for 15 min, unless otherwise noted. The mixture was then heated at 120 °C in a sealed tube for 13–24 h (see Tables 1 and 2). After cooling, the mixture was filtrated through a pad of silica gel (3 g, toluene). The filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel: 6 g, toluene/hexane) to afford carbazole **3**.

4.2.1. *N*-Phenylcarbazole (3a)[4a,17] (Table 1, entry 5). The general procedure using 2-(dicyclohexylphosphino)biphenyl (**5**) gave *N*-phenylcarbazole (**3a**) (51.9 mg, 85%) as a colorless solid: R_f=0.37 (toluene/hexane=1:5); mp 89–90 °C (lit.[17] mp 89–90 °C); ^1H NMR δ 7.23–7.31 (m, 2H), 7.37–7.41 (m, 4H), 7.42–7.48 (m, 1H), 7.54–7.62 (m, 4H), 8.14 (d, *J*=7.8 Hz, 1H); ^{13}C NMR δ 109.9, 120.0, 120.4, 123.5, 126.0, 127.3, 127.6, 130.0, 137.9, 141.0; IR (KBr) ν 3020, 1595 cm^{-1}; MS *m*/*z* 243 (M$^+$, 100%), 139 (12), 121 (9); HRMS Calcd for $C_{18}H_{13}N$ (M$^+$): 243.1048. Found: 243.1040. Anal. Calcd for $C_{18}H_{13}N$: C, 88.86; H, 5.39; N, 5.76%. Found: C, 88.89; H, 5.32; N, 5.76%.

4.2.2. *N*-[2-(2′-Bromobiphenyl)]aniline (9) and *N*-(2-biphenyl)aniline (10)[5e]. The general procedure using 2-(dicyclohexylphosphino)biphenyl (**5**) at 60 °C gave *N*-phenylcarbazole (**3a**) (20.1 mg, 33%) and a mixture of mono N-arylation products **9** and **10** (10:1, determined by ^1H NMR, 16.8 mg, 21%). A small amount of the mixture was separated by HPLC (Finepak SIL, JASCO Corp., 4.6 mm i.d., 250 mmL, EtOAc/hexane=1:40, 1.0 mL min^{-1}) to provide compounds **9** (retention time 5.40 min) and **10** (retention time 6.95 min) in pure forms and for use as analytical samples. Data for **9**: R_f=0.53 (toluene/hexane=1:1); mp 84–87 °C; ^1H NMR δ 5.27 (s, 1H), 6.92 (ddd, *J*=7.5, 7.2, <1 Hz, 1H), 6.99 (ddd, *J*=7.8, 7.2, 1.5 Hz, 1H), 7.04 (dd, *J*=7.5, <1 Hz, 1H), 7.15 (dd, *J*=7.8, 1.7 Hz, 1H), 7.20–7.39 (m, 7H), 7.69 (dd, *J*=7.7, 0.9 Hz, 1H); ^{13}C NMR δ 116.6, 119.1, 120.5, 121.6, 124.6, 128.0, 129.0, 129.4, 129.5, 130.5, 130.8, 132.1, 133.3, 139.8, 141.0, 143.0; IR (neat) ν 3010 cm^{-1}; MS *m*/*z* 325 [M$^+$(^{81}Br), 22%], 323 [M$^+$(^{79}Br), 20], 244 (81), 167 (32), 64 (100); HRMS Calcd for $C_{18}H_{14}N^{79}Br$ (M$^+$): 323.0310. Found: 323.0311. Data for **10**: R_f=0.53 (toluene/hexane=1:1); ^1H NMR δ 5.52 (s, 1H), 6.83 (ddd, *J*=7.3, 7.3, 1.2 Hz, 1H), 6.88–6.97 (m, 3H), 7.14–7.19 (m, 4H), 7.29–7.36 (m, 6H); ^{13}C NMR δ 117.6, 118.4, 121.2, 121.2, 127.6, 128.4, 129.0, 129.5, 131.0, 131.7, 139.2, 140.3, 143.5; IR (neat) ν 3405 cm^{-1}; MS *m*/*z* 245 (M$^+$, 100%), 167 (32); HRMS Calcd for $C_{18}H_{15}N$ (M$^+$): 245.1204. Found: 245.1198.

4.2.3. *N*-Benzylcarbazole (3b)[4b,18] (Table 2, entry 4). The general procedure using 2-(di-*tert*-butylphosphino)binaphthyl (**8**) gave *N*-benzylcarbazole (**3b**) (39.0 mg, 60%) as a colorless solid: R_f=0.53 (toluene/hexane=1:1); mp 119–120 °C (lit.[4b] mp 118–120 °C); ^1H NMR δ 5.50 (s, 2H), 7.11–7.14 (m, 2H), 7.22–7.27 (m, 5H), 7.35 (d, *J*=7.3 Hz, 2H), 7.42 (dd, *J*=7.3, 0.9 Hz, 2H), 8.13 (dd, *J*=7.6, 0.9 Hz, 2H); ^{13}C NMR δ 46.7, 109.0, 119.4, 120.5, 123.2, 126.0, 126.6, 127.6, 128.9, 137.3, 140.8; IR (KBr) ν 3030, 2930, 1595, 1450 cm^{-1}; MS *m*/*z* 257 (M$^+$, 100%), 166 (24), 109 (17), 91 (92); HRMS Calcd for $C_{19}H_{15}N$ (M$^+$): 257.1204. Found: 257.1203. Anal. Calcd for $C_{19}H_{15}N\cdot 0.1H_2O$: C, 88.07; H, 5.91; N, 5.41%. Found: C, 88.08; H, 5.89; N, 5.40%.

