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Stereochemical properties of *N*-benzoylated carbazole derivatives

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ABSTRACT

The atropisomeric properties of 2′,6′-disubstituted *N*-benzoylated carbazole derivatives were investigated. It was found that the bulky *t*-butyl and iodo groups restricted rotation about the N–C7′ and C7′–C1′ bonds to separate four stereoisomers, in which rotation about the C7′–C1′ bond was in perfect concert with rotation about the N–C7′ bond. The relation of the rotation of the N–C7′ and C7′–C1′ axes was investigated by comparing the stereochemistry of variously 2′,6′-disubstituted *N*-benzoyl-carbazole derivatives. It was suggested that the concerted rotation of the N–C7′ and C7′–C1′ axes might occur even in less hindered compounds.

1. Introduction

In the course of our study on stereochemical and physicochemical analyses of biologically active molecules,[1] we reported the atropisomeric properties of the indole derivatives (*N*-2′,6′-disubstituted benzoyl-2-methylindoles) (Fig. 1(a)).[2]

The isolation of each enantiomer of **1** (a*R* and a*S*) with high stereochemical stability confirmed that the rotation about the C7′–C1′ axis is fully restricted by substituents at C2′ and C6′ to form a twisted conformation. Recently, we have reported the atropisomeric properties of the 2′-alkyl-6′-iodo-substituted *N*-benzoyl-3-bromocarbazoles (Fig. 1(b)).[3] Interestingly, the *t*-butyl-substituted one was found to be a gear molecule,[4] in which rotation about the C7′–C1′ bond was in perfect concert with rotation about the N–C7′ bond. This unique behavior prompted us to investigate the specific stereochemical properties of variously 2′- and 6′-disubstituted *N*-benzoyl carbazoles. In this study, adding significant data to the preceding results, we determined the mode of rotation about the N–C7′ and C7′–C1′ axes utilizing ^{1}H NMR spectroscopy and X-ray crystallography, in combination with calculations.

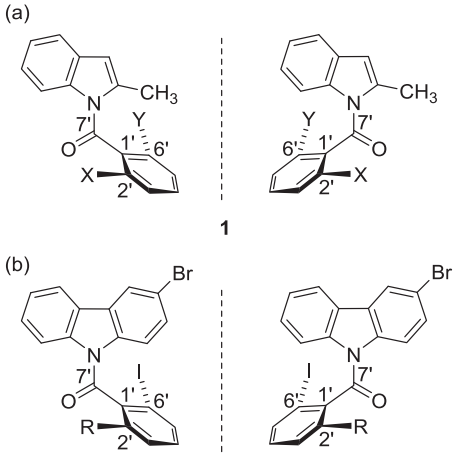

Fig. 1. (a) Atropisomers of 2′,6′-disubstituted *N*-benzoyl-2-methylindole (**1**). (b) Atropisomers of 2′-alkyl-6′-iodo-substituted *N*-benzoyl-3-bromocarbazoles.

2. Results/discussion

Following the established method,[3] *N*-benzoyl carbazole derivatives (**2**–**14**) were synthesized, as shown in Scheme 1.

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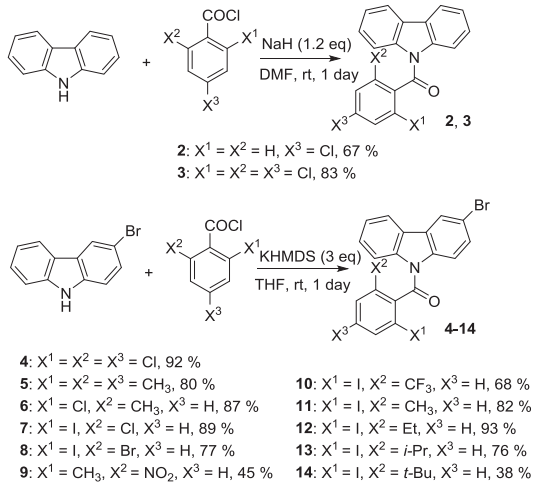


Scheme 1. Synthesis of *N*-benzoylated carbazole derivatives.

First, the conformations of compounds **2** and **3** were examined based on the ^{1}H NMR spectra in DMSO-d_6. The aromatic protons of the carbazole moiety of compound **2**, which bears the *N*-4-chlorobenzoyl group, were observed as two multiplet peaks: 2H protons (H1 and H8) were observed at 8.18 ppm, and 6H protons (H2, H3, H4, H5, H6, and H7) were observed at 7.37 ppm without separation of each proton (Fig. 2(a) for **2**). On the other hand, *N*-(2′,4′,6′-trichloro)benzoylated compound **3** was characterized by a different pattern, in which H1 and H8 protons were differentiated (Fig. 2(b) for **3**). While H1 shifted to a lower field (8.66 ppm) caused by the deshielding effect of the carbonyl group of the benzoyl moiety, H8 shifted upfield (6.24 ppm) due to the shielding effect of the benzene ring.

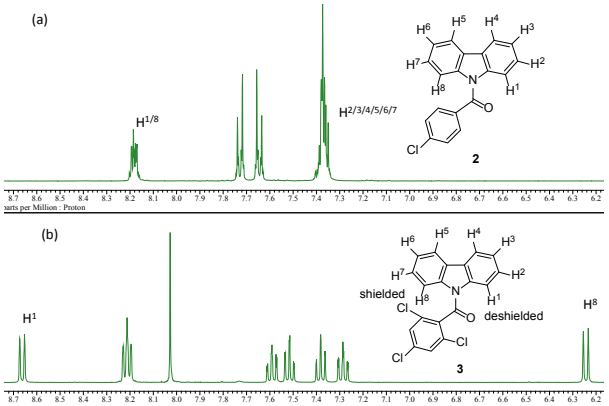


Fig. 2. ^{1}H NMR (400 MHz, in DMSO-d_6) spectra of compounds **2** (a) and **3** (b) at 23 °C.

We also succeeded in obtaining **3** as a single crystal, and its X-ray analysis[5] yielded meaningful information (Fig. 3).

The dihedral angle (ϕ) C6′-C1′-C7′-O of 75.19° in compound **3** confirmed that the benzene ring is nearly orthogonal to the carbazole ring. It is obvious that the substituents at the 2′-,6′-positions of benzoyl affects the N–C7′ and C7′–C1′ axes to form a twisted conformation similar to the *N*-benzoylated 2-methylindole derivative **1**.[2]

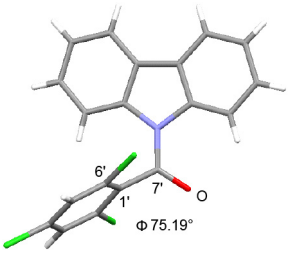


Fig. 3. X-ray crystal structure of **3**.

