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Deformative Transition of Menschutkin Reaction and Helical Atropisomers in a Congested Polyheterocyclic System

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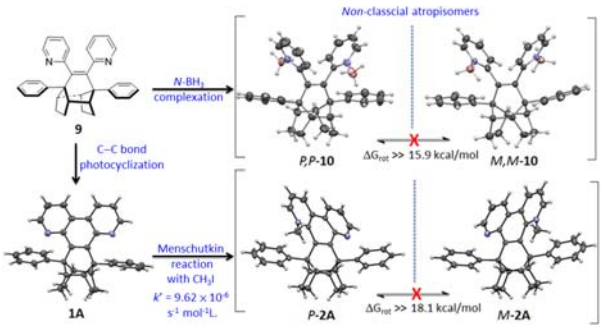
Graphic Abstract



Abstract

A 4,7-phenanthroline polycyclic **1A** designed for probing the limits of the Menschutkin reaction was synthesized in a six-step sequence. The rotational barrier of the phenyl ring nearby the *N*-methyl group in *rac*-**2A** was estimated to be >>18.1 kcal/mol from VT-NMR experiments making them a new type of helical atropisomers. The methylation rate of **9** and **1A** with MeI was found to be 2.22×10^{-4} and 9.62×10^{-6} $s^{-1}mol^{-1}L$, respectively, thus, the formation rate of (*P*/*M*)-**2A** is one of the slowest rates ever reported for a Menschutkin reaction. The *N*-methyl protons in (*P*/*M*)-**2A** exhibit a significant upfield shift ($\Delta\delta$ 1.0 ppm) in its ^{1}H-NMR, compared to those without a nearby phenyl, indicating a strong CH-π interaction is involved. Conformational flexibility in dipyridylethene **9** is clearly shown by its

complexation with BH_3 to form helical atropisomers (*P,P*/*M,M*)-**10**. The pKa values of the conjugate acids of **1A** and **9** in acetonitrile were determined to be 4.65 and 5.07, respectively, which are much smaller compared to that of pyridine **14a** (pKa = 12.33), implying that the basicity, nucleophilicity, and amine alkylation rates of **1A** and **9** are markedly decreased by the severe steric hindrance of the flanking phenyl rings in the polyheterocycles.

Introduction

Bimolecular nucleophilic substitution (S_N2) reaction plays an important role in organic syntheses[1] and biochemical processes[2]. Since the Menschutkin reaction[3] which converts a tertiary amine to a quaternary ammonium salt by reaction with an alkyl halide, is a classical model for S_N2 reaction. The alkylation of various alkyl and heteroatom-substituted pyridines to quaternary ammonium ions can provide information regarding electronic, steric, and solvent effects in chemical reactions, it has intrigued chemists for decades to study the kinetics and transition state (TS) structures of this reaction.[4] Linear free energy relationship, statistic algorithm, and theoretical calculations have long been used in studying the steric and electronic effects on Menschutkin reactions. For example, Brown and co-workers[4m-w] have tried to quantify the steric effects in amine alkylations by measuring the reaction rates of mono- and multiple alkyl substituted pyridines with iodoalkanes and various other alkyl halides. Their studies indicated that on the one hand, the introduction of alkyl group(s) to the *ortho*-position(s) of pyridines increased the steric environment which in turn increased the activation energy and decreased the reaction rate. On the other hand, similar steric effects on the reaction rates were observed when bulkier alkyl halides reacted with unsubstituted pyridines.

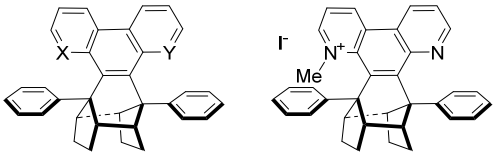
Clarke and Rothwell[4l] also demonstrated that the effects of *ortho*-substitution on the S_N2 reaction of pyridine could primarily be attributed to steric hindrance. However, Arnett and

Reich reported that the S_N2 reactions of pyridines show considerably higher activation free energies when positive charges are developed on the pyridines. The differences are caused by the higher intrinsic barriers of the reactions with methyl iodide, in which the breaking of the C–I bond requires additional reorganization energy.[4i] Consequently, the effect of *ortho*-alkyl substituents on the quaternization of pyridines was considered to be predominantly steric in nature, and the effect was important in determining the TS structure, activation energy, and reactivity of Menschutkin reaction.

The CH-π interaction has been difficult to measure because (1) it is relatively weak (0.5–2.5 kcal/mol)[5] and (2) most molecules without special design are usually quite flexible in geometries. Most of the reported CH-π interactions have been focused on the studies of single crystals in which the distances between the tips of the C-H bond to the center of phenyl rings are smaller than 2.90 Å,[6] the sum of the van der Waals radii of the interacting H and C atoms. Note that weak molecular forces play important roles in the molecular assembly in supramolecular chemistry,[7c,d,7g,7j] biochemistry,[7h,i,7n,7p,7k] crystallography,[7m,7o,7q] asymmetric catalysis,[7e,f] and reaction mechanisms.[7a,b] Recently, the interactions between CH-π and π-π of an aromatic ring with intra- and/or intermolecular functional groups were studied using quantum mechanical modeling and these results suggest that CH-π and π-π interactions can direct a reaction stereoselectively.[7a]

We report here the synthesis of a rigid polycyclic 4,7-phenanthroline compound **1A** to

study the steric effect of a flanking phenyl ring on its methylation reactions (with methyl iodide, $CH_3SO_3CH_3$, and Meerwein's reagent) and BX_3 (BH_3·THF and BF_3·OEt_2) complexation. These reactions, if successful, would provide us non-classical atropisomers and ring current shielding between flanking phenyl ring and the *N*-alkyl substituent. The synthetic route of the fluorinated compounds **1B** and **1C** can be regarded as one of the ideal model for preparation of **2A**; however, we were surprised by the overwhelming importance of steric effects over the opposing ring current shielding of fluorine, as revealed by the ^{19}F-NMR spectra. Even with the counter-effect the largest steric deshielding on record still showed up.[8a] The interest of such a phenomenon to one of us dates back to 1969 in a report on the determination of the C(15) stereochemistry of the Lycopodium alkaloid annotinine.[8b]