4.2.4. *N*-(4-Methoxybenzyl)carbazole (3c)[19] (Table 2, entry 5). The general procedure using 2-(di-*tert*-butylphosphino)binaphthyl (**8**) gave *N*-(4-methoxybenzyl)carbazole (**3b**) (51.2 mg, 71%) as a colorless solid: R_f=0.32 (toluene/hexane=1:1); mp 122–123 °C; ^1H NMR δ 3.73 (s, 3H), 5.46 (s, 2H), 6.78 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H), 7.24 (dd, *J*=7.8, 7.4 Hz, 2H), 7.37 (d, *J*=7.6 Hz, 2H), 7.42 (dd, *J*=7.6, 7.4 Hz, 2H), 8.12 (d, *J*=7.8 Hz, 2H); ^{13}C NMR δ 46.2, 55.4, 109.1, 114.3, 119.3, 120.5, 123.1, 125.9, 127.8, 129.4, 140.8, 159.1; IR (KBr) ν 3050, 2835, 1595, 1460 cm^{-1}; LRMS *m*/*z* 287 (M$^+$, 30%), 166 (11), 121 (100), 77 (12); HRMS Calcd for $C_{20}H_{17}NO$ (M$^+$): 287.1310. Found: 287.1300. Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87%. Found: C, 83.43; H, 5.95; N, 4.85%.

4.2.5. *N*-Octylcarbazole (3d)[20] (Table 2, entry 6). The general procedure using 2-(di-*tert*-butylphosphino)binaphthyl (**8**) gave *N*-octylcarbazole (**3d**) (46.5 mg, 67%) as a colorless syrup: R_f=0.50 (toluene/hexane=1:5); ^1H NMR δ 0.86 (t, *J*=6.7 Hz, 3H), 1.24–1.40 (m, 10H), 1.86 (tt, *J*=7.3, 7.3 Hz, 2H), 4.28 (t, *J*=7.3 Hz, 2H), 7.21 (ddd, *J*=7.6, 7.6, 1.2 Hz, 2H), 7.39 (dd, *J*=7.8, 1.2 Hz, 2H), 7.45 (ddd, *J*=7.8, 7.6, 1.0 Hz, 2H), 8.09 (dd, *J*=7.6, 1.0 Hz, 2H); ^{13}C NMR δ 14.2, 22.7, 27.4, 29.1, 29.3, 29.5, 31.9, 43.2, 108.8, 118.8, 120.5, 122.9, 125.7, 140.5; IR (neat) ν 3055, 2925, 1600, 1455 cm^{-1}; MS *m*/*z* 279 (M$^+$, 79%), 245 (19), 180 (100); HRMS Calcd for $C_{20}H_{25}N$ (M$^+$): 279.1987. Found: 279.1982. Anal. Calcd for $C_{20}H_{25}N$: C, 85.97; H, 9.02; N, 5.01%. Found: C, 85.99; H, 8.93; N, 4.91%.

4.2.6. *N*-Cyclohexylcarbazole (3e)[21] (Table 2, entry 7). The general procedure using cyclohexylamine (**1e**) (0.0229 mL, 0.200 mmol), dibromobiphenyl (**2**) (68.6 mg, 0.220 mmol), $Pd_2(dba)_3$ (18.3 mg, 0.0200 mmol), 2-(di-*tert*-butylphosphino)binaphthyl (**8**) (23.9 mg, 0.0600 mmol), NaO*t*-Bu (57.7 mg, 0.600 mmol), and toluene (0.8 mL) gave *N*-cyclohexylcarbazole (**3e**) (40.0 mg, 80%) as a colorless solid: R_f=0.53 (toluene/hexane=1:5); mp 143–144 °C (lit.[21] mp 143 °C); ^{1}H NMR δ 1.31–1.61 (m, 3H), 1.82–1.87 (m, 1H), 1.94–2.04 (m, 4H), 2.33–2.47 (m, 2H), 4.49 (tt, J=12.3, 3.9 Hz, 1H), 7.20 (dd, J=7.8, 7.6 Hz, 2H), 7.43 (ddd, J=8.1, 7.6, 1.2 Hz, 2H), 7.56 (d, J=8.1 Hz, 2H), 8.10 (dd, J=7.6, 1.2 Hz, 2H); ^{13}C NMR δ 25.8, 26.7, 30.9, 55.5, 110.4, 118.6, 120.4, 123.4, 125.4, 139.8; IR (KBr) ν 3055, 2920, 1590, 1455 cm^{-1}; MS *m*/*z* 249 (M^+, 100%), 206 (43), 167 (92); HRMS Calcd for $C_{18}H_{19}N$ (M^+): 249.1517. Found: 249.1517. Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62%. Found: C, 86.48; H, 7.60; N, 5.58%.

4.2.7. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosylamine (1f). To a suspension of NaH (39 mg, 1.63 mmol) in DMF (2 mL) was slowly added 4,6-*O*-benzylidene-β-D-glucopyranosylazide[22] (120 mg, 0.409 mmol) at 0 °C. After stirring at rt for 5 min, the reaction mixture was cooled to 0 °C. To this mixture was slowly added benzyl bromide (0.15 mL, 1.26 mmol), and the mixture was stirred at rt for 2 h. After addition of MeOH at 0 °C, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 6 g, EtOAc/hexane=1:20) to afford 2,3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosylazide (176 mg, 90%) as a white solid: R_f=0.88 (EtOAc/toluene=1:2); mp 112 °C; $[\alpha]_D^{27}$ +69.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 3.36 (dd, J=8.7, 8.4 Hz, 1H), 3.42 (ddd, J=9.9, 9.6, 4.8 Hz, 1H), 3.64 (dd, J=9.6, 9.3 Hz, 1H), 3.69 (dd, J=10.5, 9.9 Hz, 1H), 3.75 (dd, J=9.3, 8.7 Hz, 1H), 4.32 (dd, J=10.5, 4.8 Hz, 1H), 4.65 (d, J=8.4 Hz, 1H), 4.77 and 4.92 (2d, J=11.4 Hz, each 1H), 4.81 (s, 2H), 5.52 (s, 1H), 7.25–7.33 (m, 13H), 7.45–7.48 (m, 2H); ^{13}C NMR δ 68.1, 68.4, 75.2, 75.7, 81.2, 81.3, 81.4, 90.6, 101.2, 126.0, 127.8, 128.0, 128.1, 128.3, 128.3, 128.4, 128.5, 129.1, 137.1, 137.7, 138.2; IR ν 2115 cm^{-1}; MS *m*/*z* 473 (M^+, 1%), 431 (1), 382 (18), 91 (100); HRMS Calcd for $C_{27}H_{27}N_3O_5$ (M^+): 473.1951. Found: 473.1960. Anal. Calcd for $C_{27}H_{27}N_3O_5$: C, 68.48; H, 5.75; N, 8.87%. Found: C, 68.51; H, 5.86; N, 8.64%.