We next examined the *N*-(2′,4′,6′-trisubstituted)benzoyl-3-bromocarbazole derivatives. For *N*-(2′,4′,6′-trichloro)benzoyl-3-bromocarbazole **4**, two sets of resonance corresponding to *cis* and *trans* conformations were observed in ^{1}H NMR (*cis*:*trans*=1:1.3). Because the rotational barrier of the N–C7′ axis is less than that required for the isolation of each conformer at room temperature, compound **4** was observed as one peak on non-chiral HPLC. It should be noted that ^{1}H NMR of *N*-(2′,4′,6′-trimethyl)benzoyl-3-bromocarbazole **5**, which showed broad signals at room temperature, was observed as two sharpened sets of resonance corresponding to *cis* and *trans* conformations (*cis*:*trans*=1:1.2) at 0 °C (Fig. 4). In view of the steric bulkiness (van der Waals radius) of the methyl (2.0 Å) versus Cl (1.75 Å), this appears strange. The comparatively higher steric hindrance of methyl versus Cl may destabilize the ground states, thus lowering the interconversion barrier. As a consequence, the peaks of the methyl derivative are broad.

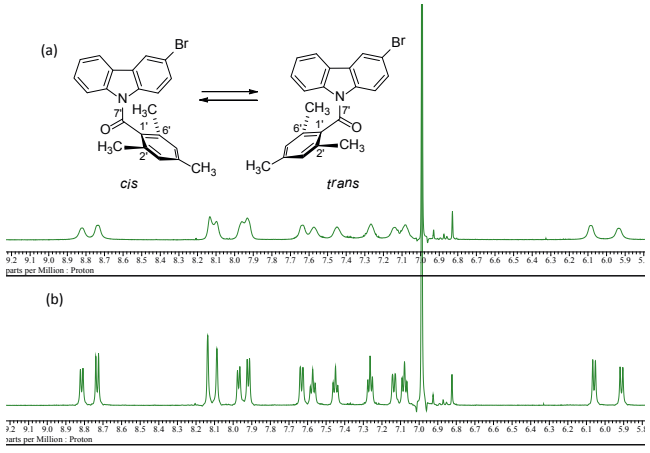
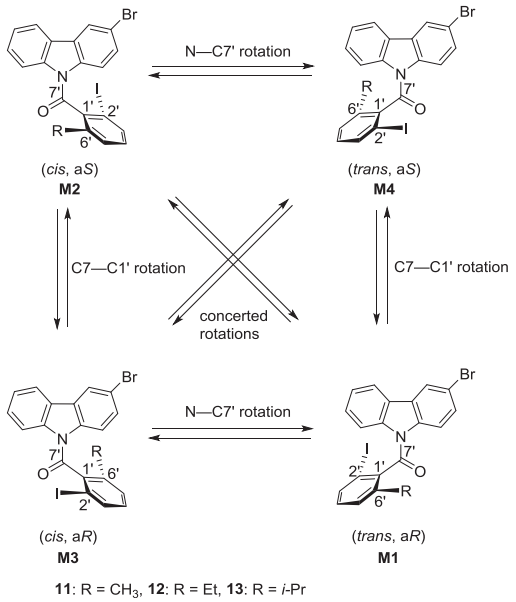


Fig. 4. ^{1}H NMR (400 MHz, in CD_2Cl_2) spectra of compounds **5**. (a) at 23 °C and (b) at 0 °C.

We next focused on the C2′ and C6′ differently substituted derivatives **6**–**11**. In all of these compounds, as well as in **4** and **5**, two sets of resonance corresponding to *cis* and *trans* conformations are observed in ^{1}H NMR (*cis*:*trans*=1:1.2–1.3)[6], although one peak is observed on non-chiral HPLC at room temperature. It is clear that the rotational barrier of the N–C7′ axis is less than that required for the isolation of each conformer at room temperature. Since we succeeded in eliciting atropisomerism about the C7′–C1′ bond in *N*-benzoyl-2-methylindole derivative **1** by introducing substituents at C2′ and C6′ of benzoyl,[2] we attempted separation of the atropisomers of **6**–**11** at room temperature using chiral HPLC. Although incomplete separation was observed for compounds **6**–**10**, *N*-2′-

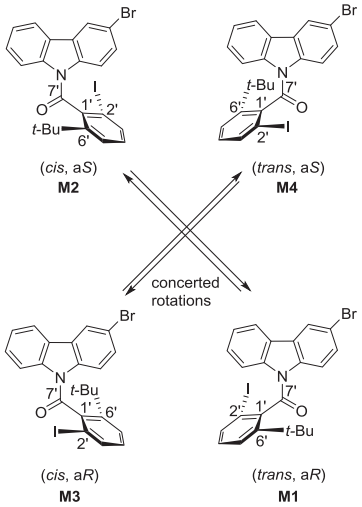
iodo-6′-methylbenzoyl-3-bromocarbazole **11**[3] was separated into two peaks (CHIRALPAK IB), which means that the rotation of the C7′–C1′ axis was reduced without relation to the rotation of the N–C7′ axis (Scheme 2). The atropisomers of compound **11** (**11A** and **11B**) were successfully isolated using preparative chiral HPLC (CHIRALPAK IB) and stereochemical stability with the activation free energy barrier to rotation value ($\Delta G^{\ddagger}$)[7] of 108 kJmol^{-1} was observed.[3] The similar barrier height in compound **11** in comparison with that in *N*-(2′-iodo-6′-methylbenzoyl)-2-methylindole ($\Delta G^{\ddagger}$ value[7] of 109 kJ mol^{-1}) is likely explained by the similar steric or electronic effect due to the methyl group versus the aromatic C–H. Furthermore, we performed VT NMR studies of compound **11**, which allowed us to follow the interconversion of the *cis*/*trans* conformers (see the Supplementary data). In the VT NMR spectra of **11** in DMSO-d_6, the coalescences of the signals for the *cis*/*trans* conformers occurred at 80 °C, which indicates that these conformers interconverted with the $\Delta G^{\ddagger}$ value of 75.8 kJ mol^{-1}.[8] It should be noted that the possible interconversion pathways for stereoisomers of **11** may be complicated, as shown in Scheme 2. Although we have limited information on the ordering of priority of the interconverting pathways, it is clear that the energy barrier of the interconversion of the *cis*/*trans* conformers (75.8 kJ mol^{-1}) is lower than that of the interconversion of atropisomers (108 kJ mol^{-1}).



Scheme 2. Interconversion pathways for stereoisomers of **11**–**13**.

