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A synthetic approach to carbazoles using electrochemically generated hypervalent iodine oxidant

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ABSTRACT

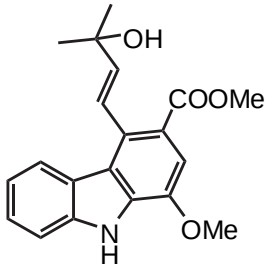
Carbazoles were successfully synthesized by oxidative cyclization of the corresponding diaryl derivatives using electrochemically generated hypervalent iodine oxidant. Electron-withdrawing nitro and donating methoxy groups at the *para* position of the acetamide group interfered with cyclization. Glycozoline (**8**) was successfully synthesized in five steps with 50% overall yield.

1. Introduction

In our previous synthetic investigation of biologically active substances, we developed an electrochemically generated hypervalent iodine, which possesses comparable or superior properties to commercially available oxidants, such as PIFA [Phenyliodine(III) bis(trifluoroacetate)].[1] Application of the oxidant to alkoxyamides carrying aromatic moieties has provided ready accessibility to quinolinone and azaspiro derivatives (Eq. 1).[1]

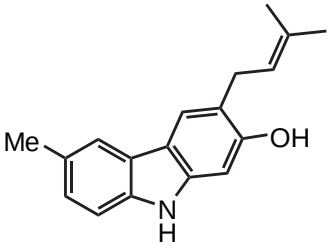
In particular, the former was successfully converted into a series of tetrahydropyrroloiminoquinone-class marine alkaloids.[2] To further pursue its scope and limitation as an oxidant, we developed an oxidative cyclization approach to carbazole synthesis (Eq. 2, Fig. 1).

The relatively rigid tricyclic structure concomitant with biological activity[3] prompted the development of a number of synthetic methodologies, such as $Pd(OAc)_2$-mediated cyclization of diphenylamine,[4] Diels–Alder reaction,[5] allene-mediated electrocyclic reaction,[6] coupling of indole derivatives with unsaturated ketones or Vilsmeier reagent,[7] $AlCl_3$-mediated cyclization of diaryl amine phthalimide,[8] oxidative iron-mediated arylamine cyclization,[9] and radical cyclization of sulfonamide.[10] However, we adopted construction of carbazoles through a nitrenium ion intermediate or its equivalent. In addition to well-known nucleophilic substitution at the carbon adjacent to the nitrogen function (Eq. 3),[11] we carried out anodic oxidation of alkylated anilines, which provided the iminium intermediates (Eq. 4), leading to cyclized products.[12] In contrast to these observations, direct nucleophilic attack of the nitrogen atom, as in our previous approach,[1] was expected to yield the corresponding carbazoles, although oxidation of acetanilide derivatives with PIFA caused introduction of IC_6H_4 or CF_3CO_2 groups to the nitrogen function or to the *para* position of the acetamide groups, depending on the electron density of the substrates.[13] A further literature search revealed microwave-enhanced Cadogan reaction using diaryls carrying a nitro group (300 W, 15 min, then 210 °C), and selenylation of diaryl



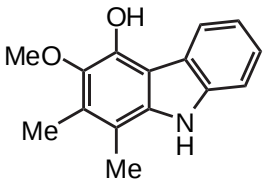
Clausamine E (cytotoxicity)

J.Nat. Prod. **2000**, *63*, 125



Siamenol (anti-HIV)

J. Nat. Prod. **2000**, *63*, 427



Carbazomycin B (anti-inflammatory)

*J. Antibiot.***1980**, *33*, 683

Fig. 1. Natural carbazoles.

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derivatives, followed by deselenylation.[14] Our oxidant carrying the CF_3CH_2O function as a ligand, instead of the CF_3CO_2 group of PIFA, may provide simple and mild oxidation of diaryl derivatives, without undesired side reactions, such as introduction of oxygen or reagent onto the aromatic rings.