To a solution of 2,3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosylazide (136 mg, 0.287 mmol) in toluene (4 mL) was added Lindlar catalyst (70 mg). The reaction mixture was stirred for 12 h under H_2 atmosphere (1 atm) at rt. Then the catalyst was removed by filtration through Celite and the filtrate was concentrated to give a residue, which was recrystallized from EtOH to afford glucosylamine **1g** (98.5 mg, 76%) as a white solid: R_f=0.34 (EtOAc/toluene=1:2); mp 111–112 °C (decomp.); $[\alpha]_D^{27}$ −38.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.91 (br s, 2H), 3.21 (dd, J=8.6, 8.6 Hz, 1H), 3.42 (ddd, J=9.6, 9.3, 5.0 Hz, 1H), 3.65 (dd, J=9.3, 9.1 Hz, 1H), 3.71 (dd, J=10.4, 9.6 Hz, 1H), 3.80 (dd, J=9.1, 8.6 Hz, 1H), 4.22 (d, J=8.6 Hz, 1H), 4.32 (dd, J=10.4, 5.0 Hz, 1H), 4.80 and 4.94 (2d, J=11.4 Hz, each 1H), 4.84 and 4.92 (2d, J=10.5 Hz, each 1H), 5.56 (s, 1H), 7.26–7.38 (m, 13H), 7.47–7.51 (m, 2H); ^{13}C NMR δ 67.3, 69.0, 75.2, 75.5, 82.1, 82.1, 86.8, 101.1, 126.1, 127.8, 127.9, 128.2, 128.3, 128.3, 128.4, 128.5, 129.0, 137.5, 138.3, 138.6; IR ν 3400, 3335 cm^{-1}; MS *m*/*z* 447 (M^+, 1%), 356 (2), 248 (37), 91 (100); HRMS Calcd for $C_{27}H_{29}NO_5$ (M^+): 447.2046. Found: 447.2056. Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13%. Found: C, 72.32; H, 6.55; N, 2.74%.

4.2.8. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α- and β-D-glucopyranosylcarbazole (3f) (Table 2, entry 8). Ar gas was bubbled into a mixture of glucosylamine (**1f**) (20 mg, 0.0447 mmol), dibromobiphenyl (**2**) (42.0 mg, 0.135 mmol), $Pd_2(dba)_3$ (41 mg, 0.0447 mmol), 2-(di-*tert*-butylphosphino)-binaphthyl (**8**) (53.0 mg, 0.133 mmol), and NaO*t*-Bu (12.9 mg, 0.134 mmol) in toluene (0.8 mL) for 15 min. The reaction mixture was then heated at 60 °C in a sealed tube for 24 h. After cooling, the mixture was purified by column chromatography (silica gel: 2 g, EtOAc/hexane=1:40) to afford an anomeric mixture of glucosylcarbazole (**3f**). The mixture was separated by preparative TLC using EtOAc/hexane=1:8 as an eluent to give α-anomer (**3fα**)[9] (5.1 mg, 19%) as a colorless syrup and β-anomer (**3fβ**) (8.9 mg, 33%) as a colorless syrup. Data for **3fα**: R_f=0.23 (EtOAc/hexane=1:8); $[\alpha]_D^{21}$ −14.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 3.50 (dd, J=10.5, 10.2 Hz, 1H), 3.73 and 3.83 (2d, J=11.9 Hz, each 1H), 3.93 (br d, J=1.8 Hz, 1H), 4.02–4.07 (m, 2H), 4.30 (dd, J=10.5, 5.1 Hz, 1H), 4.42 and 4.53 (2d, J=12.2 Hz, each 1H), 4.60–4.71 (m, 1H), 5.39 (s, 1H), 6.47 (d, J=1.8 Hz, 1H), 6.54 (d, J=6.3 Hz, 2H), 6.81–6.90 (m, 4H), 7.11–7.36 (m, 11H), 7.65 (br d, J=7.8 Hz, 4H), 8.03 (d, J=7.5 Hz, 2H); IR (neat) ν 3030, 2920, 1455 cm^{-1}; MS *m*/*z* 597 (M^+, 13%), 167 (23), 91 (100); HRMS Calcd for $C_{39}H_{35}NO_5$ (M^+): 597.2515. Found: 597.2522. Data for **3fβ**: R_f=0.20 (EtOAc/hexane=1:8); $[\alpha]_D^{25}$ +31.7 (*c* 0.97, $CHCl_3$); ^{1}H NMR δ 3.35 (d, J=10.0 Hz, 1H), 3.79 (m, 1H), 3.93 (dd, J=10.5, 10.2 Hz, 1H), 4.00–4.08 (m, 2H), 4.06 (d, J=10.0 Hz, 1H), 4.40 (dd, J=8.8, 8.8 Hz, 1H), 4.46 (dd, J=10.5, 4.9 Hz, 1H), 4.83 (d, J=11.2 Hz, 1H), 5.00 (d, J=11.2 Hz, 1H), 5.73 (s, 1H), 5.88 (d, J=8.8 Hz, 1H), 6.34 (d, J=7.6 Hz, 2H), 6.93 (dd, J=7.6, 7.6 Hz, 2H), 7.05 (dd, J=7.6, 7.6 Hz, 1H), 7.28–7.64 (m, 16H), 8.09 (d, J=7.6 Hz, 2H); ^{13}C NMR δ 68.9, 69.4, 75.2, 75.6, 78.8, 82.0, 82.4, 85.5, 101.5, 109.8, 112.8, 120.4, 126.2, 127.8, 127.9, 128.1, 128.2, 128.5, 128.6, 129.2, 136.7, 137.4, 138.5; IR (neat) ν 3030, 2875, 1455 cm^{-1}; MS *m*/*z* 597 (M^+, 6%), 167 (12), 91 (100); HRMS Calcd for $C_{39}H_{35}NO_5$ (M^+): 597.2515. Found: 597.2513.