We next examined carbazoles with bulkier substituents, ethyl, isopropyl, and *t*-butyl groups (compounds **12**,[3] **13**,[3] **14**[3]). For all compounds, two sets of resonance corresponding to *cis* and *trans* conformers (*cis*:*trans*=1:1.2) were observed in the ^{1}H NMR spectra. Although compound **12** was observed as one peak on the non-chiral column, it was partially separated on the chiral column (CHIRALPAK IB) at room temperature, and hence we managed to isolate the atropisomers (**12A**, **12B**) with preparative HPLC. The stereochemical stability with a $\Delta G^{\ddagger}$ value[7] of 110 kJ mol^{-1} for **12A** and **12B** may account for the increased stability of the C7′–C1′ axis in **12**. Examination of the VT NMR studies of compound **12** elucidated that the coalescences of the *cis*/*trans* conformers of compound **12** occurred at 105 °C, and the barrier to the *cis*/*trans* interconversion was determined to have the $\Delta G^{\ddagger}$ value of 81.0 kJ mol^{-1} (see the Supplementary data). On the contrary, compound **13** was observed as one peak on all chiral columns examined at room temperature, and we failed to isolate atropisomers of **13**. For compound **13**, coalescence does not occur even at 120 °C in VT NMR (see the Supplementary data) and we therefore gave up the attempt to determine the energy barrier of the interconversion of *cis*/*trans* conformers of compound **13**. By comparing the energy barrier ($\Delta G^{\ddagger}$) of the interconversion between *cis*/*trans* conformers of compounds **11**–**13**, it is suggested that the steric hindrance caused by alkyl substituents also reduces the rotation of the N–C7′ axis.

Finally, surprising results were provided by compound **14**. **14** was observed as two separated peaks (*cis*, *trans*) on non-chiral HPLC, and four stereoisomers [(*cis*, a*S*), (*cis*, a*R*), (*trans*, a*S*), (*trans*, a*R*)] were resolved on a chiral column (CHIRALPAK IB), as shown in Scheme 3. All the isomers that can potentially result since each axis can assume two orientations (*cis*/*trans* for the N–C7′ axis, a*R*/a*S* for the C7′–C1′ axis) were successfully isolated using preparative chiral HPLC. Fortunately, the (*trans*, a*S*) isomer and (*cis*, a*S*) isomer could be analyzed by X-ray crystallography to determine the absolute stereochemistry,[3] and hence the (*trans*, a*R*) isomer and (*cis*, a*R*) isomer were determined. Using the enantiomerically pure stereoisomer (*cis*, a*S*), the stereochemical stability was examined by chiral HPLC analysis at 37 °C in toluene after 9 days. We found that (*cis*, a*S*) was converted into (*trans*, a*R*) with a $\Delta G^{\ddagger}$ value[7] of 102 kJ mol^{-1}, and no interconversion between any other pair [i.e., (*cis*, a*S*)/(*cis*, a*R*), (*cis*, a*S*)/(*trans*, a*S*)] was seen. Similarly, enantiomerically pure (*trans*, a*S*) was converted into (*cis*, a*R*) with a $\Delta G^{\ddagger}$ value[7] of 103 kJ mol^{-1}; no interconversion between any other pair [i.e., (*trans*, a*S*)/(*trans*, a*R*), (*trans*, a*S*)/(*cis*, a*S*)] was observed over 7 days.[3] It is clear that rotation about the C7′–C1′ axis must be in perfect concert with rotation about the N–C7′ axis at 37 °C for at least 7 days (Scheme 3). Although such behavior has been observed in tertiary aromatic amide systems,[9] complete geared rotation without slippage was observed here for the first time. In order to estimate the stability of this gear system, conversion of the enantiomerically pure (*cis*, a*S*) into (*trans*, a*R*) at higher temperature was followed by analytical HPLC until the gear slipped. In previous papers on molecular gear systems, gear slippage was observed at ambient temperature.[9] However, the slippage in this system was finally observed only after 27 h heating at 100 °C.[3]



Scheme 3. Interconversion pathways for stereoisomers of **14**.

Being interested in the process that initiates this gear system, we performed detailed separation analysis of **6**–**13** on a chiral column (CHIRALPAK IB) at 37 °C and 2 °C (Fig. 5). First, the

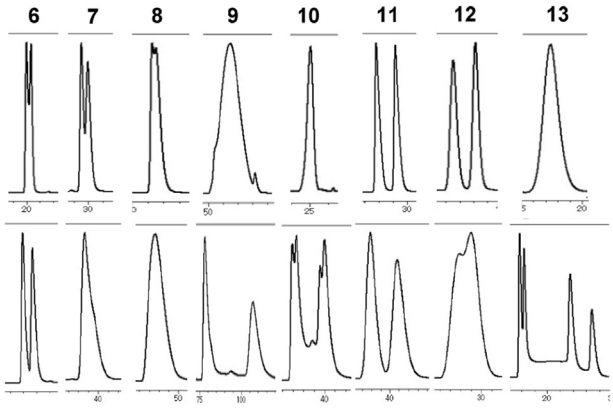


Fig. 5. Chromatograms of **6**–**13**: at 37 °C (upper) and at 2 °C (lower).

separation of compound **6**, which was partially separated on the chiral column (CHIRALPAK IB) at room temperature, was examined. While **6** was poorly resolved at 37 °C, better separation of the peaks was observed at 2 °C. On the contrary, the chromatograms of *N*-2′-chloro-6′-iodobenzoyl-3-bromocarbazole **7**, *N*-2′-bromo-6′-iodobenzoyl-3-bromocarbazole **8**, *N*-2′-iodo-6′-methylbenzoyl-3-bromocarbazole **11**, and *N*-2′-ethyl-6′-iodobenzoyl-3-bromocarbazole **12** broadened at lower temperature (2 °C). Generally, enantiomers that are partially resolved at ambient temperature can be resolved at a lower one.[10] Even allowing for the possibility that the lower column temperature reduced its efficiency caused by slower adsorption-desorption kinetics, such a significant decrease in the resolution observed in these cases seemed unusual. In comparison with the steric bulkiness (van der Waals radius) of Br (1.85 Å) versus Cl (1.75 Å), and van der Waals volume of ethyl (38.9 $Å^3$)[11] versus methyl (21.6 $Å^3$),[10] it also appeared strange that the relatively steric hindrance did not contribute to allowing the baseline separation of the enantiomers. As mentioned above, however, the atropisomers of **11** were isolated at room temperature by preparative chiral HPLC with a $\Delta G^{\ddagger}$ value of 108 kJ mol^{-1}, and those of **12** were isolated at room temperature with a $\Delta G^{\ddagger}$ value of 110 kJ mol^{-1}, which means that the decrease in the resolution of chromatograms observed at 2 °C is not related to the stability of the atropisomeric properties of the compounds. Considering all the results together, the broad chromatograms of **7**, **8**, **11**, and **12** at 2 °C may represent the earliest stage of the separation of the *cis*/*trans* isomers arising from the N–C7′ axis. Meanwhile, in *N*-2′-methyl-6′-nitrobenzoyl-3-bromocarbazole **9** and *N*-2′-iodo-6′-trifluoromethylbenzoyl-3-bromocarbazole **10**, the single broad peak observed at 37 °C was partly separated at 2 °C with the appearance of the interconversion plateau. Similarly, the chromatogram of *N*-2′-iodo-6′-isopropylbenzoyl-3-bromocarbazole **13** showed four peaks that were almost completely separated, which is similar to that of gear compound **14** at room temperature. We assume that the substituents at the *ortho* positions in **9**, **10**, and **13** cause a half-barrier to the rotation about the N–C7′ and C7′–C1′ axes at the same time. Therefore, the two peaks representing the atropisomers may be divided into two halves, which appeared as broad peaks at 37 °C, and as four partly separated peaks with the appearance of the interconversion plateau at 2 °C. The chromatograms of **6**–**13** may be helpful for understanding the process by which the rotation of both the N–C7′ and C7′–C1′ axes becomes slow.

