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Synthesis and Reactivity of 5,10,15-Triaryl Doubly N-Confused Bilanes

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Abstract: A series of 5,10,15-tris(pentafluorophenyl) doubly N-confused bilanes were synthesized in a stepwise manner with the aid of sterically demanding N-protecting groups, in which the difference in reactivity between regular pyrrole and N-confused pyrrole plays a crucial role in the synthetic strategy. Some doubly N-confused bilanes were converted into porphyrinoids or a unique 2:2 copper(II) complex with a helical structure. In addition, the conformations and electronic states of the doubly N-confused bilanes were investigated theoretically, giving fruitful information about the effect of confusion on the bilane skeleton.

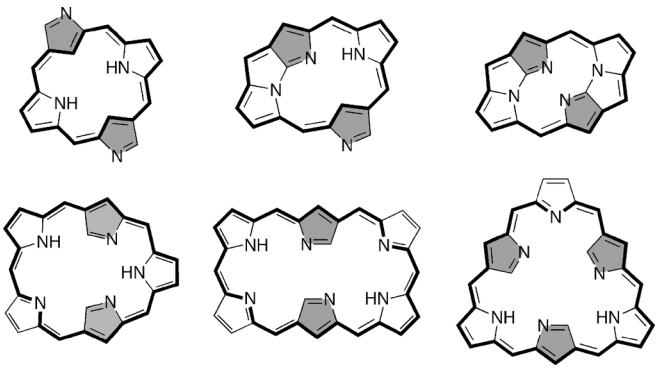
Keywords: bilanes · confused compounds · macrocycles · porphyrinoids · pyrroles

Introduction

Bilane is composed of four pyrrole units and three methylene carbon atoms, forming a linear precursor for porphyrin and vitamin B_{12} in biosynthesis.[1] Although bilanes containing three identical substituents on the methylene carbon atoms are obtained directly in an acid-catalyzed condensation reaction of pyrrole and aldehyde,[2] the yields are usually low, and thus, stepwise construction would be suitable for efficient preparation. The stepwise method is essential for the synthesis of asymmetrically *meso*-[3] and β-substituted bilanes.[4] The bilanes thus synthesized are important precursors for corroles and asymmetrically substituted porphyrins.[3]

We have recently been interested in isomers of porphyrins and related macrocycles. Due to the high reactivity of α-carbon atoms, pyrrole rings are usually connected to methine or *meso*-carbon atoms in an α,α′-fashion.[5] Meanwhile, we have managed to connect pyrrole rings in an α,β′-fashion to the *meso*-carbon atoms, giving a wide variety of N-confused porphyrinoids.[6] One important feature of N-confused porphyrinoids is the high reactivity of the N-confused pyrrole ring.[7] In particular, unique intramolecular fusion reactions of N-confused porphyrinoids offer a way to peculiar fused porphyrinoids.[8]

During the course of these studies, it became important to prepare multiply N-confused oligopyrroles because they were requisite compounds for the construction of multiply N-confused porphyrinoids.[9] Despite rich examples of N-confused porphyrinoids, the study of N-confused oligopyrroles is still in its infancy.[10]



The significance of the study on confusion is categorized into two elements. One is the creation of new molecules with unique structures and interesting properties. Another is the systematic study of the isomers of porphyrins and related oligopyrrolic compounds. There is no doubt that understanding of the effects of conformation, polarization, hydrogen bonding, and so forth is important for the development of porphyrin chemistry. However, it is often difficult to elucidate them only with a single compound or regular oligopyrrolic compound. The concept of confusion enables us to create a library of compounds with similar structures and properties. A comparison of regular and confused oligopyrrolic compounds would provide much information about those effects.

Herein, the synthesis and reactivity of a series of 5,10,15-tris(pentafluorophenyl) doubly N-confused bilanes are re-

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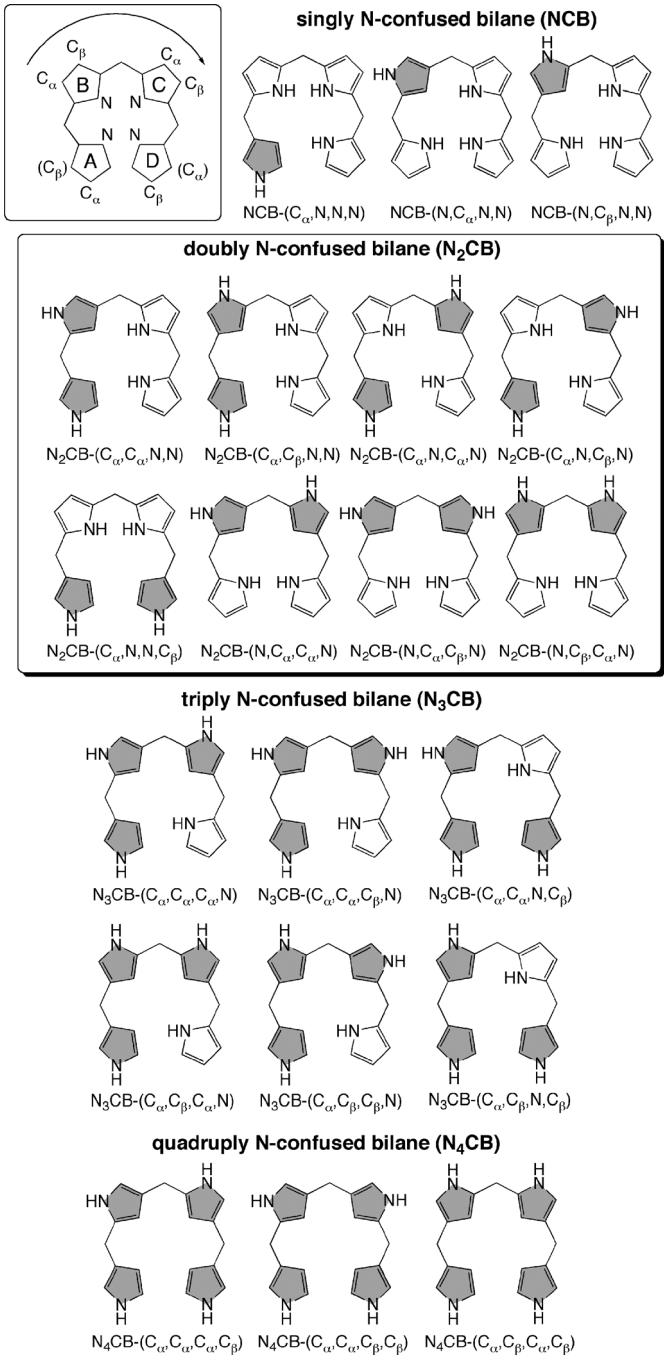
ported in detail. The use of pentafluorophenyl groups is very important to stabilize any intermediates. It is also beneficial to avoid scrambling reactions. Although two isomers of doubly N-confused bilanes have already been reported, they are described again for comparison.[11]