4.2.9. *N*-*tert*-Butylcarbazole (3g) (Table 2, entry 10). The general procedure using 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl (**6**) gave *N*-(*tert*-butyl)carbazole (**3g**) (23.6 mg, 42%) as a colorless solid: R_f=0.38 (toluene/hexane=1:5); mp 122–123 °C; ^{1}H NMR δ 2.00 (s, 9H), 7.19 (ddd, J=7.8, 7.1, 0.7 Hz, 2H), 7.37 (ddd, J=8.7, 7.1, 1.5 Hz, 2H), 7.86 (dd, J=8.7, 0.7 Hz, 2H), 8.10 (dd, J=7.8, 1.5 Hz, 2H); ^{13}C NMR δ 31.2, 59.2, 113.9, 118.6, 120.0, 124.6, 125.2, 140.6; IR (KBr) ν 3050, 2970, 1590, 1440 cm^{-1}; MS *m*/*z* 223 (M^+, 17%), 167 (100), 140 (16); HRMS Calcd for $C_{16}H_{17}N$ (M^+): 223.1361. Found: 223.1359. Anal. Calcd for $C_{16}H_{17}N\cdot 0.1H_2O$: C, 85.37; H, 7.70; N, 6.22%. Found: C, 85.34; H, 7.63; N, 6.29%.

4.3. Synthesis of murrastifoline-A

4.3.1. 4-Toluenesulfonic acid 2-amino-5-methylphenyl ester[13] (14). To a solution of 2-amino-5-methylphenol (**13**, 3 g, 24.4 mmol) in CH_2Cl_2 (45 ml) were added Et_3N (3.74 ml, 26.8 mmol) and TsCl (5.11 g, 26.6 mmol) at 0 °C. After stirring at 0 °C for 15 min, the reaction mixture was extracted with $CHCl_3$ and washed with H_2O. The organic layer was dried and concentrated to give a residue, which was recrystallized from Et_2O to afford tosylate **14** (6.04 g, 89%) as a brown solid: R_f=0.23 (EtOAc/petroleum ether=1:5); mp 81–82 °C (lit.[13b] 81–82 °C); ^{1}H NMR δ 2.15 (s, 3H), 2.46 (s, 3H), 3.64 (br s, 2H), 6.61 and 6.83 (2d, J=8.0 Hz, each 1H), 6.66 (s, 1H), 7.33 and 7.78 (2d, J=8.3 Hz, each 2H); MS m/z 277 (M^+, 41%), 122 (100), 94 (89); HRMS Calcd for $C_{14}H_{15}NO_3S$ (M^+): 277.0773. Found: 277.0773. Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05%. Found: C, 60.46; H, 5.42; N, 4.83%.

4.3.2. 4-Toluenesulfonic acid 2-amino-3-iodo-5-methylphenyl ester (15). To a solution of tosylate **14** (2.00 g, 7.21 mmol) in DMF (40 mL) was slowly added NIS (1.78 g, 7.93 mmol) at 0 °C. The reaction mixture (protected from light) was stirred for 3 h at rt, then diluted with Et_2O, and washed with 30 wt % of aqueous $Na_2S_2O_3$ solution and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 60 g, EtOAc/petroleum ether=1:7) to afford iodide **15** (2.01 g, 69%) as an orange solid: R_f=0.45 (EtOAc/petroleum ether=1:5); mp 141–142 °C; ^{1}H NMR δ 2.13 (s, 3H), 2.47 (s, 3H), 4.06 (br s, 2H), 6.69 (s, 1H), 7.34 (s, 1H), 7.35 and 7.78 (2d, J=8.3 Hz, each 2H); ^{13}C NMR δ 19.9, 21.8, 84.6, 123.7, 128.5, 129.0, 130.0, 132.6, 135.2, 137.7, 138.4, 145.9; IR (neat) ν 3460 cm^{-1}; MS m/z 403 (M^+, 18%), 248 (100), 121 (12); HRMS Calcd for $C_{14}H_{14}NO_3IS$ (M^+): 402.9739. Found: 402.9741. Anal. Calcd for $C_{14}H_{14}NO_3IS$: C, 41.70; H, 3.50; N, 3.47%. Found: C, 41.93; H, 3.66; N, 3.26%.