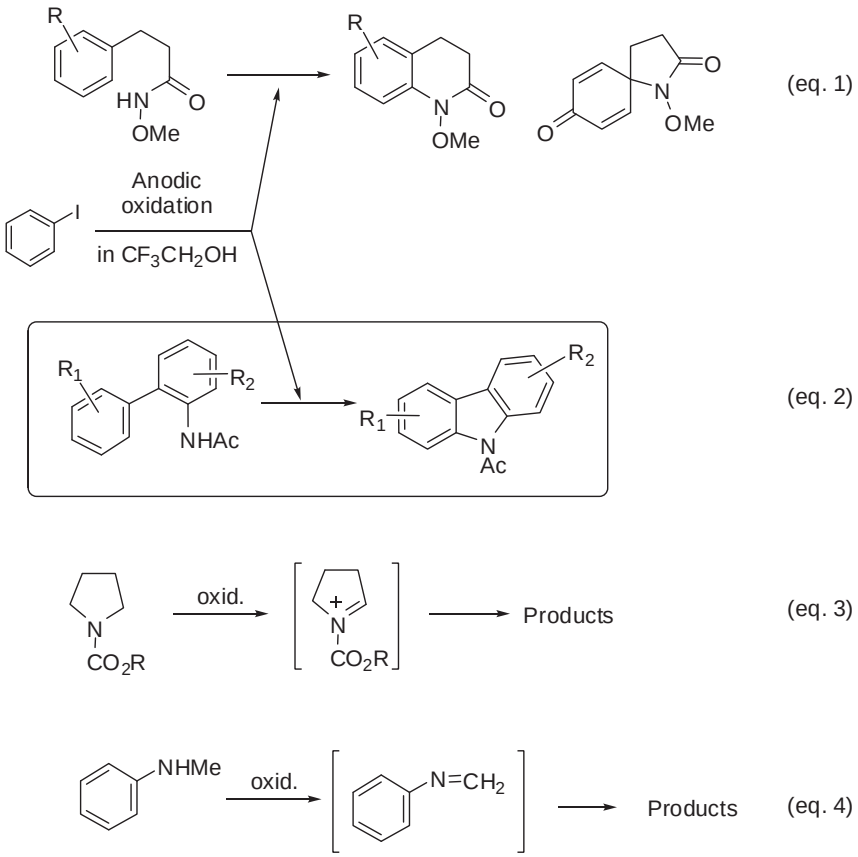
2. Results and discussion

2.1. Oxidative cyclization of diaryl derivatives

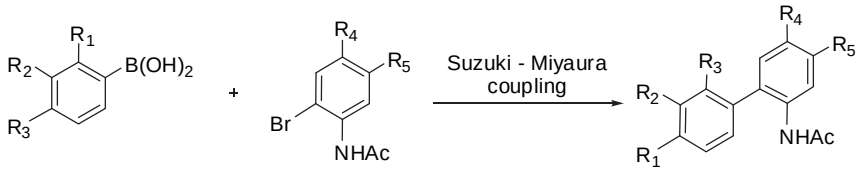
Our synthesis was commenced by preparation of the diaryl substrates by the Suzuki–Miyaura reaction of the corresponding borates **1a**–**d** and bromoacetanilides **2a**–**d** in the presence of Pd(0) providing the corresponding diaryl derivatives **3a**–**j** (Scheme 2).

The substrates for oxidative cyclization were treated with an oxidant solution produced by anodic oxidation of iodobenzene in CF_3CH_2OH in advance (oxidant to substrate ratio=3:1).

As shown in Table 1, the oxidation reaction provided the corresponding carbazoles in 0–91% yields. A plausible reaction mechanism is started by S_N2 attack of the amide oxygen to the oxidant to give the imidate-type intermediate, and subsequent nucleophilic attack from the adjacent aromatic ring to achieve the desired cyclization (Scheme 3). Detailed comparison of each entry revealed that, in contrast to the symmetrical structure to give the corresponding products in high yields (entries 1, 4, and 9), the electron-donating effect of the MeO group to *para* and *ortho* positions gave cyclization at the appropriate positions (entries 2 and 12), and the MeO group adjacent to the diaryl bond interfered



Scheme 1.



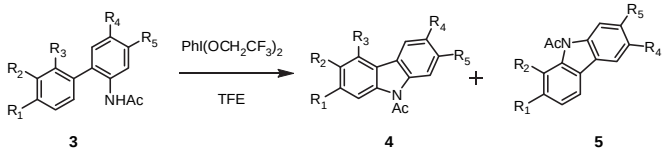
1a: R_1= R_2= H, R_3= OMe
1b: R_1= R_3= H, R_2= OMe
1c: R_2= R_3= H, R_1= OMe
1d: R_1= R_2= R_3= H