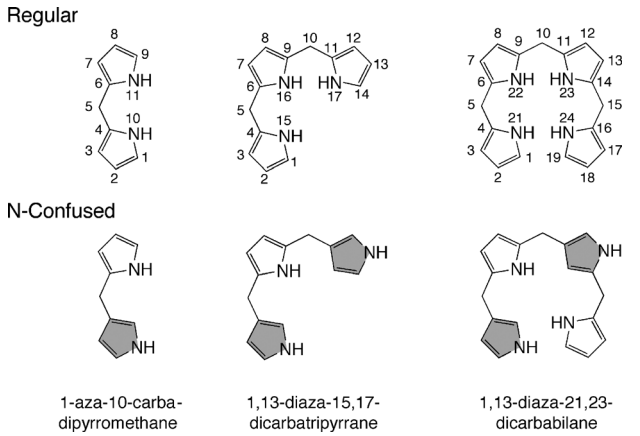
Results and Discussion

Nomenclature: Because many isomers exist in N-confused bilanes, we assign trivial names to distinguish them. Based on previously reported nomenclature for a series of porphyrin isomers,[9g] N, C_α, and C_β are used to indicate the site of N confusion, as shown in the upper-left corner of Scheme 1. First, oligopyrrole is arranged in a circular pattern, in which a vacant site is placed downward. Second, each pyrrole ring is assigned as rings A, B, and so on in a clockwise manner starting from the lower left ring. N-Confused pyrrole rings are placed in an alphabetically favorable manner. Finally, the positions of the nitrogen atoms are indicated from rings A to D, such as (C_α,N,N,N) and (C_α,C_β,N,N). These signs are placed after the abbreviated names, NCB for singly N-confused bilane, N_2CB for doubly N-confused bilane, N_3CB for triply N-confused bilane, and N_4CB for quadruply N-confused bilane. Isomers of NCB, N_2CB, N_3CB, and N_4CB are listed in Scheme 1 with trivial names. Previously, NCB-(C_α,N,N,N) and NCB-(N,C_α,N,N) were prepared from N-confused dipyrromethane for the synthesis of N-confused corroles and norroles.[12] Importantly, this rule can also be applied to higher analogues, such as penta- and hexapyrrane.



Scheme 1. Structures and trivial names for bilane isomers.

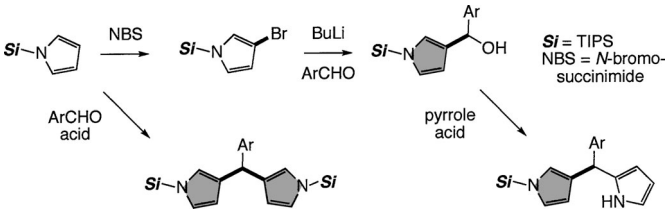
The numbering systems for dipyrromethane, tripyrrane, and bilane were reviewed. To retain systematic numbering, the positions of the nitrogen atoms in regular oligopyrroles are numbered at the end, as shown in Scheme 2. In the case of bilane, the 20-position is vacant, according to IUPAC recommendations.[13] Starting from regular oligopyrroles, nitrogen atoms are replaced with carbon atoms and the positions are indicated by "carba". Similarly, the carbon atoms are replaced with nitrogen atoms and then the positions are indicated by "aza". Specific examples of N-confused oligopyrroles are also shown in Scheme 2 with their compound names.



Scheme 2. Numbering systems for oligopyrroles.

General strategy: The introduction of N-confused pyrrole rings relied on steric repulsion imposed by an N-protecting group of the pyrrole ring.[5] Acylation, halogenation, and acid condensation reactions with pyrrole or dipyrromethane usually proceed regioselectively at the α position. When sterically demanding N-protecting groups, such as triisopropylsilyl (TIPS), are introduced, reactions proceed preferen-

tially at the β position.[14] With the aid of the TIPS group, singly and doubly N-confused dipyrromethane could be prepared as summarized in Scheme 3.[11,12] The β-substituted



Scheme 3. Preparation of singly and doubly N-confused dipyrromethanes.