4.3.3. 2-Amino-2′-bromo-5-methyl-3-(4-toluenesulfonyloxy)-1,1′-biphenyl (16). To a solution of $Pd(PPh_3)_4$ (22.8 mg, 0.0198 mmol) in benzene (1 mL) was added iodide (**15**) (200 mg, 0.495 mmol) in benzene (5 mL) under Ar. Then, 2 M aqueous Na_2CO_3 solution (1.9 mL, 3.96 mmol) and 2-bromophenylboronic acid (120 mg, 0.595 mmol) in EtOH (2.4 mL) were added to the mixture. The reaction mixture was heated at reflux for 2 h under vigorous stirring. After cooling, the mixture was diluted with Et_2O and washed with brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 10 g, EtOAc/hexane=1:10) to afford biphenyl **16** (213 mg, 99%) as a pale yellow syrup; R_f=0.37 (EtOAc/petroleum ether=1:5); ^{1}H NMR δ 2.22 (s, 3H), 2.44 (s, 3H), 3.42 (s, 2H), 6.72 and 6.91 (2d, J=1.2 Hz, each 1H), 7.22 (2ddd, J=8.4, 7.5, 1.2 Hz, each 1H), 7.31 and 7.79 (2d, J=8.4 Hz, each 2H), 7.36 (dd, J=7.5, 1.2 Hz, 1H), 7.63 (dd, J=8.4, 1.2 Hz, 1H); ^{13}C NMR δ 20.2, 21.6, 122.8, 123.7, 126.8, 127.7, 128.4, 128.7, 129.0, 129.4, 129.6, 131.4, 132.5, 132.9, 134.5, 136.7, 138.7, 145.3; IR (neat) ν 3480 cm^{-1}; MS m/z 433 [M(^{81}Br)$^+$, 11%], 431 [M(^{79}Br)$^+$, 11], 278 (58), 276 (59), 197 (100); HRMS Calcd for $C_{20}H_{18}NO_3^{81}BrS$ (M^+): 433.0170. Found: 433.0169. Anal. Calcd for $C_{20}H_{18}NO_3BrS$: C, 55.56; H, 4.20; N, 3.24%. Found: C, 55.33; H, 4.28; N, 3.02%.

4.3.4. 2,2′-Dibromo-5-methyl-3-(4-toluenesulfonyloxy)-1,1′-biphenyl (17). To a solution of aminobromobiphenyl **16** (128 mg, 0.197 mmol) in AcOH (2.5 mL) was slowly added $NaNO_2$ (40.9 mg, 0.593 mmol) in concd H_2SO_4 (0.04 mL) at 0 °C, then the mixture was stirred for 1 h at rt. The reaction mixture was slowly added to CuBr (85.1 mg, 0.593 mmol) in 47 wt % aqueous HBr solution (1.7 mL) at 80 °C, and stirred for 1.5 h at 80 °C. After cooling, the reaction mixture was extracted with Et_2O and washed successively with 1 M aqueous NaOH solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 15 g, EtOAc/petroleum ether=1:20) to afford dibromobiphenyl **17** as white crystals: R_f=0.43 (EtOAc/petroleum ether=1:5); mp 163 °C; ^{1}H NMR δ 2.05 (s, 3H), 2.46 (s, 3H), 6.62 (s, 1H), 7.09 (s, 1H), 7.20 (d, J=6.9 Hz, 2H), 7.26–7.43 (m, 4H), 7.65 and 7.81 (2dd, J=8.1, <1 Hz, each 1H); ^{13}C NMR δ 21.4, 21.9, 118.8, 120.2, 123.5, 124.0, 128.1, 128.8, 129.7, 130.5, 130.8, 133.5, 139.9, 141.5, 143.3, 150.0; IR (neat) ν 2920, 1600, 1580 cm^{-1}; MS m/z 498 [M(^{81}Br$_2$)$^+$, 14%], 496 [M(^{81}Br,^{79}Br)$^+$, 24], 494 [M(^{79}Br$_2$)$^+$, 12], 416 (22), 414 (18), 343 (12), 341 (23), 339 (12), 335 (23), 155 (100); HRMS Calcd for $C_{20}H_{16}O_3^{79}Br_2S$ (M^+): 493.9187. Found: 493.9183.

4.3.5. 2,2′-Dibromo-5-methyl-1,1′-biphenyl-3-ol (18). To a solution of tosylate **17** (47.8 mg, 0.0963 mmol) in EtOH (4 mL) was added 1 M aqueous KOH solution (0.3 mL) at rt. The reaction mixture was heated at reflux for 1 h. After cooling, the mixture was extracted with Et_2O and washed with 10 wt % aqueous citric acid solution and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 3 g, Et_2O/petroleum ether=1:10) to afford hydroxybiphenyl **18** (25 mg, 76%) as a light yellow oil; R_f=0.48 (EtOAc/petroleum ether=1:5); ^{1}H NMR δ 2.33 (s, 3H), 5.62 (s, 1H), 6.65 (d, J=1.7 Hz, 1H), 6.90 (d, J=1.7 Hz, 1H), 7.21–7.28 (m, 2H), 7.40 (ddd, J=7.5, 7.5, 1.2 Hz, 1H), 7.66 (dd, J=7.5, 1.2 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.2, 108.7, 116.0, 123.5, 123.6, 127.3, 129.5, 130.9, 132.7, 138.8, 141.9, 142.3, 152.2; IR (neat) ν 3500 cm^{-1}; MS m/z 344 [M(^{81}Br$_2$)$^+$, 49%], 342 [M(^{81}Br,^{79}Br)$^+$, 100], 340 [M(^{79}Br$_2$)$^+$, 51], 263 (58), 261 (58), 182 (93); HRMS Calcd for $C_{13}H_{10}O^{79}Br_2$ (M^+): 339.9099. Found: 339.9102.