1A, X = Y = N
1B, X = CH, Y = CF
1C, X = Y = CF

(*P*/*M*)-**2A**

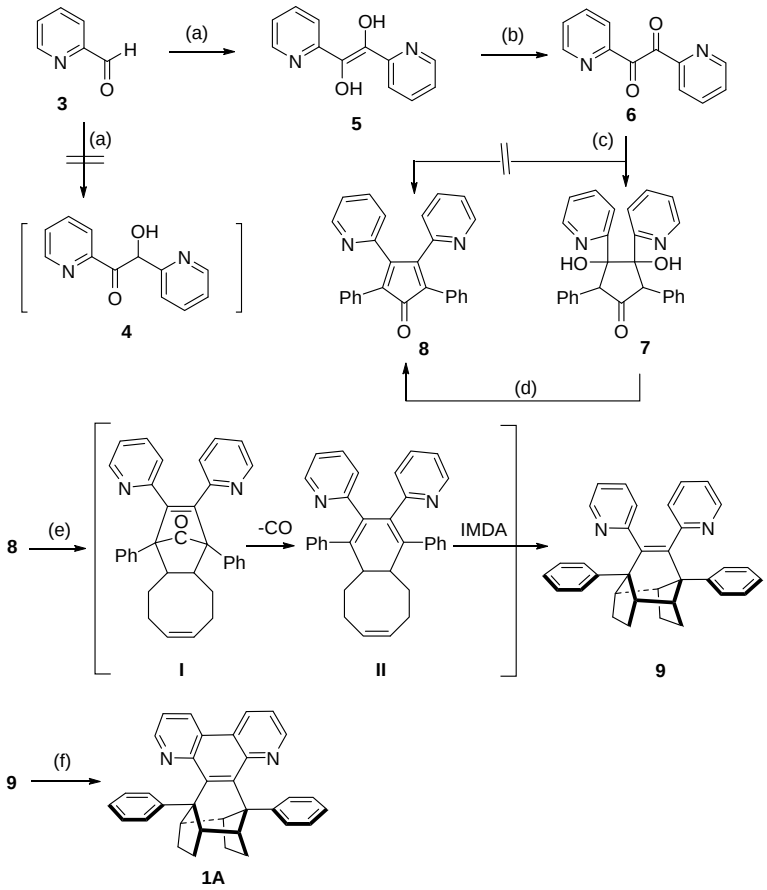
Results and Discussion

The synthesis of **1A** from **8**[13b] involves a two-step sequence, which includes the application of tandem Diels-Alder reaction[9] followed by an iodine induced photocyclization[10] (see Scheme 1). The compound **8** is accessible from a commercial compound **3** by a short

reaction sequence involving condensation of **3** with catalytic amount of sodium cyanide,[11] oxidation of **5** with iodine,[12] aldol condensation of **6** with dibenzyl ketone,[13b] and dehydration of 1,3-diphenyl-2-propanone **7** with $POCl_3$.[13c] Compound **9** is obtained through the tandem Diels-Alder reactions between **8** and 1,5-cyclooctadiene based on similar reaction conditions of other polycarbocyclic structures.[14a,b] Intermolecular Diels-Alder reaction between the cyclopenta-2,4-diene-1-one **8** with 1,5-cyclo-octadiene led to the formation of a carbonyl bridged intermediate **I**, which underwent a decarbonylation to afford the bicyclic cyclohexa-1,3-diene **II**. The bicyclic cyclohexa-1,3-diene **II** then underwent an intramolecular Diels-Alder (IMDA) reaction due to conformational flexibility of the fused eight-membered ring and resulted in the formation of the polycyclic **9** in only 4–9% yield. It is disappointing to obtain product **9** in such a low yield; however, similar yields (4–25%) were reported[14c] in the synthesis of related tetracyclic compounds. The pyridinyl substituents in the cyclohexa-1,3-diene intermediate **II** may be electronically unfavorable for an IMDA reaction causing its low yield. Apparently, the synthetic pathways of **2A** are slightly different from those of **1A** due to the retardation by intramolecular hydrogen bonding interactions in **5** and **7** and unfavorable electronic effects in IMDA reaction of pyridinyl diene.

The photochemical behavior of the stilbazoles (styrylpyridines) and 1,2-bis-pyridylethylenes have been extensively explored for several decades, which in general leads to C–C cyclization.[15a-d] To our surprise, Berdnikova recently reported the photochemical

reactions of 2-styrylquinolines by Hg lamp irradiation, leading to unexpected C–N cyclization



Scheme 1. (a) Cat. NaCN, EtOH, reflux, 3 h, 67% ; (b) I_2, DCM, rt, 15 h, 37% ; (c) KOH, dibenzyl ketone, EtOH, reflux, 1 h, 84% (d) $POCl_3$, pyridine, 85 ^{o}C, 66%, (e) 1,5-cyclooctadiene, reflux, 24 h, 4–9%; (f) cat. I_2, Rayonet, 254 nm, THF, 8 h, 75%.

instead of the traditional C–C cyclization.[15e] The photocyclization of **9** (with a stilbazole unit) to **1A** (4,7-phenanthroline) was performed under the irradiation of a Rayonet photoreactor (λ_{max} = 254 nm) at room temperature for 8 h, which gave the desired C–C cyclization of phenanthroline structure **1A** in 75% yield (Scheme 1, f). The structure of **1A** was determined by ^{1}H and ^{13}C NMR, DEPT-135, HRMS and eventually confirmed by a single crystal X-ray structural analysis (Figures 1, S11, and 12, SI).

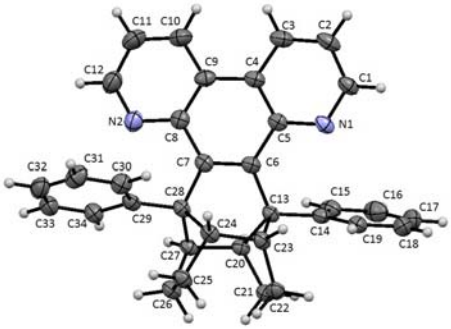
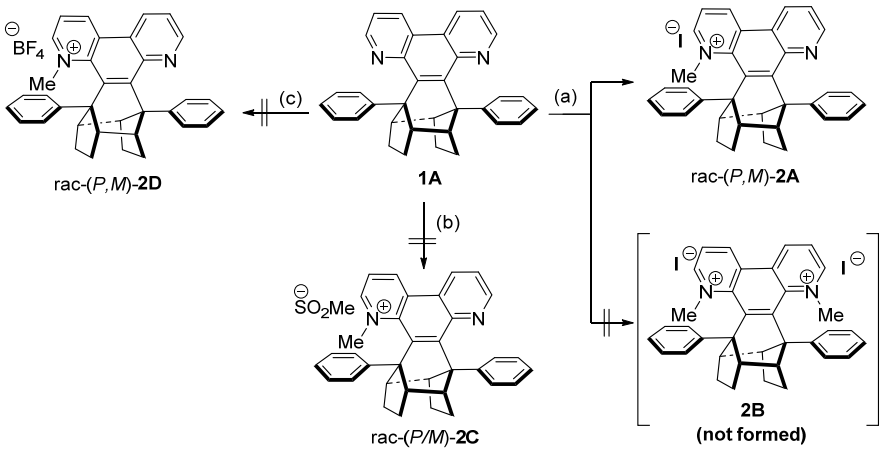


Figure 1. X-ray crystal structures of **1A**.

In the current series the access of **1A** permitted us to examine the amine alkylations under a highly congested environment. The N atoms of the phenanthroline part of **1A** are in close proximity with the centroid of the phenyl groups with a distance of ca. 2.70 Å for both N1 to C14-C19 and N2 to C29-C34 (Figure 1). The distance is significantly smaller than the sum of van der Waals radii of C and N atoms (3.2 Å),[16] which implies that the molecular spaces between the phenanthroline and the phenyl group in **1A** are very congested. Importantly, for the classical S_N2 reaction the steric environments surrounding the nucleophilic center exert a crucial influence as the electrophile must be collinearly accommodated.[3d] We speculated that the phenanthroline would be difficult to undergo an S_N2 reaction with methyl iodide. Indeed, heating **1A** with a large excess of MeI in MeCN under reflux for 2 d did not lead to noticeable product. A noticeable reaction required 7 d of reflux (Scheme 2).