pyrrole (or N-confused pyrrole), singly N-confused dipyrromethane, and doubly N-confused dipyrromethane are important building blocks for the synthesis of N-confused oligopyrroles. It should be noted that singly and doubly N-confused dipyrromethane derivatives could be prepared without nitrogen protection.[15] The effectiveness of TIPS protection is illustrated by the X-ray structure of N,N′-diprotected doubly N-confused dipyrromethane (Figure 1), in which the

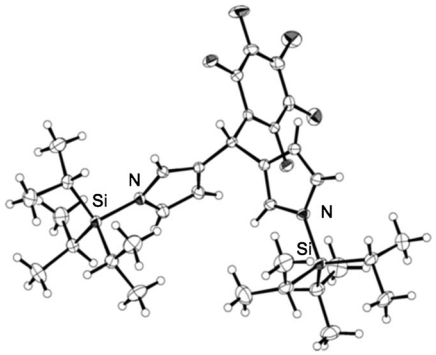
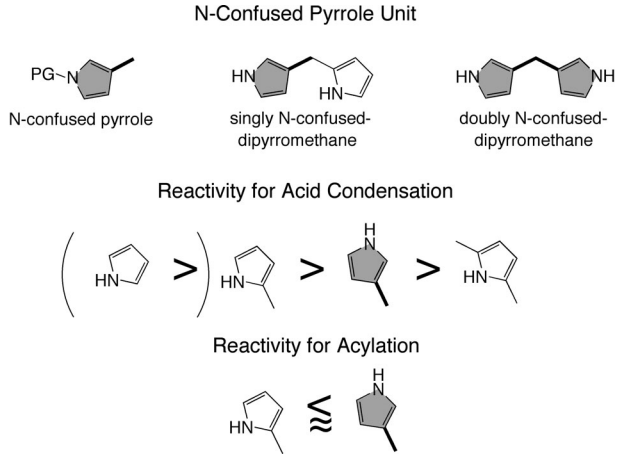


Figure 1. X-ray structure of N,N′-protected doubly N-confused dipyrromethane. Thermal ellipsoids are shown at the 30% probability level.

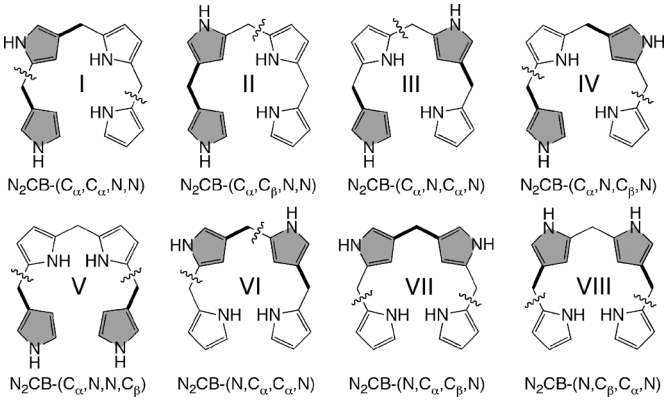
α positions of pyrrole rings are blocked by isopropyl groups.

The difference in reactivity between regular pyrrole and N-confused pyrrole is an important factor for the synthesis of N-confused oligopyrroles (Scheme 4). In acid condensation reactions, regular pyrrole usually shows a higher reactivity than that of N-confused pyrrole.[9f,g] Thus, it is better to avoid acid condensation for the synthesis of N-confused pyrrole in the presence of α-free regular pyrroles. The use of intact pyrrole is most favorable because excess amounts can be used readily. In the case of acylation reactions, regular pyrrole and N-confused pyrrole behave in a similar manner.[12] Nevertheless, N-confused pyrrole showed a higher reactivity than that of regular pyrrole for limited substrates (e.g., Scheme 15 below). To date, site-selective acylation in a reproducible fashion has been difficult. Importantly, a mixture of acylated products could be separated by standard silica gel column chromatography.



Scheme 4. Strategy for the synthesis of N-confused oligopyrroles.

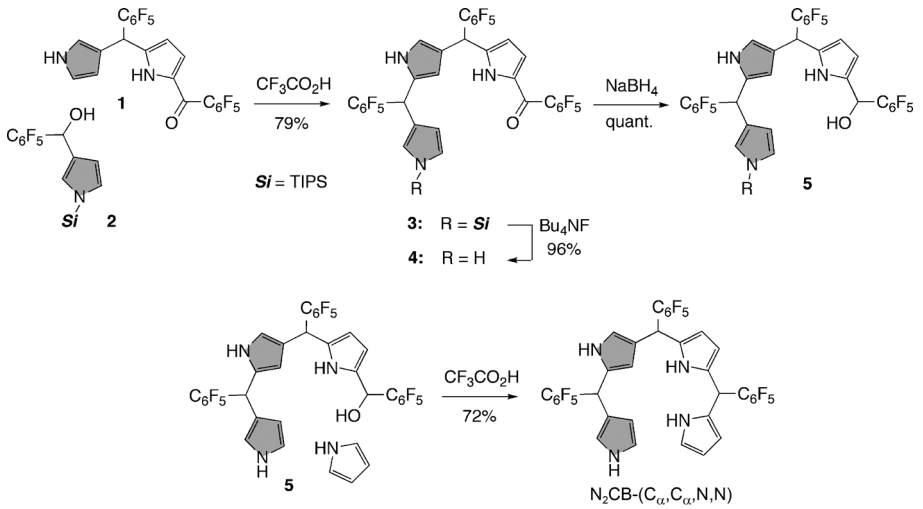
Based on the findings summarized in Scheme 4, retrosynthetic analysis for N_2CBs was achieved (Scheme 5). Each isomer is labeled with Roman numerals for clarity. Isomer-



Scheme 5. Retrosynthetic analysis of N_2CBs.

s II and VII could be synthesized from doubly N-confused dipyrromethane. Isomers III and VI could be prepared from singly N-confused dipyrromethane. Isomers I and IV require both an N-confused pyrrole derivative and singly N-confused dipyrromethane. Isomer V could be synthesized simply from an N-confused pyrrole derivative and regular dipyrromethane. Isomer VIII might be derived from doubly N-protected dipyrromethane, although this has not yet been developed. In general, the synthesis of N_2CBs with neighboring N-confused pyrrole rings is troublesome, except when doubly N-confused dipyrromethane is chosen as a starting precursor.