2a: R_4= R_5= H
2b: R_4= OMe, R_5= H
2c: R_4= NO_2, R_5= H
2d: R_4= H, R_5= OMe

3a: R_1= OMe, R_2= R_3= R_4= R_5= H (95%)
3b: R_2= OMe, R_1= R_3= R_4= R_5= H (74%)
3c: R_3= OMe, R_1= R_2= R_4= R_5= H (89%)
3d: R_1= R_2= R_3= R_4= R_5= H (60%)
3e: R_4= OMe, R_1= R_2= R_3= R_5= H (76%)
3f: R_2= R_4= OMe, R_1= R_3= R_5= H (84%)
3g: R_4= NO_2, R_1= R_2= R_3= R_5= H (93%)
3h: R_2= OMe, R_4= NO_2, R_1= R_3= R_5= H (23%)
3i: R_5= OMe, R_1= R_2= R_3= R_4= H (88%)
3j: R_2= R_5= OMe, R_1= R_3= R_4= H (90%)

Scheme 2. Synthesis of the diaryls **3**.

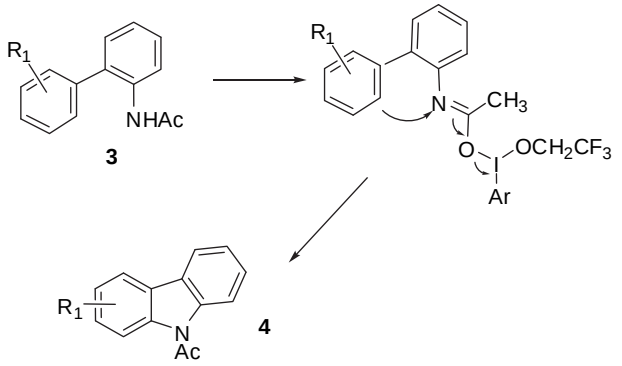
Table 1
Cyclization of the diaryls



3 4 5

Entry	Diaryls (**3**)	Yields, %[b]		
		3[a]	**4**	**5**
1	**3a**	0	91	0
2	**3b**	28	40 (59)	24 (33)
3	**3c**	0	42	0
4	**3d**	17	73 (88)	0
5	**3e**	0	0	0
6	**3f**	20	0	0
7	**3g**	56	0	0
8	**3h**	88	0	0
9	**3i**	15	83 (97)	0
10	**3i**[c]	0	47	0
11	**3i**[d]	49	32 (63)	0
12	**3j**	8	44 (48)	40 (44)

[a] Recovered starting materials.
[b] In parentheses are conversion yields.
[c] PIFA as an oxidant at 0 °C.
[d] PIFA as an oxidant at −20 °C.



Scheme 3. A plausible reaction mechanism.

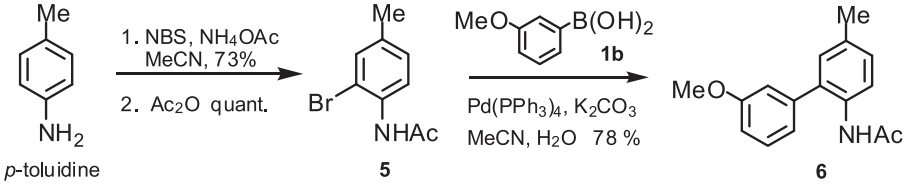
with smooth coupling, leading to the product in moderate yield (entry 3).

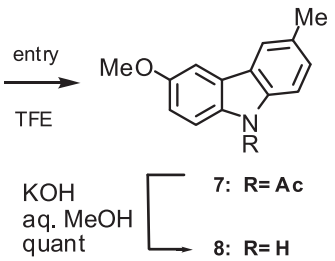
Upon introduction of functional groups to the *para* position of the acetamide group, neither electron-donating nor -withdrawing group effected the desired cyclization, but complex mixtures were produced (entries 5–8), although nitro groups did not cause marked consumption of the starting materials (entries 7–8). The resonance effect of the aromatic substituents to the nitrogen function was different from the stabilization of the imidate intermediate by the MeO group (Eq. 1, Scheme 1). On the other hand, the MeO group at the *meta* position of the acetamide group, which had no direct resonance effect on the acetamide moiety, provided no undesired reaction pathway, leading to the corresponding products (entries 9–12).