The product was confirmed to be the mono-*N*-methyl phenanthrolinium iodide **2A** by ^{1}H- and ^{13}C-NMR, DEPT-135, HRMS and X-ray single crystal structural analysis (Figure 3a), but the dimethylated product **2B** was not obtained. If the methylation reagents were replaced by

methyl methanesulfonate and Meerwein's reagent (CH_3OBF_4), no methylation products **2C** and **2D** were obtained (Scheme 2b and 2c), even though Meerwein's reagent is considered to be a strong methylation reagent.[17]



Scheme 2. conditions and reagents: (a) 100 eq. MeI/CH_3CN, reflux 7 d, 51%. (b) 100 eq. $MeOSO_2Me$ /CH_3CN, reflux 7 d, no reaction. (c) 6.6 eq. Me_3OBF_4, dry CH_2Cl_2, 0°C, 10 hr, no reaction.

In principle, 2-substituted pyridines and 4,7-phenanthroline derivatives could be regarded as good control compounds of the reactions discussed above; furthermore, there have been many reports discussing their methylation reactions.[4] For example, Gallo and coworkers explored the methylation rates of the 2-substituted pyridines with methyl iodide at 298 and 303 K, respectively.[4i,w] They found that the relative methylation rate of **14e** (R = *t*-Bu) decreased by a factor of 5000 compared to that of **14a** (R = H) implying that steric effect of the

2-substituents in compounds **14a–e** plays a very important role (Figure 2). On the other hand, the reflux of 4,7-phenanthroline with methyl halides could lead to high yields of dimethylated salts in a short time.[18] The methylation of **1A** with excess methyl iodide under reflux was quite sluggish which did not run to completeness even after 28 d. We estimated the amine alkylation rates (*k'*) of **9** and **1A** with excess methyl iodide to be roughly 2.22×10^{-4} and 9.62×10^{-6} $s^{-1}mol^{-1}L$ under seal tube heating condition, respectively (Table S1 and S2, SI); in contrast, the methylation rate of 2-*t*-butylpyridine (**14e**) was found to be 6.36 $s^{-1}mol^{-1}L$.[4i,w] Thus, the relative methylation rate of **1A** is ~6 orders of magnitude smaller than that of a hindered 2-*t*-butylpyridine **14e** (see Figure 2). Apparently, the intramolecular steric effect on the amine alkylations of polycyclic **9** and **1A** is even more severe when compared to that of **14e** with a 2-*t*-butyl group on the pyridine.

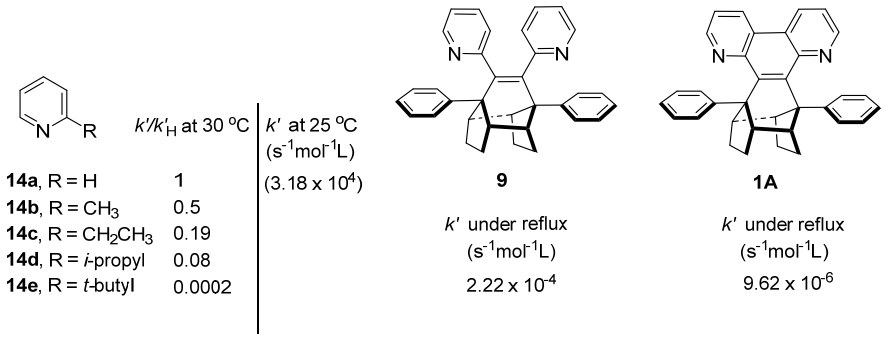


Figure 2. The relative methylation rates of 2-substituted pyridines **14a-e** at 30°C,[4i] **9**, and **1A** with methyl iodide in acetonitrile. The methylation rate of **14a** at 25°C was from reference 4w.

^{1}H NMR signals of the bridgehead protons of **2A** at C24 and C27 appeared as two

multiplets at δ 3.57 and 2.91 ppm (Figure 3b) because they experienced different magnetic environments due to the restricted rotation of the flanking phenyl ring. X-ray single crystal structures of **2A** revealed that there are two stable enantiomers, which could be identified as atropisomers *P*- and *M*-**2A** (*vide infra*). The assignment of *P* and *M* descriptors was done by viewing the cross between the two lines containing N1-N2 and C14-C29 in their X-ray structures (Figure 4). On the one hand, if the turn is clockwise the absolute configuration is *P*; on the other hand, if the turn is counterclockwise, then the absolute configuration is *M*. If the flanking phenyl rings in **2A** could undergo free rotation at high temperature, the stereoisomers *P*-**2A** and *M*-**2A** would interconvert to each other. Variable-temperature NMR (VT-NMR) experiment was then implemented to measure the rotational energy barrier of the flaking phenyl ring nearby the *N*-Me group of **2A** (Figure 5). However, even at 393 K there was very

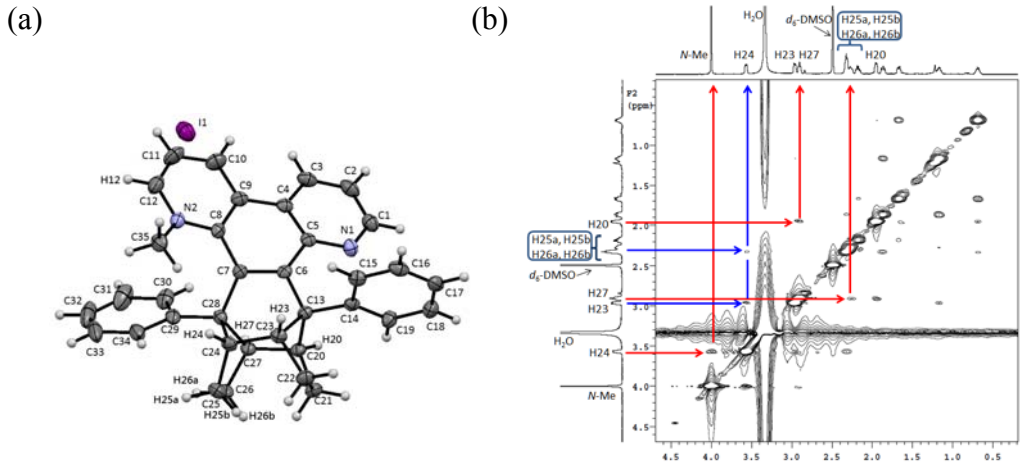


Figure 3. (a) X-ray single crystal structure of **2A** and (b) its partial NOESY spectrum.