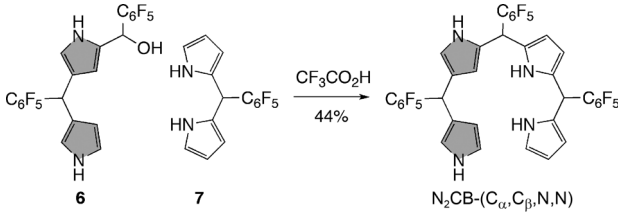
Synthesis of N_2CB-(C_α,C_α,N,N) (isomer I): The synthesis of isomer I required the reaction of N-confused pyrrole derivative **2** with singly N-confused dipyrromethane **1** (Scheme 6). Because acid condensation for the synthesis of the N-confused pyrrole ring is unfavorable, the α′ position of the regular pyrrole moiety in **1** was blocked by the acyl group to facilitate reaction at the N-confused pyrrole moiety. Treat-



Scheme 6. Synthesis of N_2CB-(C_α,C_α,N,N) (isomer I).

ment of an equimolar mixture of **1** and **2** with CF_3CO_2H gave doubly N-confused tripyrrane derivative **3** in 79% yield. Deprotection of **3** with Bu_4NF gave **4** in 96% yield and subsequent reduction with $NaBH_4$ gave doubly N-confused tripyrrane monocarbinol **5** quantitatively. Finally, acid condensation of **5** with pyrrole afforded isomer I in 72% yield.

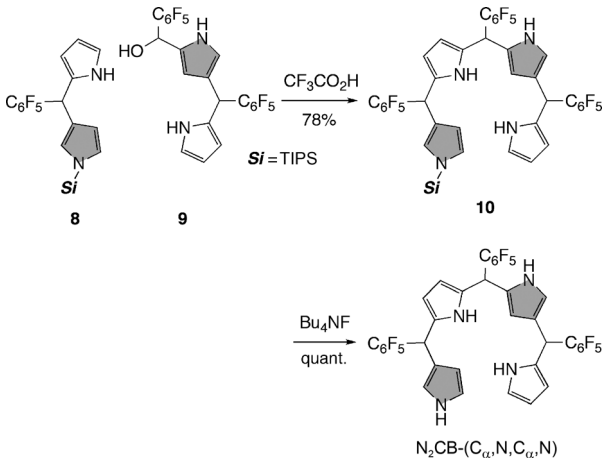
Synthesis of N_2CB-(C_α,C_β,N,N) (isomer II): The synthesis of isomer II was reported previously.[11] Acid-catalyzed condensation of doubly N-confused dipyrromethane monocarbinol **6** with regular dipyrromethane **7** gave isomer II in 44% yield (Scheme 7).



Scheme 7. Synthesis of N_2CB-(C_α,C_β,N,N) (isomer II).

Synthesis of N_2CB-(C_α,N,C_α,N) (isomer III): Isomer III can be constructed from two singly N-confused dipyrromethane units (Scheme 8). Thus, the reaction of N-protected N-confused dipyrromethane **8** with N-confused dipyrromethane monocarbinol **9** gave N-protected N_2CB **10**. In this reaction, an excess amount of **8** was used to prevent self-condensation of **9**. The reaction yield reached up to 78% when 7 equivalents of **8** were used. Importantly, 92% of **8** (corresponding to 5.5 equiv) was recovered after the reaction, indicating a smaller loss of the N-confused dipyrromethane unit. Deprotection of **10** with Bu_4NF proceeded smoothly to give isomer III in 97% yield.

Synthesis of N_2CB-(C_α,N,C_β,N) (isomer IV): A key intermediate for the synthesis of isomer IV was symmetrical doubly N-confused tripyrrane **12** (Scheme 9). Acid condensation of N-protected singly N-confused dipyrromethane **8** with **2** and subsequent deprotection with Bu_4NF afforded **12** in 63% yield (2 steps). Acylation of **12** gave monoacyl doubly N-confused tripyrrane **13** in 55% yield and reduction of **13** gave the corresponding carbinol **14** quantitatively. Finally, acid condensation of **14** with pyrrole gave isomer IV in 76% yield.