Additionally, we carried out *in silico* conformational analysis[12] of **11**–**14** to elucidate the process by which this molecular gear system starts moving. In order to obtain the initial 3D molecular coordinates of the compounds, the X-ray crystal structure of (*cis*, a*S*) was used. Ab initio calculations were performed using the RHF/CEP-4G basis set with a Gaussian program.[13] To cover all conformational spaces, rotational steps of the single bonds were 15°. As mentioned above, compounds **11**–**14** can rotate around the N–C7′ and C7′–C1′ axes, which results in the energy surface shown in Fig. 6. There were four stable conformers (**M1**, **M2**, **M3**, and **M4**), corresponding to (*trans*, a*R*), (*cis*, a*S*), (*cis*, a*R*), and (*trans*, a*S*), respectively, as shown in Scheme 2. Based on the energy barriers of the pathways on the energy surface of compounds **11**–**13**, it is clear that the interconversion between conformers **M1** and **M2**, and between **M3** and **M4**, is easy, which implies that the concerted rotation of the N–C7′ and C7′–C1′ axes should occur even in compounds **11**–**13** (Scheme 2). The calculated activation barrier of geared rotation at the RB3LYP/LanL2DZ level[14] for compounds **11**–**13** also supports this (Fig. 6). For compound **11**, the interconversion between conformers **M2** and **M3**, and between **M1** and **M4**, seems somewhat difficult, which may result in the isolation of the atropisomers (**11A** and **11B**) with a $\Delta G^{\ddagger}$ value of 108 kJ mol^{-1}. On the contrary, the four conformers (**M1**, **M2**, **M3**, and **M4**) should be easily interconverted into each other in compounds **12** and **13** so that the stereoisomers would not be isolated. For compound **13**, the calculated results agreed with the experimental results showing that the separation of stereoisomers of compound **13** failed. However, considering that the atropisomers of compound **12** were isolated by preparative HPLC, these calculated results need further consideration. Based on the energy surface of compound **14**, it is clear that the interconversion between conformers **M1** and **M2**, and between **M3** and **M4**, is easy in comparison with other pathways. It is important to note that all of the energy barriers of the interconversion pathways are relatively high in compound **14**, which implies that each conformer (**M1**, **M2**, **M3**, **M4**) should be isolated at ambient temperature. These calculated results are consistent with the experimental results showing that complete geared rotation without slippage was observed in compound **14**.

3. Conclusions

By introducing various substituents at the 2′ and 6′ positions of *N*-benzoyl-carbazole derivatives, the mode of rotation about the N–C7′ and/or C7′–C1′ axes was investigated. Utilizing the results of ^{1}H NMR studies and HPLC chromatography, and in silico conformational analysis, the effects of the substituents on both axes were elucidated. Although the separation of the *cis*/*trans* diastereomers was not possible, it was revealed that the steric or electronic effects of the substituents caused a certain barrier to rotation about the N–C7′ bond in compounds **11**–**13**. Detailed separation analysis of **6**–**13** on a chiral column showed the process by which the rotation of both the N–C7′ and C7′–C1′ axes became slow. Although the cue that initiates the gear system is still unclear, this study will contribute to knowledge of the stereochemical properties of the 2′,6′-disubstituted *N*-benzoylated carbazole derivatives.

4. Experimental section

4.1. General information

Materials were obtained from commercial suppliers and used without further purification, unless otherwise noted. Melting points were recorded on a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were recorded on a spectrometer at 600 MHz, 400 MHz for ^{1}H NMR, and 150 MHz, 100 MHz for ^{13}C NMR. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard, and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), and broad (br). IR spectra were recorded on a JASCO