Upon comparison of reactivity with PIFA, the electrochemically generated oxidant relatively afforded clear reaction of **3i** to **4i** even at ambient temperature (97% conversion yield, 43 h, entry 9), whereas PIFA at the same temperature gave a complex mixture. At 0 °C with PIFA, the cyclic products were produced in 47% yield (5 h, entry 10). When reacted at −20 °C for 48 h, the PIFA conditions gave **4i** in 63% yield, although the reaction was stopped at this stage (entry 11).

2.2. Synthesis of glycozoline (8)

Glycozoline (**8**), the antibacterial and antifungal carbazole isolated from the roots of *Glycosmis pentaphylla* (Retz.) DC, was synthesized to confirm availability of the electrochemically generated hypervalent iodine oxidant, although synthesis of this carbazole natural product has been reported.[15] The synthesis was started by bromination of *p*-toluidine, followed by *N*-acetylation to give the acetanilide **5** in high overall yield (Scheme 4). The Suzuki–Miyaura coupling with the corresponding borate **1b** under standard conditions provided the diaryl **6** in 78% yield. The key oxidation using the electrochemically generated oxidant (ca. 3 equiv.mol to **6**) proceeded smoothly to give the carbazole **7** in 87% yield. To confirm its effectiveness, the diaryl **6** was also exposed to PIFA at 0 °C, and to anodic oxidation under constant potential electrolytic conditions (anode: glassy carbon beaker; cathode: platinum wire; potential: 1.44 V; concentration: 0.25 mM; supporting salt: $LiClO_4$). The former produced **7** in 58% yield, while anodic oxidation gave no desired product, but a polymeric mixture. Finally, abstraction of the *N*-protecting group under alkaline conditions, gave **8** in quantitative yield, and all of spectroscopic data of the synthetic sample were superimposable on the reported data.[15,16] Consequently, the synthesis of glycozoline (**8**) was accomplished in 50% overall yield from *p*-toluidine.





entry	reagent	condition	yield (%)
1	$PhI(OCH_2CF_3)_2$	r.t.	87
2	PIFA	0 °C	58
3	C.P.E	r.t.	0

Scheme 4. Synthesis of glycozoline (**8**).

3. Conclusion

Oxidative cyclization of the phenyl acetanilide derivatives using our electrochemically generated hypervalent iodine oxidant provided the corresponding carbazoles in moderate to good yields. The reactivity was affected by substitution pattern in both aromatic rings. Application of this methodology to synthesis of natural products was successfully demonstrated to provide glycozoline (**8**) in good overall yield. Further investigation is required to understand the scope and limitations of the electrochemically generated oxidant.

4. Experimental

4.1. General

IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM AL-400, JEOL JNM ECX-400, and JEOL JNM α-400 spectrometers in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard, otherwise stated. High-resolution mass spectra were obtained on JEOL JMS-700 (FAB) or Waters LCT Premier XE (ESI). Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F_{254}, E. Merck AG, Germany) using UV light and/or 5% phosphomolybdic acid in ethanol for detection. Preparative reversed phase TLC was carried out using Silica gel 60 RP-18 F254S, Merck. Kanto Chemical silica 60N (spherical, neutral, 63–210 μm) was used for column chromatography. All reactions were carried out under an argon atmosphere, unless otherwise noted. When necessary, solvents were dried prior to use. Dry tetrahydrofuran (THF) and dry diethyl ether (Et_2O) were purchased from Kanto Chemical Co., Inc. Other anhydrous solvents were also obtained through activated commercially available alumina column, and stored over MS4Å under an argon atmosphere.

4.2. Synthesis of bromoacetanilides

The bromoacetanilides used in this investigation were known compounds.[17] We synthesized them as follows.

To a stirred solution of 1-bromo-4-methoxy-2-nitrobenzene (294.5 mg, 1.27 mmol) in EtOH (5 mL) and AcOH (5 mL) was added iron powder (284.5 mg, 5.08 mmol) and refluxed at 100 °C for 1 h. The mixture was cooled to room temperature and diluted with water. The mixture was neutralized with K_2CO_3 and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated to give 262.5 mg of a bromide: ^{1}H NMR δ (CD_3OD) 7.18 (d, 1H, J=8.4 Hz), 6.39 (d, 1H, J=2.8 Hz), 6.16 (dd, 1H, J=8.4, 2.8 Hz), 4.88 (s, 2H), 3.69 (s, 3H).