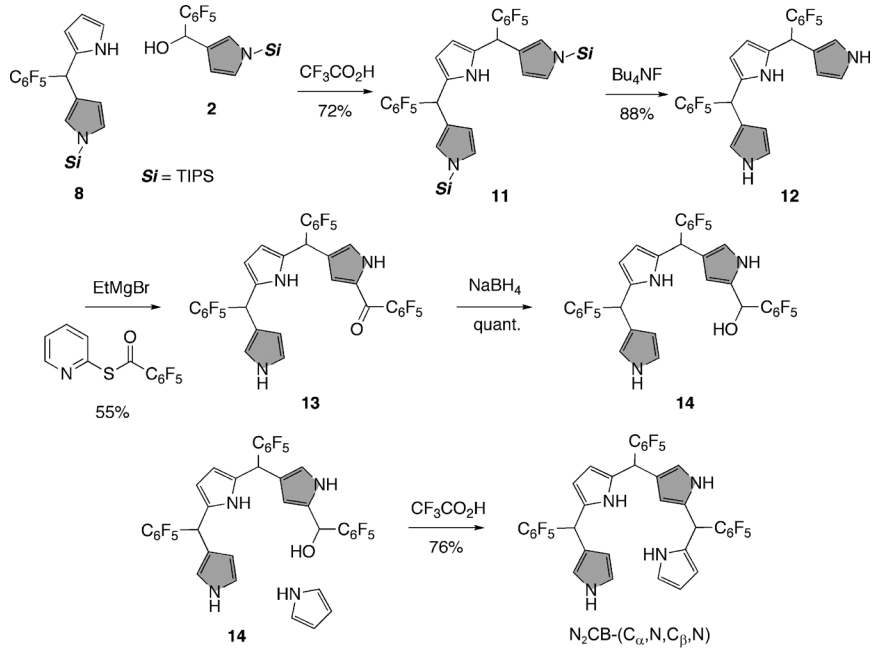


Scheme 8. Synthesis of N_2CB-(C_α,N,C_α,N) (isomer III).

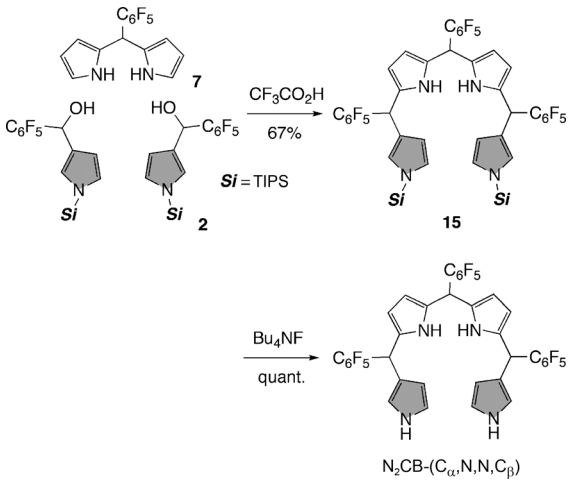
Synthesis of N_2CB-(C_α,N,N,C_β) (isomer V): Isomer V has a symmetrical structure and can be prepared in fewer steps (Scheme 10). The acid-catalyzed condensation reaction of regular dipyrromethane **7** with **2** gave N-protected N_2CB **15** in 67% yield. Deprotection of **15** with Bu_4NF gave isomer V quantitatively.

Synthesis of N_2CB-(N,C_α,C_α,N) (isomer VI): So far, it has been difficult to prepare the parent isomer VI by the strategy shown above because acid condensation toward N-confused pyrrole is essential at some stage. Nevertheless, the acyl derivative could be prepared by the acid condensation of monoacyl doubly N-confused tripyrrane **4**. Thus, the reaction of **4** with pyrrolyl carbinol **16** gave the monoacyl isomer VI (**17**) in 24% yield (Scheme 11).

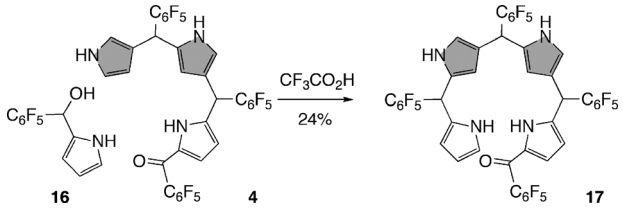
Synthesis of N_2CB-(N,C_α,C_β,N) (isomer VII): The synthesis of isomer VII has already been reported.[11] Upon treatment of doubly N-confused dipyrromethane dicarbinol **18** with pyrrole in the presence of CF_3CO_2H, isomer VII was obtained in 84% yield (Scheme 12).



Scheme 9. Synthesis of N_2CB-(C_α,N,C_β,N) (isomer IV).



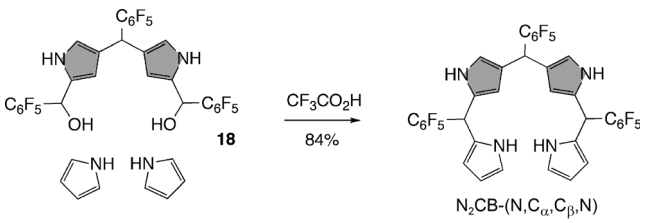
Scheme 10. Synthesis of N_2CB-(C_α,N,N,C_β) (isomer V).



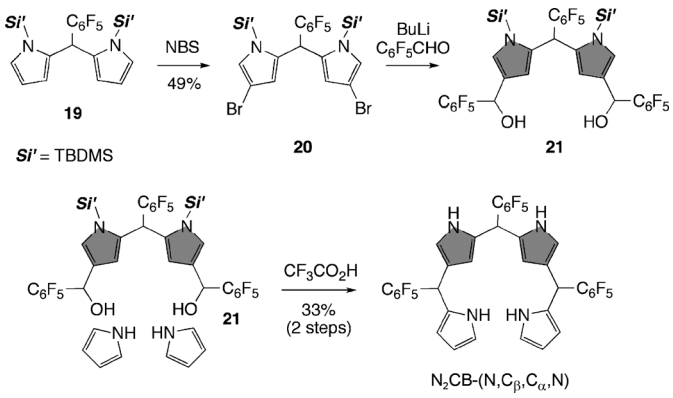
Scheme 11. Synthesis of monoacyl isomer VI (**17**).