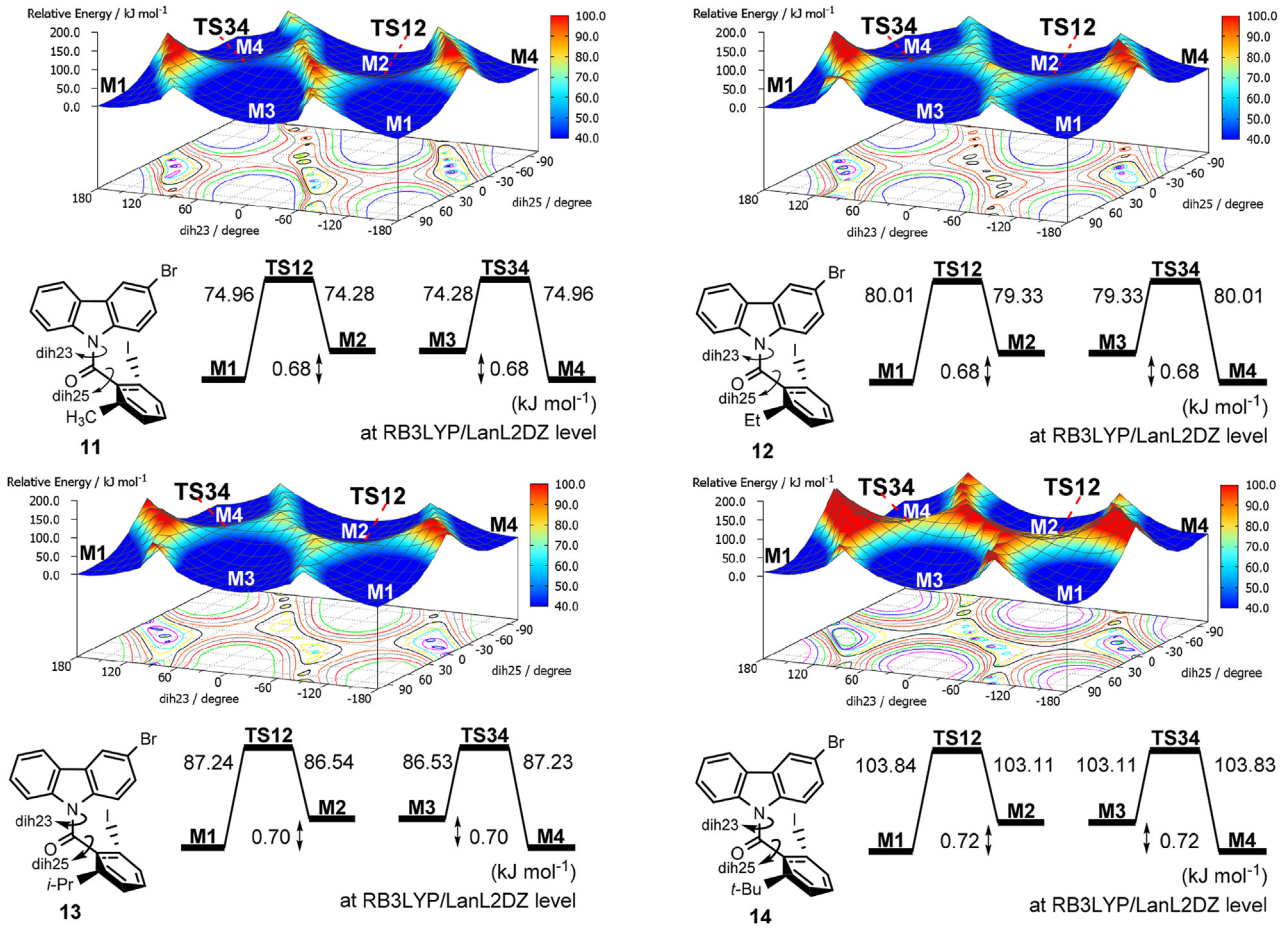


Fig. 6. Energy surface for **11**, **12**, **13**, and **14**.

FT/IR-4200 FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Shimadzu LCMS-IT-TOF mass spectrometer (in ESI mode). Optical rotations were determined with a JASCO P-2200 digital polarimeter. Analytical thin-layer chromatography was performed on Merck silica gel 60 F-254 plates. Column chromatography was performed using silica gel (45–60 μm, Fuji Silysia Chemical Ltd.). High-pressure liquid chromatography (HPLC) was performed with a Shimadzu Prominence system.

4.2. 9-(4-Chlorobenzoyl)-carbazole (2)

To a solution of carbazole (67 mg, 0.40 mmol) in DMF (2 mL) at 0 °C under argon was added successively NaH (19.2 mg, 0.48 mmol), and 4-chlorobenzoyl chloride (61 μL, 0.48 mmol). After being stirred at 23 °C for 20 h, the reaction was quenched with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation in vacuo, the residue was purified by silica gel column chromatography (AcOEt/hexane=1/10) to give **2** as colorless crystals (82.1 mg, 0.27 mmol, 67%), mp 158 °C; R_f (10% AcOEt/hexane) 0.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, m), 7.67 (2H, m), 7.51 (4H, m), 7.35 (4H, m), ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C=O), {139.1, 138.9, 134.1, 130.7, 129.4, 126.9, 126.2, 123.7, 120.3, 115.8}(Ar); IR (KBr): 1678 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{12}ClNO$: 306.0680 $[M+H]^+$; found: 306.0671.

4.3. 9-(2,4,6-Trichlorobenzoyl)-carbazole (3)

2,4,6-Trichlorobenzoyl chloride (75 μL, 0.48 mmol) was subjected to reaction with carbazole (67 mg, 0.40 mmol) following the same procedure as that used for the synthesis of **2** described above to afford the product **3** (125 mg, 0.33 mmol, 83%) as colorless crystals. Mp 120–121 °C; R_f (20% AcOEt/hexane) 0.31; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (1H, dd, *J*=8.0, 1.2 Hz, H1), 8.20 (1H, dd, *J*=8.0, 2.0 Hz, H5), 8.20 (1H, dd, *J*=8.0, 1.2 Hz, H4), 8.02 (2H, s, H3′,H5′), 7.59 (1H, dt, *J*=8.0, 1.2 Hz, H2), 7.51 (1H, dt, *J*=8.0, 1.2 Hz, H3), 7.38 (1H, t, *J*=8.0 Hz, H6), 7.28 (1H, dt, *J*=8.0, 2.0 Hz, H7), 6.25 (1H, d, *J*=8.0 Hz, H8); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (C=O), {138.5, 137.4, 136.8, 134.3, 132.4}(Ar), 129.9 (C3′,C5′), 128.9 (C2), 128.6 (C7), {127.0, 126.6}(Ar), 126.1 (C3), 125.3 (C6), {121.7, 120.9}(C4,C5), 117.8 (C1), 113.0 (C8); IR (KBr): 1686 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{10}Cl_3NO$: 373.9901 $[M+H]^+$; found: 373.9898.

4.4. 9-(2,4,6-Trichlorobenzoyl)-3-bromocarbazole (4)

2,4,6-Trichlorobenzoyl chloride (75 μL, 0.48 mmol) was subjected to reaction with 3-bromocarbazole (98 mg, 0.40 mmol) following the same procedure as that used for the synthesis of **2** described above to afford the product **4** (166 mg, 0.37 mmol, 92%, *cis*:*trans*=1:1.3) as colorless crystals. Mp 212 °C; R_f (20% AcOEt/hexane) 0.35; *cis*-**4**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (1H, dd, *J*=7.2, 1.2 Hz, H8), 8.51 (1H, d, *J*=2.4 Hz, H4), 8.28 (1H, dd, *J*=7.2, 1.2 Hz, H5), 8.03 (2H, s, H3′,H5′), 7.63 (1H, dt, *J*=7.2, 1.2 Hz, H7), 7.53 (1H, dt, *J*=7.2, 1.2 Hz, H6), 7.47 (1H, dd, *J*=8.8, 2.4 Hz, H2), 6.19 (1H, d, *J*=8.8 Hz, H1); *trans*-**4**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (1H, d, *J*=8.8 Hz, H1), 8.53 (1H, d, *J*=2.0 Hz, H4), 8.28 (1H, dd, *J*=7.2, 1.2 Hz, H5), 8.03 (2H, s, H3′,H5′), 7.75 (1H, dd, *J*=8.8, 2.0 Hz, H2), 7.40 (1H, dt, *J*=7.2, 1.2 Hz, H6), 7.33 (1H, dt, *J*=7.2, 1.2 Hz, H7), 6.25

(1H, dd, J=7.2, 1.2 Hz, H8); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (*C*=O for *trans*), 162.7 (*C*=O for *cis*), {138.8, 137.7, 137.6, 137.3, 137.1, 135.8, 134.0, 133.9, 129.7, 128.8, 126.3, 125.5, 118.5, 117.9}(Ar), {131.4, 132.3, 123.0, 129.9}(C3′ ×2, C5′ ×2), 131.1 (C2 for *cis*), 129.4 (C7 for *cis*), 125.8 (C6 for *cis*), 124.5 (C4 for *cis*), 121.6 (C5 for *cis*), 117.8 (C8 for *cis*), 114.9 (C1 for *cis*), 131.4 (C2 for *trans*), 129.2 (C7 for *trans*), 125.5 (C6 for *trans*), 123.8 (C4 for *trans*), 122.3 (C5 for *trans*), 119.5 (C1 for *trans*), 113.0 (C8 for *trans*); IR (KBr): 1693 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_9BrCl_3NO$: 451.9006 $[M+H]^+$; found: 451.9004.