A solution of the bromide (252.9 mg, 1.25 mmol) in Ac_2O (3 mL) was stirred overnight The solvent was evaporated, and the residue was purified by silica gel flash chromatography (hexane–EtOAc=5:1) to give 307.6 mg of **2b** (quant.): ^{1}H NMR δ 8.06 (s, 1H), 7.60 (br s, 1H), 7.38 (d, 1H, J=8.0 Hz), 6.56 (d, 1H, J=8.0 Hz), 3.80 (s, 3H), 2.22 (s, 3H).

4.3. Synthesis of diaryl ethers

*4.3.1. Typical Procedure of the Suzuki–Miyaura coupling to compound **4**. 4.3.1.1. N-(3′-Methoxybiphenyl-2-yl)acetamide (**3b**).* To a solution of **2a** (54.0 mg, 0.25 mmol) in MeCN (10 mL) and H_2O (0.5 mL) were added **1b** (41.8 mg, 0.28 mmol), K_2CO_3 (52.1 mg, 0.38 mmol), and $Pd(PPh_3)_4$ (29.1 mg, 0.025 mmol): the mixture was refluxed at 100 °C under Ar. After being reacted at the same temperature overnight, the mixture was cooled to room temperature, then diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by silica gel column chromatography (hexane/EtOAc=3/1) to give 45.0 mg of **3b** (74%)[18]: ^{1}H NMR δ 8.27 (d, 1H, J=8.0 Hz), 7.41–7.34 (m, 2H), 7.26–7.23 (m, 2H), 7.16 (dd, 1H, J=7.6, 7.2 Hz), 6.95 (dd, 2H, J=8.4, 2.7 Hz), 6.89 (s, 1H), 3.83 (s, 3H), 2.02 (s, 3H); ^{13}C NMR δ 168.5, 160.3, 139.7, 134.9, 132.2, 130.3, 130.1, 128.7, 124.5, 121.7, 121.6, 115.0, 113.8, 55.6, 24.9.

*4.3.1.2. N-(3′,5-Dimethoxybiphenyl-2-yl)acetamide (**3f**).* IR (film) 2938, 2835, 1662 cm^{-1}; ^{1}H NMR δ 8.03 (d, 1H, J=9.2 Hz), 7.38 (dd, 1H, J=8.0, 7.6 Hz), 7.00 (br s, 1H), 6.95–6.91 (m, 3H), 6.89 (d, 1H, J=2.0 Hz), 6.80 (d, 1H, J=2.8 Hz), 3.83 (s, 3H), 3.80 (s, 3H), 2.00 (s, 3H); ^{13}C NMR δ 168.2, 159.9, 156.3, 139.5, 134.2, 129.9, 127.7, 123.9, 121.2, 115.2, 114.5, 113.6, 113.4, 55.5, 55.3, 24.3. ESI-HRMS calcd for $C_{16}H_{18}NO_3$ 272.1287 (M^++H), found, m/z 272.1282.

*4.3.1.3. N-(3′-Methoxy-5-nitrobiphenyl-2-yl)acetamide (**3h**).* IR (film) 3400, 2939, 2836, 1707 cm^{-1}; ^{1}H NMR δ 8.65 (d, 1H, 9.1 Hz), 8.22 (dd, 1H, J=9.1, 2.5 Hz), 8.12 (d, 1H, J=2.5 Hz), 7.52 (br s, 1H), 7.46 (dd, 1H, J=8.4, 7.6 Hz), 7.03 (ddd, 1H, J=8.4, 2.5, 2.5 Hz), 6.95 (ddd, 1H, J=7.6, 2.5, 1.5 Hz), 6.89 (dd, 1H, J=2.5, 1.5 Hz), 3.86 (s, 3H), 2.07 (s, 3H); ^{13}C NMR δ 168.3, 160.5, 143.0, 140.6, 136.9, 131.4, 130.7, 125.3, 124.2, 120.9, 119.9, 114.7, 114.6, 55.4, 24.9. ESI-HRMS calcd for $C_{15}H_{15}N_2O_4$ 287.1032 (M^++H), found, m/z 287.1012.