Synthesis of N_2CB-(N,C_β,C_α,N) (isomer VIII): Isomer VIII was synthesized from N,N′-diprotected regular dipyrromethane (Scheme 13). In the early stage of synthetic study, we tried to prepare N,N′-bis-TIPS-dipyrromethane as a key intermediate. Although the desired compound was obtained by protection of regular dipyrromethane with TIPSCl under basic conditions, the product yield was low. Additionally, isomerization from regular dipyrromethane to N-confused dipyrromethane was observed under acidic conditions, such as in the presence of $AlCl_3$. Thus, less bulky *tert*-butyldimethylsilyl (TBDMS) groups were used in place of TIPS groups. Protection of regular dipyrromethane with TBDMSCl proceeded smoothly to give N,N′-bis-TBDMS-dipyrromethane **19** in 79% yield. Bromination of **19** occurred preferentially at the β position to give dibromo N,N′-bis-TBDMS-dipyrromethane **20** in 49% yield. Treatment of **20** with *n*BuLi followed by C_6F_5CHO afforded a crude product containing **21**. Although isolation of **21** in a pure form was difficult, acid condensation of the crude product with pyrrole successfully gave isomer VIII in 33% yield (2 steps); deprotection of the TBDMS groups occurred simultaneously.

Relative energy and conformation of N_2CB: To investigate the effect of confusion on the stability and structure of bilane skeletons, a conformational search on unsubstituted



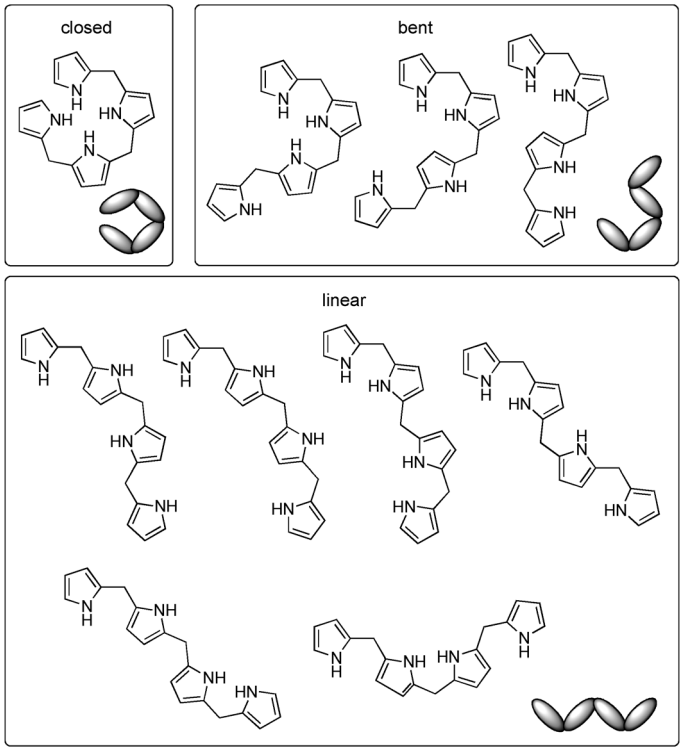
Scheme 12. Synthesis of N_2CB-(N,C_α,C_β,N) (isomer VII).



Scheme 13. Synthesis of N_2CB-(N,C_β,C_α,N) (isomer VIII).

N_2CBs was performed theoretically. Of course, numerous conformations for N_2CBs exist, so a thorough study was not achieved. Nevertheless, significant results were obtained through a synergy of systematic and arbitrary protocols.

Conformational studies were achieved as follows: When 3D structures were ignored, 10 representative conformers could be described for regular bilane, which were categorized into three groups: closed, bent, and linear (Scheme 14). These three categories were also applied to conformers of N_2CBs. Starting from an arbitrary conformation, conformers were generated by rotating 6 C–C bonds that connect the pyrrole rings in steps of 60°, namely, 6 dihedral angles were considered for each C–C bond and 46656 ($=6^6$) conformers were taken into consideration. The tentative stable conformers among the 46656 conformers were calculated by the Monte Carlo method at the PM3 level of semi-empirical calculations. Then, starting from the tentative stable conformer, 729 ($=3^6$) conformers were systematically generated by rotating the same 6 C–C bonds again in steps of 120°. All 729 conformers were optimized at the PM3 semi-empirical calculations and the stable closed, bent, and linear conformers were selected. Finally, the stable closed, bent, and linear conformers were further optimized at the B3LYP/6-31G** DFT level of calculations. Molecular symmetry and overlapping of the conformers were not considered during these studies.



Scheme 14. Representative conformers of regular bilane.

The relative energies for stable conformers of N_2CBs and regular bilane thus obtained are summarized in Figure 2. In the case of regular bilane, a closed conformer is most stable, which is consistent with the favorable formation of tetrapyrrolic porphyrins in pyrrole/aldehyde condensation reactions.[16] Bent and linear conformers are less stable by 1.0–1.2 kcal mol^{-1}. The predominance of closed conformers remains in isomers I–V of N_2CB. Interestingly, closed conformers become less stable in isomers VI–VIII, for which linear or bent conformers are most stable. Thus, the position of the N-confused pyrrole affects the conformation of the bilanes. A characteristic feature of isomers VI–VIII is the presence of adjacent N-confused pyrrole rings in the bilane skeleton. As a result, isomers VI–VIII might be not favorable for intramolecular cyclization reactions to give tetrapyrrolic N-confused porphyrinoids, although the relationship between bilane conformations and intramolecular cyclization reactions is not clear. Meanwhile, N_2CBs are less stable than regular bilane by only 3.7–5.7 kcal mol^{-1}. The loss of stability by confusion in the bilane skeleton is not so significant, which is in marked con-