4.5. 9-(2,4,6-Trimethylbenzoyl)-3-bromocarbazole (5)

To a solution of 3-bromocarbazole (73.8 mg, 0.3 mmol) in THF (2 mL) KHMDS (1.8 mL in 0.5 M solution of toluene, 0.9 mmol) was added and stirred at room temperature for 30 min. 2,4,6-trimethylbenzoyl chloride (109.6 mg 0.6 mmol) in THF (2 mL) was added to the mixture at 0 °C. After stirring for 20 h at room temperature, the reaction was quenched with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation in vacuo, the residue was purified by silica gel column chromatography (AcOEt/hexane=1/10) to give **5** (93.6 mg, 0.24 mmol, 80%, *cis*:*trans*=1:1.3 at 0 °C) as white solids. Mp 131.5 °C; R_f (10% AcOEt/hexane) 0.43; *cis*-**5**: ^{1}H NMR (600 MHz, CD_2Cl_2 at 0 °C): δ 8.85 (1H, d, J=5.6 Hz, H8), 8.11 (1H, s, H4), 8.00 (1H, d, J=5.6 Hz, H5), 7.60 (1H, t, J=5.6 Hz, H7), 7.48 (1H, t, J=5.6 Hz, H6), 7.17 (1H, d, J=6.0 Hz, H2), 7.01 (2H, s, H3′,H5′), 5.94 (1H, d, J=6.0 Hz, H1), 2.40 (3H, s, CH_3), 2.09 (6H, s, CH_3 ×2); *trans*-**5**: ^{1}H NMR (600 MHz, CD_2Cl_2 at 0 °C): δ 8.76 (1H, d, J=6.0 Hz, H1), 8.23 (1H, s, H4), 7.95 (1H, d, J=5.2 Hz, H5), 7.60 (1H, d, J=6.0 Hz, H2), 7.29 (1H, t, J=5.2 Hz, H6), 7.09 (1H, t, J=5.2 Hz, H7), 7.01 (2H, s, H3′,H5′), 6.09 (1H, d, J=5.2 Hz, H8), 2.40 (3H, s, CH_3), 2.09 (6H, s, CH_3 ×2); ^{13}C NMR (150 MHz, CD_2Cl_2 at 0 °C): δ 169.2 (*C*=O for *trans*), 169.1 (*C*=O for *cis*), {139.6, 139.5, 138.5, 137.3, 136.9, 135.8, 133.4, 133.3, 133.2, 127.8, 127.4, 124.6, 124.2, 116.5, 115.8}(Ar), 128.8 (C2 for *cis*), 128.1 (C3′, C5′ for *cis*), 127.7 (C7 for *cis*), 123.8 (C6 for *cis*), 122.0 (C4 for *cis*), 118.9 (C5 for *cis*), 117.0 (C8 for *cis*), 114.4 (C1 for *cis*), 20.4 (*C*H_3 for *cis*), 17.9 (*C*H_3 ×2 for *cis*), 129.5 (C2 for *trans*), 128.1 (C3′, C5′ for *trans*), 127.0 (C7 for *trans*), 123.0 (C6 for *trans*), 121.5 (C4 for *trans*), 119.4 (C5 for *trans*), 118.5 (C1 for *trans*), 112.9 (C8 for *trans*), 20.4 (*C*H_3 for *trans*), 17.9 (*C*H_3 ×2 for *trans*); IR (KBr) 1682 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}BrNO$: 392.0645 $[M+H]^+$; found: 392.0658.

4.6. 9-(2-Chloro-6-methylbenzoyl)-3-bromocarbazole (6)

2-Chloro-6-methylbenzoyl chloride (113.4 mg, 0.6 mmol) was subjected to reaction with 3-bromocarbazole (73.8 mg, 0.3 mmol) following the same procedure as that used for the synthesis of **5** described above to afford the product **6** (104.4 mg, 0.26 mmol, 87%, *cis*:*trans*=1:1.2) as white solids. Mp 113 °C; R_f (10% AcOEt/hexane) 0.35; *cis*-**6**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (1H, d, J=8.0 Hz, H8), 8.48 (1H, d, J=2.4 Hz, H4), 8.27 (1H, d, J=8.0 Hz, H5), 7.59 (2H, m, H7, H3′), 7.48 (3H, m, H6, H5′, H4′), 7.33 (1H, m, H2), 5.89 (1H, d, J=8.4 Hz, H1), 2.17 (3H, s, CH_3); *trans*-**6**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (1H, d, J=8.8 Hz, H1), 8.51 (1H, d, J=2.0 Hz, H4), 8.24 (1H, d, J=8.0 Hz, H5), 7.73 (1H, dd, J=8.8, 2.0 Hz, H2), 7.59 (1H, m, H3′), 7.48 (2H, m, H5′, H4′), 7.33 (1H, m, H6), 7.19 (1H, t, J=8.0 Hz, H7), 5.97 (1H, d, J=8.0 Hz, H8), 2.17 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4 (*C*=O for *trans*), 166.3 (*C*=O for *cis*), {139.0, 137.6, 137.5, 137.4, 136.3, 135.8, 135.7, 129.0, 128.9, 125.7, 125.3, 118.0, 117.4}(Ar), {130.5, 130.5, 128.1, 128.1}(C4′ ×2, C5′ ×2), 132.6 (C3′ for *cis*), 131.2 (C2 for *cis*), 129.5 (C7 for *cis*), 125.8 (C6 for *cis*), 124.3 (C4 for *cis*), 121.4 (C5 for *cis*), 117.7 (C8 for *cis*), 115.0 (C1 for *cis*), 19.1 (*C*H_3 for *cis*), 132.6 (C3′ for *trans*), 131.2 (C2 for *trans*), 128.7 (C7 for *trans*), 125.0 (C6 for *trans*), 123.7 (C4 for *trans*), 122.1 (C5 for *trans*), 119.5 (C1 for *trans*), 113.1 (C8 for *trans*), 19.1 (*C*H_3 for *trans*); IR (KBr) 1686 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{13}BrClNO$: 397.9942 $[M+H]^+$; found: 397.9933.