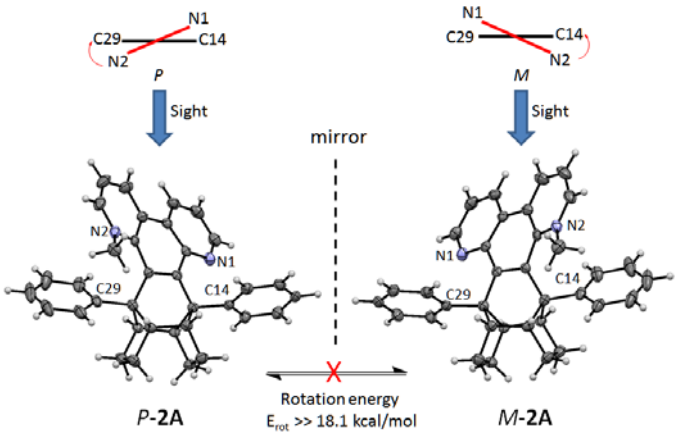


Figure 4. Stereochemical descriptors of *P*- and *M*-**2A**.

little merging movement on the bridgehead proton signals of H24 and H27, implying a very high energy barrier for the single bond (C29-C28) rotation of the phenyl ring. The energy barrier for the restricted rotation of the phenyl ring of **2A** was estimated to be >> 18.1 kcal/mol by VT-NMR. Hence, the highly rigid stereoisomers *P*- and *M*-**2A** were unable to interconvert

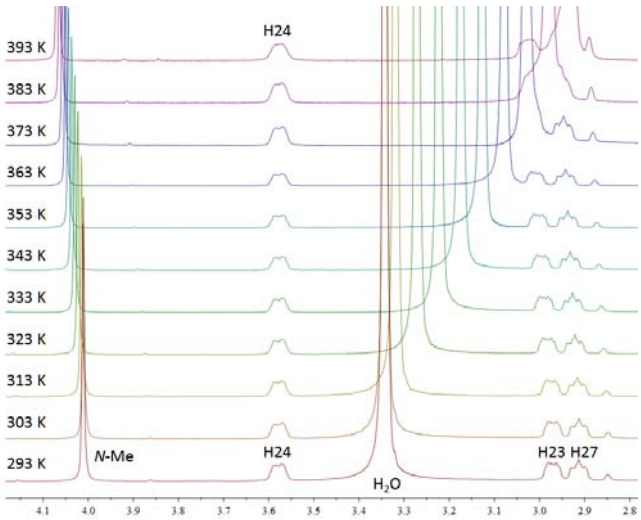


Figure 5. VT-^{1}H-NMR (500 MHz) spectra of the protons H23, H24, and H27 and *N*-Me of **2A** in DMSO-d_6.

to each other through the rotation of the flanking phenyl ring at high temperature due to the severe steric hindrance between the phenyl ring and *N*-methyl group.

We did not obtain the di-methylated product of **1A** possibly because the *N*-methyl phenanthrolinium ring of **2A** becomes more electron deficient, inductively hampering a second equivalent of *N*-methylation reaction to occur. Since the distance of N1 to the centroid of phenyl (C14-C19) was measured to be 2.64 Å in **2A**, which is even shorter by 0.06 Å compared to that in **1A**, implying that there may have a more severe steric hindrance between the unmethylated nitrogen (N1) and the flanking phenyl ring of **2A** compared to those in **1A**, thus, increasing the barrier for compound **2A** for further methylation.

In the crystal structure of **2A**, one of the *N*-methyl protons of **2A** is located 2.20 Å above the centroid of the phenyl ring (C29-C34, Figure 3a). Such a distance is shorter than the commonly used cutoff distance, 2.90 Å, for CH–π interactions.[6] As expected, shielding of the *N*-methyl signal by the phenyl ring was manifested [δ_H 4.0 (^{13}C signal δ_C 51.6 ppm)], a δ_H 1.0 ppm upfield shift in comparison with that of 4-methyl-4,7-phenanthrolinium iodide (δ_H 5.0).[19] It should be noted that a series of exquisitely designed skeletons with short contact distances of alkoxy protons with nearby phenyl groups were designed and synthesized by two research groups to measure the intramolecular CH–π interactions in solution, however, only small upfield shifts (ca. 0.1–0.3 ppm) were observed in their ^{1}H-NMR signals compared to those without nearby phenyl groups.[6a,b] Similar upfield shift of ca. 1.0 ppm was reported by

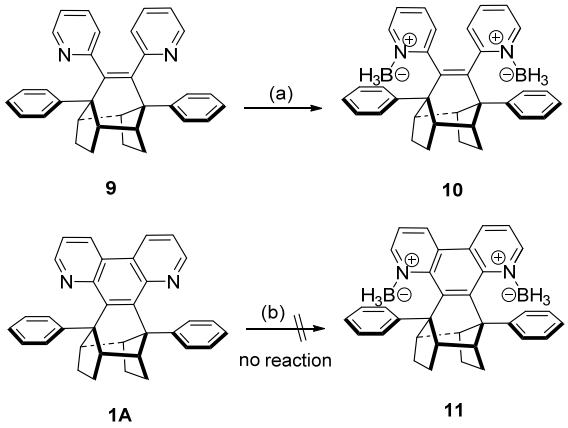
Shimizu on a molecular balance which also exploring the shielding of aryl CH by a nearby phenyl ring.[5a] To the best of our knowledge, there has been few report on the $NCH_3-\pi$ interactions in pyridinium and/or phenanthrolinium derivatives. Recently, Natsugari reported a shielding of 0.93 ppm on NCH_3 by a phenyl group on a series of 1,5-benzodiazepine derivatives.[6e]

More significant is the structures of **1A** and **2A** delineated by single crystal X-ray crystallographic analysis (Figures 1 and 3a). The torsional angle of N2-C8-C7-C28 in the crystal structure of **2A** was found to be 42.7°, which is significantly larger than those in compound **1A** (N2-C8-C7-C28, 18.0°) and **2A** (N1-C5-C6-C13, 1.3°). The torsional angle of the carbon skeleton C28- C7-C6-C13 of **2A** was found to be 22.8°, which is also noticeably larger than that (13.2°) in **1A**. Interestingly, the torsional angle of H12-C12-N2-C35 in compound **2A** was shown to be 14.3° instead of the expected coplanarity. These results imply that the presence of an *N*-methyl group in **2A** brings in an even more severe overall ring strain than that in **1A**. Significantly, while in **1A** the phenanthroline is essentially flat and it deviates from the plane containing C13-C28 and C6-C7 by 8°, the methyl salt **2A** shows a larger angle of 17°, with mutual tilting of the *N*-methylpyridinium ring and its proximal phenyl group. This altered geometry suggests that prior to reaching the S_N2 reaction transition state the **1A** molecule must undergo cooperative clockwise and counterclockwise rotations, respectively, on the part of the phenanthroline portion and the phenyl group. Both such molecular movements

are necessary to clear space for trapping the alkylating agent. The observation is reminiscent of induced fit theory[20,21] for certain enzymatic reactions, in which the substrate leads to conformational changes in the enzyme such that the active site achieves the exact configuration required for the reaction to occur.

Next, we considered complexation of **1A** with BX_3. The flat boron species should be more easily inserted into the gap between the nitrogen lone pair and the phenyl group, and the initial complex is structurally akin to the transition state of the $S_N2(C)$ reaction, just before configurational inversion of the electrophilic center. Complexation of **9**, The complexation of **1A**, with borane did give a 1:2-adduct **10** quantitatively (Scheme 3)[22] which displays distinct NMR characteristics.