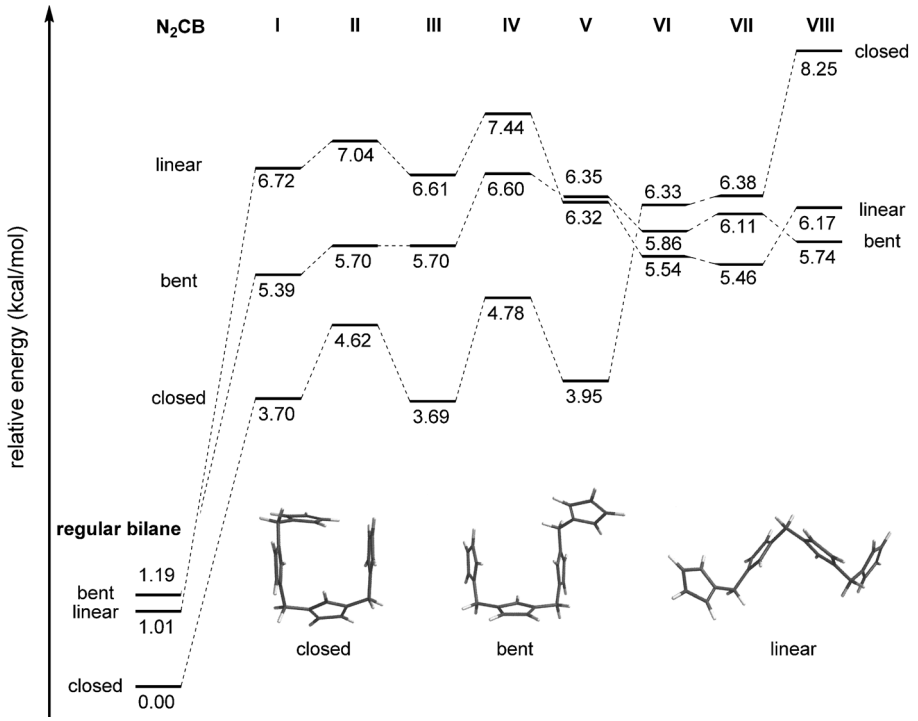


Figure 2. Relative energies for conformers of N_2CBs and regular bilane. Optimized structures for regular bilane are also shown.

trast to the large destabilization of doubly N-confused porphyrins (ca. 38 kcal mol^{-1}).[17]

Reactivity of N_2CB: To understand the reactivity of N_2CBs, predicting the most reactive pyrrole ring of the four pyrrole rings would be helpful. In other words, we want to know which pyrrole is more reactive: regular or N-confused. Because the preparation of porphyrinoids from oligopyrroles usually relies on oxidation or electrophilic acid-catalyzed condensation reactions, orbital coefficients in the HOMO can be regarded as an approximate measure of reactivity. Clearly, the HOMO of oligopyrrole is composed of pyrrole π orbitals. The HOMOs of regular bilane and N_2CBs for the closed conformers are shown in Figure 3. The pyrrole rings

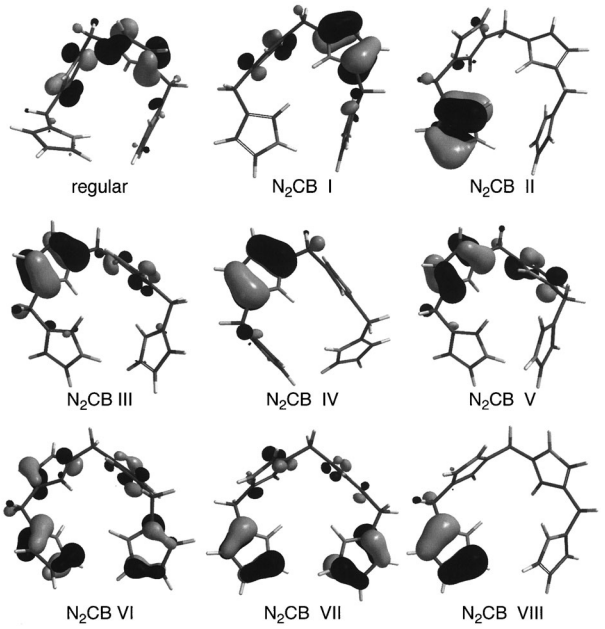


Figure 3. HOMOs of regular bilane and N_2CBs.

that are the major contributors to the HOMO of regular bilane and N_2CBs for all three conformations are listed in Table 1. Essentially, the HOMO of N_2CB is composed of regular pyrrole rings in almost all cases. In addition, it is less dependent on the conformation. The only exceptions are isomers II and VII, for which significant contribution from the N-confused pyrrole rings is recognized in the HOMO. Specifically, the β,β-linked doubly N-confused dipyrromethane unit is highly reactive. The other N-confused pyrrole rings might be less reactive than the regular pyrrole rings.