4.7. 9-(2-Chloro-6-iodobenzoyl)-3-bromocarbazole (7)

2-Chloro-6-iodobenzoyl chloride (180.5 mg, 0.6 mmol) was subjected to reaction with 3-bromocarbazole (73.8 mg, 0.3 mmol) following the same procedure as that used for the synthesis of **5** described above to afford the product **7** (135.7 mg, 0.27 mmol, 89%, *cis*:*trans*=1:1.3) as white solids. Mp 122–123 °C; R_f (10% AcOEt/hexane) 0.29; *cis*-**7**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (1H, d, J=7.6 Hz, H8), 8.50 (1H, d, J=2.4 Hz, H4), 8.28 (1H, d, J=7.6 Hz, H5), 8.02 (1H, d, J=7.6 Hz, H5′), 7.76 (1H, m, H3′), 7.63 (1H, t, J=7.6 Hz, H7), 7.52 (1H, t, J=7.6 Hz, H6), 7.41 (2H, m, H2, H4′), 5.96 (1H, d, J=8.8 Hz, H1); *trans*-**7**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (1H, d, J=8.8 Hz, H1), 8.52 (1H, d, J=2.0 Hz, H4), 8.28 (1H, d, J=7.6 Hz, H5), 8.02 (1H, d, J=7.6 Hz, H5′), 7.76 (2H, m, H3′, H2), 7.41 (2H, m, H6, H4′), 7.24 (1H, t, J=7.6 Hz, H7), 6.04 (1H, d, J=7.6 Hz, H8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2 (*C*=O for *trans*), 166.1 (*C*=O for *cis*), {140.7, 140.6, 139.1, 137.6, 137.4, 136.0, 129.1, 129.0, 126.0, 125.8, 125.4, 118.3, 117.9}(Ar), {134.2, 134.1, 130.7, 125.2}(C4′ ×2 for *cis* and *trans*, C2 for *cis*, C6 for *trans*), 138.9 (C5′ for *cis*), 130.5 (C3′ for *cis*), 129.6 (C7 for *cis*), 124.4 (C4 for *cis*), 121.5 (C5 for *cis*), 117.7 (C8 for *cis*), 115.1 (C1 for *cis*), 131.3 (C2 for *trans*), 128.8 (C7 for *trans*), 123.7 (C4 for *trans*), 122.1 (C5 for *trans*), 119.6 (C1 for *trans*), 113.3 (C8 for *trans*); IR (KBr) 1674 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{10}BrClINO$: 509.8752 $[M+H]^+$; found: 509.8767.

4.8. 9-(2-Bromo-6-iodobenzoyl)-3-bromocarbazole (8)

2-Bromo-6-iodobenzoyl chloride (207.2 mg, 0.6 mmol) was subjected to reaction with 3-bromocarbazole (73.8 mg, 0.3 mmol) following the same procedure as that used for the synthesis of **5** described above to afford the product **8** (127.5 mg, 0.23 mmol, 77%, *cis*:*trans*=1:1.3) as white solids. Mp 124 °C; R_f (10% AcOEt/hexane) 0.40; *cis*-**8**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (1H, d, J=8.0 Hz, H8), 8.50 (1H, d, J=2.0 Hz, H4), 8.28 (1H, dd, J=8.0, 1.6 Hz, H5), 8.05 (1H, d, J=7.6 Hz, H5′), 7.89 (1H, d, J=7.6 Hz, H3′), 7.63 (1H, dt, J=8.0, 1.6 Hz, H7), 7.52 (1H, t, J=8.0 Hz, H6), 7.35 (2H, m, H2, H4′), 5.96 (1H, d, J=8.8 Hz, H1); *trans*-**8**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (1H, d, J=8.8 Hz, H1), 8.52 (1H, d, J=2.0 Hz, H4), 8.26 (1H, dd, J=8.0, 1.2 Hz, H5), 8.05 (1H, d, J=7.6 Hz, H5′), 7.89 (1H, d, J=7.6 Hz, H3′), 7.50 (1H, dd, J=8.8, 2.0 Hz, H2), 7.35 (2H, m, H6, H4′), 7.24 (1H, dt, J=8.0, 1.2 Hz, H7), 6.04 (1H, d, J=8.0 Hz, H8); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1 (*C*=O for *trans*), 166.9 (*C*=O for *cis*), {142.5, 142.3, 139.1, 137.6, 137.4, 136.0, 129.6, 129.1, 126.0, 125.5, 119.5, 119.5, 118.3, 117.6}(Ar), {134.3, 134.3, 130.6, 125.2}(C4′ ×2 for *cis* and *trans*, C2 for *cis*, C6 for *trans*), 139.3 (C5′ for *cis*), 133.6 (C3′ for *cis*), 129.0 (C7 for *cis*), 125.8 (C6 for *cis*), 124.3 (C4 for *cis*), 121.5 (C5 for *cis*), 117.9 (C8 for *cis*), 115.2 (C1 for *cis*), 95.2 (C6′ for *cis*), 139.3 (C5′ for *trans*), 133.5 (C3′ for *trans*), 131.3 (C2 for *trans*), 128.8 (C7 for *trans*), 123.7 (C4 for *trans*), 122.1 (C5 for *trans*), 119.7 (C1 for *trans*), 113.4 (C8 for *trans*), 95.2 (C6′ for *trans*); IR (KBr) 1678 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{10}Br_2INO$: 553.8247 $[M+H]^+$; found: 553.8227.