*4.3.1.4. N-(3′,4-Dimethyoxybiphenyl-2-yl)acetamide (**3j**).* IR (film): 2938, 2835, 1675 cm^{-1}; ^{1}H NMR δ 8.02 (s, 1H), 7.38 (dd, 1H, J=8.4, 7.6 Hz), 7.26 (br s, 1H), 7.14 (d, 1H, J=8.4 Hz), 6.94–6.91 (m, 2H), 6.87 (s, 1H), 6.72 (dd, 1H, J=6.8, 2.4 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 2.03 (s, 3H); ^{13}C NMR δ 168.1, 160.1, 159.5, 139.3, 135.7, 130.5, 130.0, 124.0, 121.5, 114.9, 113.2, 110.4, 106.0, 55.4, 55.2, 24.7. ESI-HRMS: calcd for $C_{16}H_{18}NO_3$ 272.1287 (M^++H), found, m/z 272.1294.

4.4. Cyclization of diaryl ethers

4.4.1. Typical procedure of the oxidative cyclization. Electrochemical method: A solution of iodobenzene (89.3 mg, 0.437 mmol) in TFE (25 mL) containing $LiClO_4$ (133 mg, 1.25 mmol) was electrolyzed (CCE at 0.3 mA/cm^2, 2.5 F/mol, a glassy carbon beaker as an anode, a platinum wire as a cathode). After electrolysis, MS4Å (3 g) was added to the mixture. After 10 min, the substrate **3i** (33.8 mg, 0.14 mmol) was added. After being stirred for 48 h, was partitioned between H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on preparative TLC (hexane/EtOAc=3/1) to give 27.7 mg of 4i (83%) and 5.1 mg of 20 (15%).

PIFA method at 0 °C: To a solution of **3i** (24.5 mg, 0.101 mmol) in TFE (5 mL) was added PIFA (86.8 mg, 0.201 mmol) at 0 °C. After being stirred at the same temperature for 6 h, the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on preparative TLC (hexane/EtOAc=3/1) to give 11.3 mg of **4i** (47%).

PIFA method at −20 °C: Compound **3i** was reacted at −20 °C for 48 h with the oxidant (73 mg, 0.17 mmol) to give **4i** (6.4 mg, 32%), as well as **3i** (10.1 mg, 49%).

Compound **4i**: IR (film) 2937, 2834, 1693 cm^{-1}; ^{1}H NMR δ 8.04 (d, 1H, J=7.8 Hz), 7.91 (m, 1H), 7.88 (d, 1H, J=1.7 Hz), 7.84 (d, 1H, J=8.6 Hz), 7.41–7.33 (m, 2H), 6.98 (dd, 1H, J=8.6, 2.3 Hz), 3.92 (s, 3H), 2.86 (s, 3H); ^{13}C NMR δ 170.1, 159.7, 140.0, 138.3, 126.6, 125.8, 123.6, 120.1, 119.7, 119.1, 115.7, 111.3, 101.9, 55.7, 27.7. ESI-HRMS: calcd for $C_{15}H_{14}NO_2$ 240.1025 (M^++H), found, m/z 240.1022.

*4.4.1.1. 1-(2-Methoxy-9H-carbazol-9-yl)ethanone (**4a**).* IR (film): 2938, 2834, 1692 cm^{-1}; ^{1}H NMR δ 8.01 (d, 1H, J=7.8 Hz), 7.88–7.87 (m, 1H), 7.85 (d, 1H, J=1.5 Hz), 7.81 (d, 1H, J=8.2 Hz), 7.40–7.31

(m, 2H), 6.96 (dd, 1H, *J*=8.2, 2.3 Hz), 3.91 (s, 3H) 2.83 (s, 3H); ^{13}C NMR δ 170.1, 159.6, 139.9, 138.3, 126.6, 125.8, 123.6, 120.0, 119.6, 119.0, 115.6, 111.2, 101.9, 55.6, 27.6. ESI-HRMS: calcd for $C_{15}H_{14}NO_2$ 240.1025 (M^++H), found, *m*/*z* 240.1034.

*4.4.1.2. 1-(3-Methoxy-9H-carbazol-9-yl)ethanone (**4b**).* IR (film) 2938, 2835, 1687 cm^{-1}; ^{1}H NMR δ 8.17–8.14 (m, 2H), 7.95 (d, 1H, *J*=8.6 Hz), 7.49–7.44 (m, 2H), 7.37 (dd, 1H, *J*=8.0, 7.2 Hz), 7.05 (dd, 1H, *J*=8.6, 2.4 Hz), 3.93 (s, 3H), 2.86 (s, 3H); ^{13}C NMR δ 169.6, 156.4, 139.0, 133.1, 128.3, 127.3, 126.4, 123.4, 119.8, 117.2, 116.2, 114.8, 103.1, 55.7, 27.6. ESI-HRMS calcd for $C_{15}H_{14}NO_2$ 240.1025 (M^++H), found, *m*/*z* 240.1012.