The bridgehead hydrogen pairs at C(20)/C(23) and C(27)/C(24) become magnetically nonequivalent. Thus, the singlet at δ_H 3.02 is split into two multiplets (δ_H 3.11 and 3.51). The



Scheme 3. conditions and reagents: (a) 3.0 eq. 50% BH_3 in THF-d_8 at 0°C, 2.5 h, quantitatively and (b) 4.0 eq. 50% BH_3 in THF-d_8 at 0°C, 7 d, no reaction.

downfield shift is attributable to a hindered rotation of the phenyl ring such that its plane is closer to one of the bridgehead hydrogens (and similarly on the other half of the molecule).

Even more remarkable is the appearance of nine separate groups of absorption for the aromatic protons in **10**, which we identified by COSY, NOESY, ^{11}B, and other NMR techniques (Figures S15–20 and S28, SI). The five protons of the phenyl group (Figure 6b) experience different magnetic environments as a result of spatial interactions with the borane-bearing pyridine unit. X-ray diffraction of **10** (Figure 6a) indicates the two heterocycles are forced out of conjugation with the central double bond.

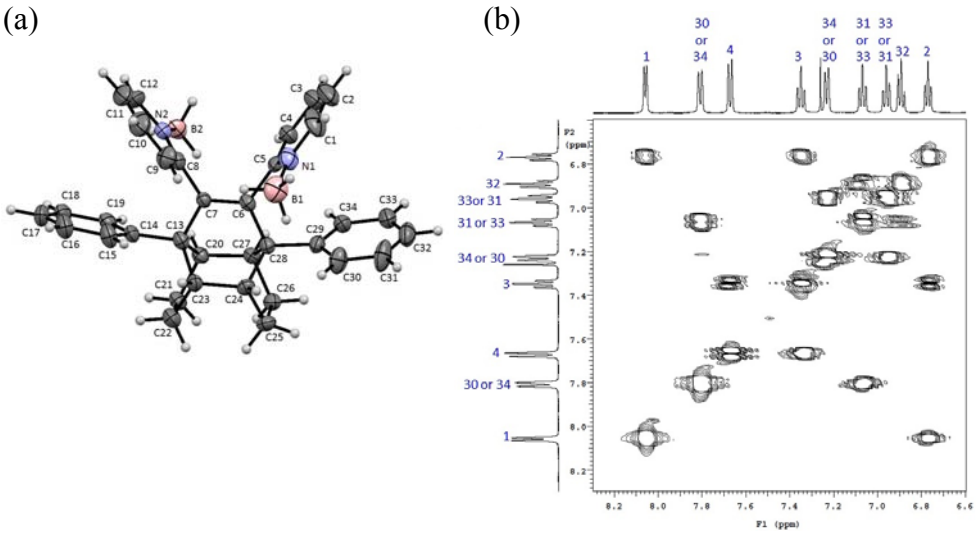


Figure 6. (a) X-ray crystal structure of **10** and (b) its partial 2D-H,H-COSY spectrum.

The dipyridine π-system and its potential conformational mobility in compound **9** allow it to react with two equivalents of BH_3 forming the bis-*N*-borane complex **10** quantitatively.

Surprisingly, because there are two rotationally hindered heterocycles, the bishelical *P,P*- and *M,M*-**10** could be regarded as novel atropisomers. The helical descriptors of **10** can be assigned by X-ray analysis, which is done by facing the two axes of C5-C6 and C8-C7 on compound **10**. On the one hand, if the turn is clockwise the helical descriptor is *P;* on the other hand, if the turn is anticlockwise the helical descriptor is *M*. If the two axes are both counterclockwise or clockwise they are described as *M,M*- or *P,P*-**10**, respectively (Figure 7). VT-NMR study was used to assess the rotational energy barrier of these molecules; unfortunately, we did not see any merging of the proton signals of **10** at the temperature limit (323 K) of chloroform, implying a very high energy barrier (at least 15.9 kcal/mol) for the rotation of the flanking phenyl and the heterocyclic groups (Figures S36 and S37, SI).

However, complexation of **1A** with borane in THF-d_8 for 7 d showed no reaction when monitored by ^{1}H-NMR (Figure S27, SI) instead of the expected bis-*N*-borane product **11**. It was undoubtedly attributed to the severe intramolecular steric hindrance of **1A** and its inability to assume a conformation amenable to the methylation transition state. Notably, we have not been able to obtain the BH_3 complexes of **1A**. Unfortunately, in our hands complexation of **9** and **1A** with BF_3 yielded only the protonated salts **12** and **13**, apparently due to adventitious moisture of the reagent. The product of the complexation of **1A** with BF_3 was identified as the *mono*-protonated **13** by X-ray single crystal structure analysis (Figure 8). However, the ^{1}H-, ^{13}C, and ^{11}B-NMR and COSY spectra of adduct **13** in MeOH-d_4 showed

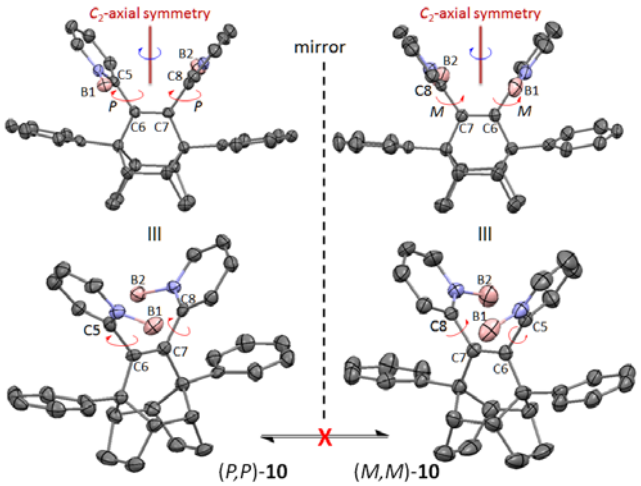


Figure 7. Helical descriptors of *P,P*- and *M,M*-**10**.

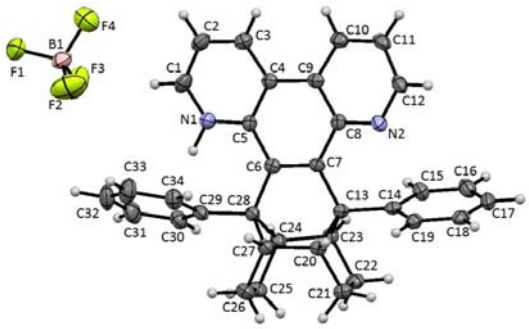


Figure 8. X-ray single crystal structure of **13**.

unambiguously symmetrical signals instead of the expected asymmetric one (Figures S23–26 and S30, SI). The discrepancy between those obtained from NMR spectroscopy and that of X-ray single crystal analysis could be resolved if one attributes the NMR results to the fast exchange between the MeOH-d_4 and *N*-H proton of adduct **13**. The fast exchange of *N*-H proton with d_4-methanol proton is justified due to strong hydrogen-bonding interactions. Interestingly, neither the *di*-*N*-protonated nor the di-*N*-methylated product of **1A** was obtained,

which might be due to similar stereoelectronic factors in **13** and **2A**. Furthermore, Uv-vis spectroscopy was applied to explore the pKa values of the conjugate acids of **9**, **1A**, and **2A**. The pKa value of the conjugate acids of **1A** and **9** in acetonitrile was determined to be 4.65 and 5.07, respectively, by titration with trifluoromethanesulfonic acid (Figure S38, SI).[23a-e] The pKa values of the conjugate acids of **1A** and **9** are much smaller compared to that of pyridine **14a** (pKa = 12.33),[23e] implying that the basicity, nucleophilicity, and amine alkylation rates of **1A** and **9** are markedly decreased by the severe steric hindrance of the flanking phenyl rings in the polyheterocycles.[23a,f] Even though the pKa_2 of the conjugate acid of mono-protonated **1A** and the pKa of the conjugate acid of **2A** were unable to be determined, they proved that steric effects of the flanking phenyl group and electro-deficient effects are prohibiting them for further protonation.