4.3.6. 2,2′-Dibromo-3-methoxy-5-methyl-1,1′-biphenyl (11). To a solution of hydroxylbiphenyl **18** (4.7 mg, 0.0137 mmol) in DMF (0.5 mL) were added NaH (1.1 mg, 0.0275 mmol) and MeI (1.7 μL, 0.0275 mmol) at 0 °C. After stirring at 0 °C for 45 min, the reaction mixture was quenched with MeOH. The mixture was extracted with Et_2O and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 0.4 g, EtOAc/petroleum ether=1:50) to give methoxybiphenyl (**11**) (3.7 mg, 77%) as a colorless oil; R_f=0.66 (EtOAc/petroleum ether=1:5); ^{1}H NMR δ 2.01 (s, 3H), 3.27 (s, 3H), 6.32 (d, J=1.6 Hz, 2H), 6.54 (d, J=1.6 Hz, 1H), 6.78 (ddd, J=7.5, 7.4, 1.8 Hz, 1H), 6.96 (ddd, J=7.4, 7.3, 1.2 Hz, 1H), 7.10 (dd, J=7.3, 1.8 Hz, 1H), 7.48 (dd, J=7.5, 1.2 Hz, 1H); ^{13}C NMR δ 21.3, 55.7, 110.7, 112.3, 123.9, 124.1, 127.2, 129.3,

131.3, 132.9, 138.0, 143.1, 144.0, 156.6; IR (neat) ν 2940, 1580 cm^{-1}; MS *m/z* 358 [M($^{81}Br_2$)$^+$, 49%], 356 [M(^{81}Br,^{79}Br)$^+$, 100], 354 [M($^{79}Br_2$)$^+$, 51], 277 (77), 275 (79), 196 (43), 181 (42), 165 (22); HRMS Calcd for $C_{14}H_{12}O_2^{79}Br_2$ (M^+): 353.9255. Found: 353.9254.

4.3.7. 4-Toluenesulfonic acid 5-methyl-2-[(4-nitrophenyl)-amino]phenyl ester (19). Ar gas was bubbled into a mixture of amine (**14**) (125 mg, 0.450 mmol), 4-bromonitrobenzene (137 mg, 0.678 mmol), $Pd_2(dba)_3$ (82 mg, 0.0895 mmol), *rac*.-BINAP (168 mg, 0.269 mmol), and NaO*t*-Bu (64.5 mg, 0.671 mmol) in toluene (5 mL) for 15 min. The reaction mixture was then heated at 120 °C in a sealed tube for 15 h. After cooling, the mixture was filtered through Celite. The filtrate concentrated to give a residue, which was purified by column chromatography (silica gel: 15 g, EtOAc/petroleum ether=1:10) to afford diarylamine **19** (233 mg, 81%) as a yellow solid; R_f=0.31 (EtOAc/petroleum ether=1:5); mp 108–109 °C; ^{1}H NMR δ 2.31 (s, 3H), 2.32 (s, 3H), 6.34 (br s, 1H), 6.68 (d, *J*=8.4 Hz, 2H), 7.00 (s, 1H), 7.08 and 7.25 (2d, *J*=7.5 Hz, each 1H), 7.16 (d, *J*=7.7 Hz, 2H), 7.65 (d, *J*=7.7 Hz, 2H), 8.03 (d, *J*=8.4 Hz, 2H); ^{13}C NMR δ 21.0, 21.8, 113.8, 123.4, 125.1, 126.0, 128.4, 128.8, 129.9, 130.2, 132.0, 135.8, 140.0, 141.7, 146.0, 149.6; IR (neat) ν 3380, 1500, 1325 cm^{-1}; MS *m/z* 398 (M^+, 36%), 243 (100), 226 (38), 197 (57); HRMS Calcd for $C_{20}H_{18}N_2O_5S$ (M^+): 398.0937. Found: 398.0937.

4.3.8. 3-Methyl-6-nitro-1-(4-toluenesulfonyloxy)carbazole (20). To a solution of diarylamine **19** (142 mg, 0.355 mmol) in AcOH (14 mL) was added $Pd(OAc)_2$ (319 mg, 1.42 mmol) at rt. The reaction mixture was heated at reflux for 5 h. After cooling, the mixture was filtered through a pad of Celite. The filtrate was extracted with Et_2O and washed with H_2O, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 14 g, EtOAc/petroleum ether=1:7) to afford carbazole **20** (75 mg, 53%) as a yellow solid: R_f=0.23 (EtOAc/petroleum ether=1:5); mp 224–225 °C; ^{1}H NMR δ 2.41 (s, 3H), 2.47 (s, 3H), 6.71 (s, 1H), 7.35 (d, *J*=8.3 Hz, 2H), 7.47 (d, *J*=9.0 Hz, 1H), 7.78 (d, *J*=8.3 Hz, 2H), 7.80 (s, 1H), 8.37 (dd, *J*=9.0, 2.0 Hz, 1H), 8.94 (br s, 1H), 8.94 (d, *J*=2.0 Hz, 1H); ^{13}C NMR δ 21.4, 21.9, 111.1, 117.6, 119.9, 122.0, 122.5, 122.8, 126.4, 128.8, 130.1, 131.5, 131.6, 131.9, 134.3, 141.6, 143.2, 146.3; IR (neat) ν 3370, 1520, 1320 cm^{-1}; MS *m/z* 396 (M^+, 10%), 348 (11), 330 (31), 241 (34), 197 (100); HRMS Calcd for $C_{20}H_{16}N_2O_5S$ (M^+): 396.0780. Found: 396.0780.

4.3.9. *N*-[2-(Trimethylsilyl)ethoxymethyl]-3-methyl-6-nitro-1-(4-toluenesulfonyloxy)carbazole (21). To a solution of carbazole **20** (779 mg, 1.96 mmol) in DMF (40 mL) was added NaH (70.7 mg, 2.95 mmol) at 0 °C. After stirring at 0 °C for 1 h, to the mixture was added 2-(trimethylsilyl) ethoxymethyl chloride (SEMCl) (0.42 mL, 2.39 mmol) and the mixture was stirred at 0 °C for 1.5 h. After addition of MeOH, the mixture was diluted with EtOAc and washed successively with water, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 50 g, EtOAc/hexane=1:7) to afford SEM protected carbazole **21** (884 mg, 86%) as a yellow solid: R_f=0.37 (EtOAc/petroleum ether=1:5); ^{1}H NMR δ −0.13 (s, 9H), 0.84 (t, *J*=7.6 Hz, 2H), 2.43 (s, 3H), 2.48 (s, 3H), 3.49 (t, *J*=7.6 Hz, 2H), 5.89 (s, 2H), 6.87 (s, 1H), 7.38 (d, *J*=7.7 Hz, 2H), 7.57 (d, *J*=8.6 Hz, 1H), 7.82 (s, 1H), 7.83 (d, *J*=7.7 Hz, 2H), 8.38 (dd, *J*=8.6, 2.0 Hz, 1H), 8.93 (d, *J*=2.0 Hz, 1H); ^{13}C NMR δ −1.4, 17.7, 21.2, 21.9, 66.2, 74.0, 110.4, 117.1, 119.7, 122.2, 122.3, 122.9, 126.7, 128.8, 130.1, 131.4, 131.7, 132.7, 135.1, 141.9, 144.7, 146.2; IR (neat) ν 1520, 1330 cm^{-1}; MS *m/z* 526 (M^+, 27%), 468 (11), 313 (26), 261 (25), 73 (100); HRMS Calcd for $C_{26}H_{30}N_2O_6SSi$ (M^+): 526.1594. Found: 526.1558.