*4.4.1.3. 1-(1-Methoxy-9H-carbazol-9-yl)ethanone (**5b**).* IR (film) 2931, 2837, 1700 cm^{-1}; ^{1}H NMR δ 8.28 (d, 1H, *J*=8.1 Hz), 7.95 (d, 1H, *J*=7.6 Hz), 7.64 (d, 1H, *J*=7.6 Hz), 7.47 (dd, 1H, *J*=7.8, 7.8 Hz), 7.35 (dd, 2H, *J*=7.8, 7.6 Hz), 7.01 (d, 1H, *J*=8.1 Hz), 4.00 (s, 3H), 2.58 (s, 3H); ^{13}C NMR δ 172.9, 148.0, 140.1, 129.1, 127.8, 127.6, 125.2, 124.5, 123.2, 119.6, 115.0, 112.7, 109.3, 55.6, 27.2. ESI-HRMS calcd for $C_{15}H_{14}NO_2$ 240.1025 (M^++H), found, *m*/*z* 240.1023.

*4.4.1.4. 1-(4-Methoxy-9H-carbazol-9-yl)ethanone (**4c**).* IR (film) 2938, 2837, 1694 cm^{-1}; ^{1}H NMR δ 8.34 (dd, 1H, *J*=6.8, 1.2 Hz), 8.21 (d, 1H, *J*=8.4 Hz), 7.80 (d, 1H, *J*=8.4 Hz), 7.47–7.36 (m, 3H), 6.87 (d, 1H, *J*=8.0 Hz), 4.07 (s, 3H), 2.88 (s, 3H); ^{13}C NMR δ 170.2, 155.7, 139.8, 137.9, 127.9, 126.3, 125.6, 123.7, 123.2, 115.5, 115.3, 108.7, 104.9, 55.5, 27.7. ESI-HRMS calcd for $C_{15}H_{14}NO_2$ 240.1025 (M^++H), found, *m*/*z* 240.1021.

*4.4.1.5. 1-(2,6-Dimethoxy-9H-carbazol-9-yl)ethanone (**4j**).* IR (film) 2938, 2834, 1685 cm^{-1}; ^{1}H NMR δ 7.96 (d, 1H, *J*=8.8 Hz), 7.86 (s, 1H), 7.79 (d, 1H, *J*=8.4 Hz), 7.35 (d, 1H, *J*=2.4 Hz), 6.98–6.94 (m, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.83 (s, 3H); ^{13}C NMR δ 169.7, 159.8, 156.4, 140.5, 132.8, 127.7, 120.1, 119.7, 116.6, 113.0, 111.1, 102.7, 102.0, 55.7, 55.7, 27.5. ESI-HRMS: calcd for $C_{16}H_{16}NO_3$ 270.1130 (M^++H), found, *m*/*z* 270.1118.

*4.4.1.6. 1-(1,7-Dimethoxy-9H-carbazol-9-yl)ethanone (**5j**).* IR (film): 2938, 2837, 1619 cm^{-1}; ^{1}H NMR δ 7.86 (d, 1H, *J*=1.8 Hz), 7.80 (d, 1H, *J*=8.2 Hz), 7.53 (dd, 1H, *J*=8.2, 1.8 Hz), 7.31 (dd, 1H, *J*=7.8, 7.8 Hz), 6.96–6.92 (m, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 2.57 (s, 3H); ^{13}C NMR δ 173.2, 160.1, 147.9, 141.4, 129.2, 128.3, 124.7, 120.2, 118.6, 112.0, 112.0, 108.1, 99.2, 55.6, 55.5, 27.1. ESI-HRMS: calcd for $C_{16}H_{16}NO_3$ 270.1130 (M^++H), found, *m*/*z* 270.1118.