Conclusion

A 4,7-phenanthroline polycyclic system **1A** designed for probing the limit of the Menschutkin reaction was synthesized in a six-step sequence including tandem Diels-Alder reaction followed by an iodine induced photocyclization. The formation of *mono*-methylated product **2A** from the amine alkylation of **1A** with MeI was found to be very sluggish due to intramolecular steric effect. The amine alkylation rates of **9** and **1A** with excess methyl iodide were determined to be roughly 2.22×10^{-4} and 9.62×10^{-6} $s^{-1}mol^{-1}L$ by ^1H NMR. Thus, the

relative methylation rate of **1A** is ~6 orders of magnitude smaller than that of a hindered 2-*t*-butylpyridine **14e**!! The rotational barrier of the phenyl ring nearby the *N*-methyl group in *rac*-**2A** was estimated to be >>18.1 kcal/mol from VT-NMR experiments making them a new type of helical atropisomers. Furthermore, the *N*-methyl group in **2A** exhibits a significant upfield shift ($\Delta\delta$ = 1.0 ppm) in its ^{1}H-NMR comparing to those without a nearby phenyl which reveals the strong intramolecular CH–π interactions in our system. The flexibility in conformational change of the dipyridylethene is clearly shown by the complexation of **9** with BH_3 to form bishelical atropisomers (*P,P*- and *M,M*)-**10** in high yield. To date, there has been no report on the determination of the absolute configurations of these helical atropisomers (*P*/*M*)-**2A** and *(P,P*/*M,M*)-**10**. The pKa values of the conjugate acids of **1A** and **9** are much smaller compared to that of pyridine **14a**, implying that the basicity, nucleophilicity, and amine alkylation rate of **1A** are markedly decreased by the severe steric hindrance of the flanking phenyl rings in the polyheterocycles.

Experimental Section

Column chromatography was performed on silica gel 70-230 or 230-400 mesh; thin-layer Chromatography (TLC) was performed on aluminum plates coated with silica gel 60 F_{254}. Melting points were determined with a melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with 500, 400, and 300 MHz spectrometer with the residual solvent

peaks (usually $CHCl_3$, DMSO and MeOH) as the internal standard. Natural abundance ^{13}C NMR spectra were recorded using pulse Fourier Transform techniques with 500, 400, and 300 MHz spectrometer operating at 125, 100, and 75.4 MHz, respectively. ^{11}B NMR spectra were measured on a 500 MHz NMR spectrometer operating at 160.5 MHz with the solvent peak (BF_3 $OEt_2/CDCl_3$ = 15%) as an external standard (δ_B 0 ppm). High-resolution mass spectrometry (HRMS) was obtained with a magnetic sector type analyzer using ESI, EI and FAB method. UV/Vis spectra were recorded with a spectrophotometer and solvents were of HPLC grade. Compounds **5**,[11f] **6**,[12] **7**,[13b] and **8**,[13b] were prepared according to literature reports.

Synthesis of 5.[11f] A suspension of pyridine 2-carbaldehyde **3** (11.30 g, 0.11 mol) and catalytic amount of sodium cyanide (1.10 g, 0.02 mol) in EtOH (200 mL) and H_2O (50 mL) was heated at reflux for 2 h. After cooling to room temperature, the solvents were removed under reduced pressure. The residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (200 × 3 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated. The resulting residue was recrystallized from CH_2Cl_2 and EtOH to afford the product 2,2'-pyridoin **5** as an orange solid (7.9 g, 67%). Mp: 155–156 ^oC (lit.[11e] 156–157 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H 13.22 (s, 2H), 8.47–8.44 (m, 2H), 7.91–7.79 (m, 4H), 7.20–7.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 156.5 (C), 145.6 (CH), 137.5 (CH), 135.8 (C), 121.1 (CH), 119.4 (CH). FAB-MS: *m/z* 214 (M^+).

Synthesis of 6.[12] A suspension of **5** (5.0 g, 23.3 mmol) and iodine (0.08 g, 23.3 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with 10% aqueous solution of $Na_2S_2O_3$ (50 mL), saturated aqueous solution of Na_2CO_3 (50 mL). The organic layer was separated and dried over anhydrous $MgSO_4$, then the solvent was evaporated under reduced pressure. The resulting residue was recrystallized from CH_2Cl_2 and MeOH to afford the product **6** as a brown solid (1.8 g, 37%). Mp: 152–153 ^oC. (lit.[11e] 156–157 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.57 (dd, J_1 = 4.1Hz and J_2 = 0.8 Hz, 2H), 8.20 (d, J = 7.8 Hz, 2H), 7.96-7.90 (m, 2H), 7.51–7.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 196.9 (C), 151.5 (C), 149.4 (CH), 137.2 (CH), 127.9 (CH), 122.3 (CH). FAB-MS: *m/z* 213 (M^+).

Synthesis of 7.[13b] Potassium hydroxide (0.38 g, 6.7 mmol) was added slowly to a vigorously stirred solution of dibenzylketone (6.26 g, 29.8 mmol) and **6** (4.76g, 22.4 mmol) in EtOH (25 mL). After 1 h, the voluminous white precipitate was filtered off with suction, washed with EtOH and dried in vacuum to afford the product **7** as a white solid (2.4 g, 84%). Mp: 242–243 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.76 (s, 2H), 8.39–8.38 (m, 2H), 7.56–7.51 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 3.0 Hz, 6H), 7.15-7.10 (m, 2H), 6.99-6.95 (m, 4H), 4.80 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 213.3 (C), 162.5 (C), 146.5 (CH), 137.3 (CH), 133.3 (CH), 131.0 (CH), 127.7 (CH), 127.1 (CH), 123.2 (CH), 122.4 (CH), 82.2 (C), 66.0 (CH). EI-MS: *m/z* 422 (M^+).

Synthesis of 8.[13b] The $POCl_3$ (6.48g, 15.3mmol) was added slowly to a solution of **7** (8.93g, 21.1 mmol) in pyridine (38 mL). The reaction mixture was stirred at 85 ^oC for 14 h. After cooling to room temperature, the solvent were removed under reduced pressure. The solid residue was dissolved in CH_2Cl_2 (500 mL) and the solution was cooled to 0 ^oC, then washed with a saturated aqueous solution of Na_2CO_3 (250 mL). The organic phase was separated and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the brownish red crude product was recrystallized from CH_2Cl_2 and EtOH to afford the product **8** as dark red solid (3.9 g, 66%). Mp: 198–199 ^oC (lit.[13c] 200–201 ^oC); ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.35–8.33 (m, 2H), 7.56–7.50 (m, 2H), 7.28–7.21 (m, 12H), 7.11–7.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 200.7 (C), 153.2 (C), 153.1 (C), 149.0 (CH), 135.9 (CH), 130.1 (C), 130.0 (CH), 128.1 (CH), 128.0 (CH), 126.7 (C), 125.0 (CH), 122.4 (CH). EI-MS: *m/z* 386 (M^+).