4.3.10. *N*-[2-(Trimethylsilyl)ethoxymethyl]-3-methyl-6-nitrocarbazol-1-ol (22). To a solution of tosylate **21** (38.3 mg, 0.0727 mmol) in MeOH (3.8 mL) was added 1 M aqueous NaOH solution (0.2 mL). The reaction mixture was heated at reflux for 1 h. After cooling, the products were extracted with Et_2O and the organic layer was washed with 10 wt % aqueous citric acid solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 2.5 g, EtOAc/petroleum ether=1:10) to give hydroxycarbazole **22** (20.6 mg, 76%) as a yellow solid and methoxycarbazole **23** (2.2 mg, 8%) as a yellow solid. Data for **22**: R_f=0.28 (EtOAc/petroleum ether=1:5); mp 172 °C; ^{1}H NMR δ −0.04 (s, 9H), 1.02 (t, *J*=8.4 Hz, 2H), 2.50 (s, 3H), 3.73 (t, *J*=8.4 Hz, 2H), 5.81 (s, 2H), 6.94 (s, 1H), 7.43 (d, *J*=9.0 Hz, 1H), 7.51 (s, 1H), 7.73 (s, 1H), 8.36 (dd, *J*=9.0, 2.3 Hz, 1H), 8.93 (d, *J*=2.3 Hz, 1H); ^{13}C NMR δ −1.4, 18.0, 21.5, 66.8, 74.2, 108.4, 113.0, 117.1, 117.6, 122.0, 123.7, 126.0, 128.6, 133.5, 141.4, 142.8, 143.8; IR (neat) ν 3240, 1520, 1320 cm^{-1}; MS *m/z* 372 (M^+, 6%), 314 (14), 254 (23), 75 (100); HRMS Calcd for $C_{19}H_{24}N_2O_4Si$ (M^+): 372.1505. Found: 372.1508.

4.3.11. *N*-[2-(Trimethylsilyl)ethoxymethyl]-1-methoxy-3-methyl-6-nitro-carbazole (23). To a solution of hydroxycarbazole **22** (13.6 mg, 0.0365 mmol) in DMF (1.3 mL) were added NaH (1.8 mg, 0.0750 mmol) and MeI (5 μL, 0.080 mmol) at 0 °C. After stirring for 50 min at 0 °C, the reaction was quenched by addition of MeOH. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 2 g, EtOAc/petroleum ether=1:50) to give methoxycarbazole **23** (14.1 mg, 100%) as a light yellow solid: R_f=0.51 (EtOAc/petroleum ether=1:5); mp 113 °C; ^{1}H NMR δ −0.11 (s, 9H), 0.87 (t, *J*=7.8 Hz, 2H), 2.54 (s, 3H), 3.57 (t, *J*=7.8 Hz, 2H), 4.02 (s, 3H), 6.05 (s, 2H), 6.85 (s, 1H), 7.53 (s, 1H), 7.57 (d, *J*=8.6 Hz, 1H), 8.34 (dd, *J*=8.6, 2.4 Hz, 1H), 8.93 (d, *J*=2.4 Hz, 1H); ^{13}C NMR δ −1.3, 18.0, 21.9, 55.7, 65.9, 74.7, 110.1, 110.8, 113.2, 117.3, 121.6, 123.5, 125.1, 129.1, 132.0, 141.5, 144.4, 146.8; IR (neat) ν 1515, 1330 cm^{-1}; MS *m/z* 386 (M^+, 12%), 309 (7), 75 (100); HRMS Calcd for $C_{20}H_{26}N_2O_4Si$ (M^+): 386.1662. Found: 386.1658.

4.3.12. *N*-[2-(Trimethylsilyl)ethoxymethyl]-8-methoxy-6-methyl-carbazol-3-amine (12). To a solution of nitrocarbazole **23** (18.0 mg, 0.0466 mmol) in THF (1.0 mL) at 0 °C was added a THF solution of $NaBH_2S_3$[16] [prepared by stirring a mixture of $NaBH_4$ (11 mg, 0.279 mmol) and sulfur

(31 mg, 0.978 mmol) in THF (0.8 mL) under Ar at rt for 40 min] under Ar. The reaction mixture was heated at reflux for 30 min. After cooling, the products were extracted with Et_2O and the organic layer was washed with H_2O and 1 M aqueous NaOH solution, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel: 2 g, EtOAc/petroleum ether=1:3) to give carbazolamine **12** (13.9 mg, 84%) as a light yellow oil: R_f=0.08 (EtOAc/petroleum ether=1:5); ^{1}H NMR δ −0.12 (s, 9H), 0.85 (t, J=8.1 Hz, 2H), 2.49 (s, 3H), 3.20–3.80 (br s, 2H), 3.53 (t, J=8.1 Hz, 2H), 3.97 (s, 3H), 5.95 (s, 2H), 6.72 (s, 1H), 6.87 (dd, J=8.4, 2.1 Hz, 1H), 7.31 (d, J=2.1 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 7.37 (s, 1H); ^{13}C NMR δ −1.3, 18.0, 21.8, 55.5, 65.1, 74.3, 105.8, 109.1, 110.9, 112.8, 115.8, 124.5, 125.0, 128.6, 129.2, 136.0, 139.7, 146.7; IR (neat) δ 3350, 2950 cm^{-1}; MS m/z 356 (M^+, 14%), 239 (11), 226 (15), 149 (17), 75 (100); HRMS Calcd for $C_{20}H_{28}N_2O_2Si$ (M^+): 356.1920. Found: 356.1922.