4.5. Synthesis of glycozoline (8)

*4.5.1. N-(3′-Methoxy-5-methylbiphenyl-2-yl)acetamide (**6**).* To a solution of **5** (177.0 mg, 0.78 mmol)[19] in MeCN (10 mL) and H_2O (0.5 mL) were added **1b** (141.0 mg, 0.93 mmol),[20] K_2CO_3 (160.8 mg, 1.17 mmol), and $Pd(PPh_3)_4$ (45.0 mg, 0.038 mmol); the mixture was refluxed at 100 °C under Ar. After being refluxed at the same temperature for 6 h, the mixture was cooled to room temperature, and partitioned between H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by silica gel column chromatography (hexane/EtOAc=4/1) to give 150.8 mg of **6** (78%): IR (film) 3267, 2938, 2834, 1664 cm^{-1}; ^{1}H NMR δ 8.08 (d, 1H, *J*=8.0 Hz), 7.37 (dd, 1H, *J*=8.4, 8.0 Hz), 7.17 (d, 2H, *J*=6.4 Hz), 7.06 (s, 1H), 6.93 (d, 2H, *J*=8.0 Hz), 6.88 (s, 1H), 3.83 (s, 3H), 2.34 (s, 3H), 2.01 (s, 3H); ^{13}C NMR δ 168.1, 159.9, 139.6, 133.9, 132.2, 132.0, 130.4, 129.9, 128.9, 121.8, 121.2, 114.6, 113.4, 55.2, 24.4, 20.7. ESI-HRMS: calcd for $C_{16}H_{18}NO_2$ 256.1338 (M^++H), found, *m*/*z* 256.1335.

*4.5.2. 1-(3-Methoxy-6-methyl-9H-carbazol-9-yl)ethanone (**7**). Electrochemical method*: A solution of iodobenzene (84.5 mg, 0.41 mmol) in TFE (25 mL) containing $LiClO_4$ (133 mg, 1.3 mmol) was electrolyzed (CCE at 0.3 mA/cm^2, 2.5 F/mol). After electrolysis, MS4Å (3 g) was added to the mixture. After 10 min, **6** (34.8 mg, 0.14 mmol) was added. After overnight, the mixture was partitioned between H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on preparative TLC to give 30.0 mg of **7** (87%).

PIFA method: To a solution of **6** (15.8 mg, 0.061 mmol) in TFE (5 mL) was added PIFA (52.4 mg, 0.12 mmol) at 0 °C. After being stirred at the same temperature for 5 h, the mixture was partitioned between H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on preparative TLC (hexane/EtOAc=3/1) to give 9.0 mg of 7 (58%).

Compound **7**: IR (film) 2937, 1687 cm^{-1}; ^{1}H NMR δ 8.15 (d, 1H, *J*=8.9 Hz), 8.00 (d, 1H, *J*=8.9 Hz), 7.74 (s, 1H), 7.41 (d, 1H, *J*=2.4 Hz), 7.27 (d, 1H, *J*=8.9 Hz), 7.03 (dd, 1H, *J*=8.9, 2.4 Hz), 3.93 (s, 3H), 2.83 (s, 3H), 2.51 (s, 3H); ^{13}C NMR δ 169.4, 156.3, 137.1, 133.3, 133.0, 128.4, 127.3, 126.5, 119.9, 117.3, 115.8, 114.6, 103.0, 55.7, 27.4, 21.1. ESI-HRMS: calcd for $C_{16}H_{16}NO_2$ 254.1181 (M^++H), found, *m*/*z* 254.1190.

*4.5.3. Glycozoline (**8**).* A solution of **7** (13.5 mg, 0.053 mmol) in MeOH (9 mL) and H_2O (3 mL) in the presence of KOH (90 mg 1.6 mmol) was heated at 80 °C for 18 h. The solution was partitioned between H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and evaporated to give 11.2 mg of **30** (quant.), mp 179–180 °C from hexane/$CHCl_3$ (lit.[16] 181–182 °C): IR (KBr) 3399, 2938, 1495, 1458 cm^{-1}; ^{1}H NMR δ 7.83 (s, 1H), 7.81 (s, 1H), 7.53 (d, 1H, *J*=2.5 Hz), 7.30 (d, 1H, *J*=8.2 Hz), 7.29 (d, 1H, *J*=8.9 Hz), 7.22 (d, 1H, *J*=8.2 Hz), 7.05 (dd, 1H, *J*=8.9, 2.5 Hz), 3.93 (s, 3H), 2.52 (s, 3H); ^{13}C NMR δ 153.7, 138.5, 134.7, 128.3, 127.1, 123.6, 123.4, 120.1, 114.8, 111.2, 110.4, 103.0, 56.0, 21.3. ESI-HRMS: calcd for $C_{14}H_{14}NO$ 212.1075 (M^++H), found, *m*/*z* 212.1072.

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