Synthesis of 9. A solution of **8** (2.0 g, 5.18 mmol) in 1,5-cyclooctadiene (50 mL) was heated at reflux for 24 h. After cooling to room temperature, the solvent were removed under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc/NEt_3 = 6:3:1) to afford the product **9** (R_f= 0.3) as a white solid (0.1 g, 4%). Mp: 290–292 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.96 (d, J = 4.3 Hz, 2H), 7.29–7.27 (m, 4H), 7.02–6.97 (m, 6H), 6.89 (t, J = 7.2 Hz, 2H), 6.64 (d, J = 7.8 Hz, 2H), 6.54–6.50 (m, 2H), 3.02 (s, 4H), 1.96 (d, J = 9.2 Hz, 4H), 1.57 (d, J = 9.0 Hz, 4H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ_C 159.0 (C), 147.3 (CH), 143.9 (C), 143.0 (C), 134.2 (CH), 128.3 (CH), 127.0 (CH), 125.8 (CH), 125.0 (CH), 119.5 (CH), 56.1 (C), 45.8 (CH), 24.8 (CH_2). EI-MS: *m/z* 466 (M^+); HR-MS *m/z* calcd for $C_{34}H_{30}N_2$ (M^+) 466.2409; found 466.2407.

Synthesis of 1A. A mixture of **9** (0.28 g, 0.60 mmol) and catalytic amount of iodine (0.02 g, 0.006 mmol) in THF was stirred at room temperature and irradiated at 300 nm in a Rayonet photoreactor for 8 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 mL), washed with 10% aq. $Na_2S_2O_3$ (50 mL), and saturated aq. Na_2CO_3 (50 mL). The organic layer was separated and dried over anhydrous $MgSO_4$, then the solvent was evaporated under reduced pressure. Flash column chromatography [eluent: hexane/EtOAc v/v = 3:7] afforded **1A** as a white solid (0.21 g, 75%). Mp: 293–295 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ_H 8.62 (d, J = 8.1 Hz, 2H), 8.18 (d, J_1 = 2.7 Hz, 2H), 7.38–7.35 (m, 4H), 7.23–7.15 (m, 8H), 2.87 (s, 4H), 2.02 (d, J = 9.1 Hz, 4H), 1.75 (d, J = 9.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_c 147.8 (C), 146.7 (CH), 145.5 (C), 142.7 (C), 129.4 (CH), 128.4 (CH), 126.8 (CH), 124.5 (CH), 123.6 (C), 119.2 (CH), 55.5 (C), 47.4 (CH), 25.4 (CH_2). EI-MS: *m/z* 464 (M^+); HR-MS *m/z* calcd for $C_{34}H_{28}N_2$(M^+) 464.2247; found 464.2246. The single crystal of **1A** was recrystallized from a mixed solvent of dichloromethane and ethanol (2:8 v/v).

X-ray single crystal data for 1A: $C_{34}H_{28}N_2$, M = 464.58, monoclinic, a = 12.9576(8) Å, b = 14.6324(9) Å, c = 14.6459(16) Å, α = 99.246(4)°, β = 102.984(4)°, γ = 113.991(3)°, V =

2371.0(3) $Å^3$, space group *P-1*, Z = 4, calculated density 1.302 Mg/m^{-3}, crystal dimensions (mm^3): 0.72 × 0.27 × 0.07 mm^3, T = 200(2) K, λ (M_{oKa}) = 1.54178 Å, μ = 0.0776 mm^{-1}, 18271 reflections collected, 8215 independent (R_{int} = 0.0374), 649 parameter refined on F^2, R_1 = 0.0731, $\omega R_2[F^2]$ = 0.1393 (all data), Goodness-of-fit (GOF) on F^2 1.028, $\Delta\rho_{max}$ = 1.452 $eÅ^{-3}$. CCDC 987532 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

Synthesis of 2A. A solution of MeI (2.84 g, 22.0 mmol) and **1A** (0.1 g, 0.22 mmol) in acetonitrile was heated at reflux for 7 d, solvent was removed under reduced pressure, and the residue was purified by flash column chromatography [eluent: CH_2Cl_2/MeOH 9:1] to afford an orange product **2A** (0.06 g, 51%), which was recrystallized from EtOH / CH_2Cl_2. Mp: 296–297 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 9.86 (d, J = 8.2 Hz, 1H), 9.23 (dd, J_1 = 8.5 Hz and J_2 = 1.4 Hz, 1H), 8.75 (d, J = 7.9 Hz, 1H), 8.37 (dd, J_1 = 4.2 Hz and J_2 = 1.5 Hz, 1H), 8.08–8.05 (m, 2H), 7.76 (d, J= 7.8 Hz, 1H), 7.58 (dd, J_1 = 8.3 Hz and J_2 = 4.2 Hz, 1H), 7.47(t, J = 7.2 Hz, 1H), 7.42(t, J = 7.2 Hz, 1H), 7.26–7.18 (m, 3H), 7.13–7.10 (m , 1H), 6.87–6.84 (m, 1H), 6.20 (d, J = 8.0 Hz, 1H), 4.0 (s, 3H), 3.57 (d, J = 6.4 Hz, 1H), 2.97–2.95 (m, H), 2.92–2.89 (m, 1H), 2.32–2.28 (m, 3H), 2.20–2.14 (m, 1H), 1.96–1.95 (m, 1H), 1.89–1.85 (m, 1H), 1.69–1.65 (m, 1H), 1.22–1.14 (m, 1H), 0.70–0.68 (m, 1H); ^{13}C NMR (125 MHz, d_6-DMSO): δ_C 153.2 (C), 149.9 (CH), 146.0 (CH),

145.5 (C), 144.6 (C), 141.9 (C), 139.8 (CH), 139.7 (CH), 135.8 (C), 132.1 (CH), 129.6 (CH), 129.2 (CH), 128.7 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.8 (CH), 126.9 (CH), 126.4 (CH), 125.2 (CH), 122.3 (C), 122.0 (CH), 58.7 (C), 57.1 (CH), 55.7 (C), 53.8 (CH), 51.6 (CH_3), 42.1 (CH), 40.6 (CH), 25.6 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 24.2 (CH_2). ESI-MS: *m/z* 479.25 (M^+); HR-MS *m/z* calcd for $C_{35}H_{31}N_2$ (M^+) 479.2482; found 479.2487. The single crystal of **2A** was obtained by recrystallization from dichloromethane/hexane (3:7 v/v).