4.3.13. 1′,8-Dimethoxy-3′,6-dimethyl-9-[2-(trimethylsilyl) ethoxymethyl]-3,9′-bi-9*H*-carbazole (*N*-SEM-murrastifoline-A) (24). Ar gas was bubbled into a mixture of dibromobiphenyl **11** (17.2 mg, 0.0483 mmol), carbazolamine **12** (15.2 mg, 0.0426 mmol), $Pd_2(dba)_3$ (7.8 mg, 0.0085 mmol), 2-(dicyclohexylphosphino)biphenyl (**5**) (9.2 mg, 0.0262 mmol), and NaO*t*-Bu (8.2 mg, 0.0852 mmol) in toluene (0.6 mL) for 10 min. The reaction mixture was then heated at 120 °C in a sealed tube for 24 h. After cooling, the mixture was purified by column chromatography (silica gel: 2 g, EtOAc/hexane=1:30) to afford SEM protected murrastifoline-A (**24**) (13.6 mg, 58%) as a colorless syrup: R_f=0.64 (EtOAc/petroleum ether=1:5); ^{1}H NMR δ −0.07 (s, 9H), 0.93 (t, J=7.5 Hz, 2H), 2.50 (s, 3H), 2.55 (s, 3H), 3.55 (s, 3H), 3.65 (t, J=7.5 Hz, 2H), 4.03 (s, 3H), 6.09 (d, J=3.9 Hz, 2H), 6.74 (d, J=0.6 Hz, 1H), 6.81 (d, J=0.6 Hz, 2H), 7.18 (d, J=7.9 Hz, 1H), 7.22 (ddd, J=7.9, 7.9, 1.2 Hz, 1H), 7.32 (ddd, J=7.9, 7.9, 1.2 Hz, 1H), 7.42 (s, 1H), 7.47 (dd, J=8.7, 1.8 Hz, 1H), 7.60 (s, 1H), 7.62 (d, J=8.7 Hz, 1H), 8.04 (d, J=1.8 Hz, 1H), 8.08 (d, J=7.8 Hz, 1H); ^{13}C NMR δ −1.3, 18.1, 21.8, 21.9, 55.7, 56.1, 65.5, 74.5, 109.5, 109.8, 110.1, 110.5, 112.9, 112.9, 119.4, 119.9, 120.1, 123.1, 123.2, 123.6, 125.4, 125.7, 126.4, 128.6, 129.4, 129.7, 130.2, 132.2, 140.4, 143.2, 146.8, 146.9; IR (neat) ν 2950, 1500 cm^{-1}; MS m/z 550 (M^+, 1%), 433 (1), 405 (1), 359 (1), 167 (12), 129 (18), 59 (100); HRMS Calcd for $C_{34}H_{38}N_2O_3Si$ (M^+): 550.2652. Found: 550.2657.

4.3.14. 1′,8-Dimethoxy-3′,6-dimethyl-3,9′-bi-9*H*-carbazole (murrastifoline-A) (4). To a solution of SEM protected murrastifoline-A (**24**, 6.2 mg, 0.011 mmol) in THF (0.2 mL) and EtOH (0.6 mL) was added 4 M aqueous HCl solution (0.3 mL) at rt. The reaction mixture was heated at reflux for 1.5 h. After cooling, the mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried and concentrated to give a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/petroleum ether=1:10) to give murrastifoline-A (**4**) (4.4 mg, 94%) as a colorless oil: R_f=0.30 (EtOAc/petroleum ether=1:5); ^{1}H NMR (acetone-d_6) δ 2.48 (s, 3H), 2.51 (s, 3H), 3.56 (s, 3H), 4.02 (s, 3H), 6.84 (s, 1H), 6.88 (s, 1H), 7.15 (d, J=8.4 Hz, 1H), 7.20 (ddd, J=8.1, 7.8, 1.2 Hz, 1H), 7.32 (ddd, J=8.4, 7.8, 1.2 Hz, 1H), 7.40 (dd, J=8.4, 2.1 Hz, 1H), 7.54 (s, 1H), 7.62 (s, 1H), 7.66 (d, J=8.4 Hz, 1H), 8.09 (d, J=2.1 Hz, 1H), 8.13 (d, J=8.1 Hz, 1H), 10.45 (s, 1H); ^{13}C NMR (acetone-d_6) δ 21.7, 21.9, 55.9, 56.1, 108.8, 110.7, 111.1, 111.7, 113.4, 113.4, 120.2, 120.5, 120.8, 123.9, 124.0, 125.1, 126.0, 126.4, 126.6, 129.9, 130.0, 130.1, 130.4, 132.0, 140.0, 144.0, 146.7, 147.8; IR (neat) ν 3420 cm^{-1}; MS m/z 420 (M^+, 6%), 270 (14), 252 (2), 58 (100); HRMS Calcd for $C_{28}H_{24}N_2O_2$ (M^+): 420.1838. Found: 420.1838.

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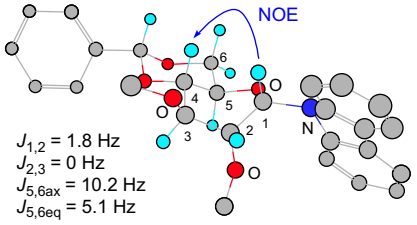

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