4.9. 9-(2-Methyl-6-nitrobenzoyl)-3-bromocarbazole (9)

2-Methyl-6-nitrobenzoyl chloride (119.8 mg, 0.6 mmol) was subjected to reaction with 3-bromocarbazole (73.8 mg, 0.3 mmol) following the same procedure as that used for the synthesis of **5** described above to afford the product **9** (55.2 mg, 0.13 mmol, 45%, *cis*:*trans*=1:1.3) as yellow solids. Mp 169 °C; R_f (33% AcOEt/hexane) 0.40; *cis*-**9**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (1H, d, J=8.0 Hz, H8), 8.50 (1H, s, H4), 8.28 (1H, m, H5), 8.27 (1H, m, H5′), 7.90 (1H, m, H3′), 7.84 (1H, m, H4′), 7.64 (1H, t, J=8.0 Hz, H7), 7.52 (1H, t, J=8.0 Hz, H6), 7.33 (1H, m, H2), 6.05 (1H, d, J=8.8 Hz, H1), 2.09 (3H,

s, CH_3); *trans*-**9**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (1H, d, J=8.8 Hz, H1), 8.54 (1H, s, H4), 8.28 (1H, m, H5), 8.27 (1H, m, H5′), 7.90 (1H, m, H3′), 7.84 (1H, m, H4′), 7.75 (1H, d, J=8.8 Hz, H2), 7.33 (1H, m, H6), 7.17 (1H, t, J=8.4 Hz, H7), 6.10 (1H, d, J=8.4 Hz, H8), 2.09 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.8 (*C*=O for *trans*), 165.7 (*C*=O for *cis*), {145.8, 139.1, 137.6, 137.3, 137.3, 136.0, 131.5, 131.4, 129.0, 128.5, 125.7, 125.2, 118.0, 117.5}(Ar), 138.4 (C3′ for *cis*), 132.3 (C4′ for *cis*), 130.5 (C2 for *cis*), 129.6 (C7 for *cis*), 125.8 (C6 for *cis*), 124.3 (C4 for *cis*), 123.8 (C5′ for *cis*), 121.5 (C5 for *cis*), 117.5 (C8 for *cis*), 114.9 (C1 for *cis*), 18.5 (CH_3 for *cis*), 138.4 (C3′ for *trans*), 132.3 (C4′ for *trans*), 131.2 (C2 for *trans*), 128.9 (C7 for *trans*), 125.1 (C6 for *trans*), 123.8 (C5′ for *trans*), 123.7 (C4 for *trans*), 122.2 (C5 for *trans*), 119.4 (C1 for *trans*), 113.0 (C8 for *trans*), 18.5 (CH_3 for *trans*); IR (KBr) 1678 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{13}BrN_2O_3$: 409.0182 $[M+H]^+$; found: 409.0165.

4.10. 9-(2-Iodo-6-trifluoromethyl)-3-bromocarbazole (10)

2-Iodo-6-trifluoromethylbenzoyl chloride (200.7 mg, 0.6 mmol) was subjected to reaction with 3-bromocarbazole (73.8 mg, 0.3 mmol) following the same procedure as that used for the synthesis of **5** described above to afford the product **10** (111.7 mg, 0.21 mmol, 68%, *cis*:*trans*=1:1.3) as colorless crystals. Mp 125 °C; R_f (10% AcOEt/hexane) 0.20; *cis*-**10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (1H, dd, J=7.6, 1.2 Hz, H8), 8.15 (1H, d, J=7.6 Hz, H3′), 8.09 (1H, d, J=2.4 Hz, H4), 7.94 (1H, dd, J=7.6, 1.2 Hz, H5), 7.92 (1H, d, J=7.6 Hz, H5′), 7.61 (1H, dt, J=7.6, 1.2 Hz, H7), 7.48 (1H, dt, J=7.6, 1.2 Hz, H6), 7.43 (1H, t, J=7.6 Hz, H4′), 7.17 (1H, d, J=9.2, Hz, H2), 5.84 (1H, d, J=9.2 Hz, H1); *trans*-**10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (1H, d, J=8.4 Hz, H1), 8.15 (1H, d, J=7.6 Hz, H3′), 8.12 (1H, d, J=2.4 Hz, H4), 7.93 (1H, dd, J=7.6, 1.2 Hz, H5), 7.92 (1H, d, J=7.6 Hz, H5′), 7.67 (1H, dd, J=8.4, 2.4 Hz, H2), 7.43 (1H, t, J=7.6 Hz H4′), 7.31 (1H, dt, J=7.6, 1.2 Hz, H6), 7.10 (1H, dt, J=7.6, 1.2 Hz, H7), 5.99 (1H, dd, J=7.6, 1.2 Hz, H8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (*C*=O for *trans*), 165.8 (*C*=O for *cis*), {139.8, 139.5, 137.9, 137.7, 136.2, 129.7, 129.3, 129.3, 128.5, 126.1, 117.5}(Ar), 143.7 (C3′ for *cis*), 131.6 (C4′ for *cis*), 129.8 (C2 for *cis*), 129.0 (C7 for *cis*), 127.0 (C5′ for *cis*), 125.4 (C6 for *cis*), 123.4 (C4 for *cis*), 120.6 (C5 for *trans*), 118.4 (C8 for *trans*), 114.9 (C1 for *cis*), 94.8 (C2′ for *cis*), 143.7 (C3′ for *trans*), 131.6 (C4′ for *trans*), 130.9 (C2 for *trans*), 127.8 (C7 for *trans*), 127.0 (C5′ for *trans*), 124.4 (C6 for *trans*), 122.5 (C4 for *trans*), 119.7 (C5 for *trans*), 119.7 (C1 for *trans*), 113.6 (C8 for *trans*), 94.8 (C2′ for *trans*); IR (KBr) 1678 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{10}BrF_3INO$: 543.9015 $[M+H]^+$; found: 543.9002.

4.11. 2-Iodo-6-trifluoromethylbenzoic acid

To a solution of 2-trifluoromethylbenzoic acid (571 mg, 3 mmol) in DMF (15 mL) at room temperature was added successively $Pd(OAc)_2$ (33.7 mg, 0.15 mmol), iodobenzenediacetate (1.450 g, 4.5 mmol), and iodine (571.2 mg, 4.5 mmol). After being stirred at 100 °C for 24 h, the reaction was diluted with AcOEt and washed with dil. HCl. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation in vacuo, the residue was purified by silica gel column chromatography (AcOEt/hexane=1/2) to give 2-iodo-6-trifluoromethylbenzoic acid (560.2 mg, 1.77 mmol, 59%) as colorless crystals. Mp 155 °C; R_f (50% AcOEt/hexane) 0.33; ^{1}H NMR (400 MHz, CD_3OD): δ 8.14 (1H, d, J=8.0 Hz, H3), 7.72 (1H, d, J=8.0 Hz, H5), 7.30 (1H, t, J=8.0 Hz, H4); ^{13}C NMR (100 MHz, CD_3OD): δ 169.0 (*C*=O), 143.1 (C3), 139.5 (C1), 130.3 (C4), {127.7, 127.4 (C6)}, {125.6, 125.5 (C5)}, 92.7 (C2); IR (KBr) 1713 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_8H_4F_3IO_2$: 314.9135 $[M-H]^-$; found: 314.9118.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all compounds, the VT NMR studies, details of computational studies, and XRD crystallography files) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.06.097.

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14. In all DFT calculations, we optimized geometries with tight convergence criteria and fine grids for numerical integration. We also reassessed all geometries and energies about conformers of compound **14** (*t*-Bu, I), and therefore the values of activation energies differ from values we previously reported.