X-ray single crystal data for 2A: $C_{35}H_{31}IN_2$, M = 606.52, monoclinic, a = 7.52510(10) Å, b = 12.2650(2) Å, c = 14.7230(3) Å, α = 81.8260(10)°, β = 83.4550(10)°, γ = 83.8270(10)°, V = 1330.52(4) $Å^3$, space group *P-1*, Z = 2, calculated density 1.514 Mg/m^{-3}, crystal dimensions (mm^3): 0.38 × 0.28 × 0.1 mm^3, T = 200(2) K, λ (Mo_{Ka}) = 0.71073 Å, μ = 1.231 mm^{-1}, 343 reflections collected, 4625 independent (R_{int} = 0.0443), 343 parameter refined on F^2, R_1 = 0.0375, $\omega R_2[F^2]$ = 0.0884 (all data), Goodness-of-fit (GOF) on F^2 1.085, $\Delta\rho_{max}$ = 0.449 $eÅ^{-3}$. CCDC 987534 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

Synthesis of 10. To a suspension of **9** (30.0 mg, 0.064 mmol) in dry THF (2.0 mL) was added to 50% BH_3·THF (0.384 mL, 1M in THF) at 0°C under nitrogen. After vigorous stirring for 2.5 h, the solvent was removed under reduced pressure to yield **10** (31.6 mg, quantitative yield) as

a colourless solid. Mp: 260–261 ^{o}C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.06 (d, J = 5.7 Hz, 2H), 7.81 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.08–7.05 (m, 2H), 6.97–6.94 (m, 2H), 6.89 (t, J = 7.3 Hz, 2H), 6.78–6.75 (m, 2H), 3.52–3.49 (m, 2H), 3.12–3.09 (m, 2H), 2.5 (br., BH_3), 2.0–1.89 (m, 4H), 1.65–1.59 (m, 2H), 1.46–1.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 156.9 (C), 147.2 (CH), 142.2 (C), 139.0 (C), 137.0 (CH), 129.0 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH), 126.8 (CH), 125.7 (CH), 122.1 (CH), 56.6 (C), 46.8 (CH), 44.5 (CH), 24.6 (CH_2), 24.5(CH_2); ^{11}B NMR (160.5 MHz, $CDCl_3$): δ_B -13.86 (br). FAB-MS: *m/z* 492 $(M\text{-}2H)^+$; HR-MS *m/z* calcd for $C_{34}H_{34}N_2B_2$ $(M\text{-}2H)^+$ 492.2908; found: 492.2904. The single crystal of **10** was obtained by recrystallization from CH_2Cl_2/hexane (2:8 v/v).

X-ray single crystal data for [10]$_6$·CH_2Cl_2: $C_{205}H_{218}B_{12}Cl_2N_{12}$, M = 3050.53, monoclinic, a = 13.1252(3) Å, b = 32.3680(8) Å, c = 41.4449(10) Å, α = 90°, β = 95.4200(10)°, γ = 90°, V = 17528.6(7) Å^3, space group *P-21/n*, Z = 4, calculated density 1.156 Mg/m^{-3}, crystal dimensions (mm^3): 0.25 × 0.17 × 0.04 mm^3, T = 200(2) K, λ (Mo_{Ka}) = 0.71073 Å, μ = 0.095 mm^{-1}, 122380 reflections collected, 30740 independent (R_{int} = 0.0685), 343 parameter refined on F^2, R_1 = 0.1540, $\omega R_2[F^2]$ = 0.3106 (all data), Goodness-of-fit (GOF) on F^2 0.987, $\Delta\rho_{max}$ = 1.027 eÅ^{-3}. CCDC 987535 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

Synthesis of 12. To a suspension of **9** (19.3 mg, 0.041 mmol) in dry THF (2.0 mL) was added $BF_3{\cdot}OEt_2$ (0.021 mL, 0.166 mmol) at 0°C under nitrogen. After vigorous stirring for 2.5 h, the solvent was removed under reduced pressure to yield **12** (19.4 mg, quantitative yield) as a colorless solid. Mp: 242–243 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.15 (d, J = 5.6 Hz, 2H), 8.00 (t, J = 7.6 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.42–7.38 (m, 6H), 7.12 (t, J = 7.6 Hz, 4H), 7.00 (t, J = 7.2 Hz, 2H), 3.28 (s, 4H), 2.04 (d, J = 9.2 Hz, 4H), 1.61 (d, J = 9.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 150.7 (C × 2), 146.0 (CH × 2), 141.6 (C × 2), 141.1 (C × 2), 140.4 (CH × 2), 130.3 (CH × 2), 128.8 (CH × 2), 127.7 (CH × 2), 127.0 (CH × 2), 124.8 (CH × 2), 57.5 (C × 2), 46.3 (CH × 4), 24.8 (CH_2 × 4); ^{11}B NMR (160.5 MHz, MeOH-d_4): δ_B 0.64. ESI-MS: *m/z* 234.3 (M^{2+}); HR-MS *m/z* calcd for $C_{34}H_{32}N_2$ (M^{2+}) 234.1277; found 234.1275.

Synthesis of 13. To a suspension of **1A** (20.0 mg, 0.043 mmol) in dry THF (3.0 mL) was added to $BF_3{\cdot}OEt_2$ (0.022 mL, 0.172 mmol) at 0°C under nitrogen. After vigorous stirring for 2.5 h, the solvent was removed under reduced pressure to yield **13** (21.2 mg, quantitative yield) as a colorless solid. Mp: 291–292 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 9.63 (d, J = 8.5 Hz, 2H), 8.44 (dd, J_1 = 5.0 and J_2 = 1.5 Hz, 2H), 7.85 (dd, J_1 = 8.5 and J_2 = 5.0 Hz, 2H), 7.64–7.62 (m, 4H), 7.51–7.48 (m, 6H), 3.09 (s, 4H), 2.16 (d, J = 9.5 Hz, 4H), 1.80 (d, J = 9.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 145.6 (C), 145.2 (C), 139.4 (C), 130.5 (CH), 129.7 (CH × 3), 128.8 (CH), 126.5 (C), 122.9 (C), 57.6 (C), 49.2 (CH), 26.1 (CH_2); ^{11}B NMR (160.5 MHz, MeOH-d_4): δ_B 1.05. ESI-MS: *m/z* 465.2 (M^+); HR-MS *m/z* calcd for $C_{34}H_{29}N_2$

(M^+) 465.2325; found 465.2332.

X-ray single crystal data for 13: $C_{34}H_{29}BF_4N_2$, M = 552.40, monoclinic, a = 8.2710(5) Å, b = 12.9503(8) Å, c = 24.7661(14) Å, α = 90°, β = 99.143(4)°, γ = 90°, V = 2619.0(3) Å^3, space group *P-21/c*, Z = 4, calculated density 1.401 Mg/m^{-3}, crystal dimensions (mm^3): 0.42 × 0.25 × 0.13 mm^3, T = 200(2) K, λ (Mo_{Ka}) = 0.71073 Å, μ = 0.101 mm^{-1}, 12509 reflections collected, 4485 independent (R_{int} = 0.0616), 370 parameter refined on F^2, R_1 = 0.1042, $\omega R_2[F^2]$ = 0.1649 (all data), Goodness-of-fit (GOF) on F^2 1.039, $\Delta\rho_{max}$ = 0.377 eÅ^{-3}. CCDC 987533 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

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Supporting Information

Crystallographic data of compounds **1A**, **2A**, **10**, and **13**; ^{1}H- and ^{13}C-NMR spectral data for compounds **1A**, **2A**, **5**–**10**, and **13**; ^{11}B NMR spectra for compounds **10**, **12**, and **13**; kinetic data for methylation rate constants, and UV/vis titrations for pKa determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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