Table 1. Pyrrole rings that are the major contributors to the HOMO of regular bilane and N_2CBs.[a]

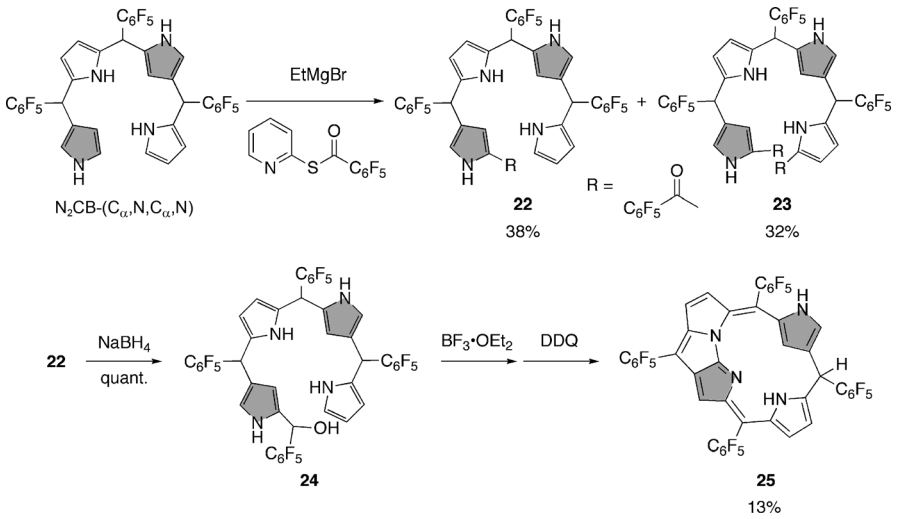
Conformer	Regular bilane	N_2CB I	II	III	IV	V	VI	VII	VIII
linear	BC	C	*B*	D	B	BC	A	A*B*	A
bent	ABC	C	*B*C	D	B	BC	A	A*B*	A
closed	BC	C	*A*	B	B	BC	AD	AD	A

[a] Normal text refers to the regular pyrrole ring, whereas italic text refers to the N-confused pyrrole ring.

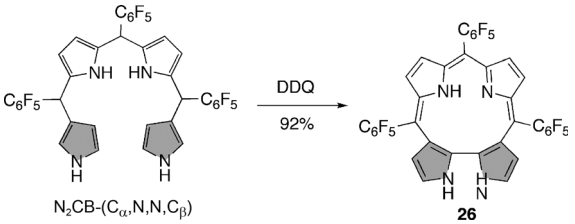
Some of the N_2CBs could be used to prepare reported N-confused porphyrinoids in an alternative synthetic pathway. A synthetic study of new N-confused porphyrinoids by utilizing other N_2CBs is the next stage of our research.

Isomer III can be used as a precursor of N-confused N-fused phlorin (Scheme 15).[9e] Thus, acylation of isomer III afforded monoacylated product **22** and diacylated product **23** in 38 and 32% yield, respectively. Reduction of **22** gave monocarbinol **24** and subsequent intramolecular acid condensation followed by DDQ oxidation afforded N-confused N-fused phlorin **25** in 13% yield. The reaction yield is comparative to that reported for the [2+2] acid condensation pathway. The lower yield was partly explained by scrambling reactions because triply N-confused hexaphyrin was detected in the crude mixture.[9a]

Isomer V can be converted into corrorin.[18] Corrorin (**26**) was previously obtained in 13% yield through a [2+2] acid-catalyzed condensation reaction of N-confused dipyrromethane. This time, the intramolecular oxidative cyclization reaction of isomer V was examined. Treatment of isomer V with DDQ (3.5 equiv) in CH_3CN gave **26** in 92% yield (Scheme 16). High efficiency of intramolecular cyclization reaction might be rationalized by the conformation of isomer V, which prefers the closed conformation, as shown in Scheme 14.

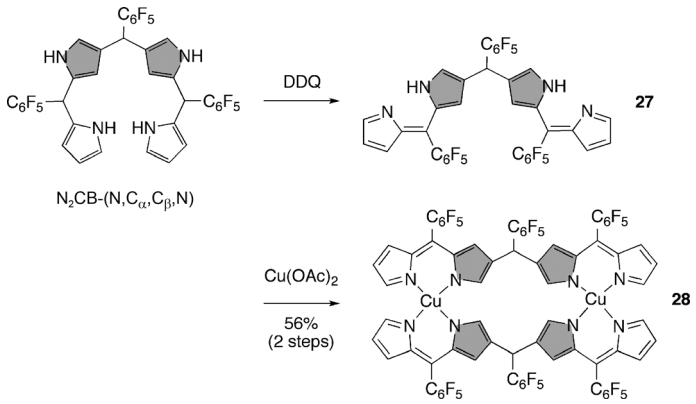


Scheme 15. Synthesis of N-confused N-fused phlorin from N_2CB-(C_α,N,C_α,N) (isomer III). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



Scheme 16. Synthesis of corrorin (**26**) from N_2CB-(C_α,N,N,C_β) (isomer V).

When isomer VII was oxidized by DDQ, no cyclized product was obtained. This is consistent with the fact that the closed conformer would be less stable in isomer VII (Figure 2). In turn, the formation of doubly N-confused biladiene **27**, which was readily decomposed on silica gel and alumina, was suggested by ^{1}H NMR spectroscopic analysis. Although isolation of **27** itself was difficult, the addition of $Cu(OAc)_2$ to a solution of **27** in toluene caused a color change from brown to red, which implied the formation of a copper complex. After passing the crude mixture through a pad of alumina and recrystallization from CH_2Cl_2/heptane, the doubly N-confused biladiene copper(II) complex **28** was obtained in 56% yield (Scheme 17). The X-ray structure of **28** is shown in Figure 4. Two copper atoms are chelated by the doubly N-confused biladienes in a 2:2 fashion, forming a unique helical structure. Similar structures were previously reported for β-alkyl-substituted bilane derivatives.[19]



Scheme 17. Oxidation and copper(II) metallation of N_2CB-(N,C_α,C_β,N) (isomer VII).

Conclusion

A series of doubly N-confused bilanes were synthesized and their reactivity was analyzed theoretically as well as experimentally. Although we succeeded in the preparation of N_2CBs, the reaction yields were limited in some cases, and thus, the development of a new synthetic method for β-selective reactions of the pyrrole ring can be expected. Nevertheless, the strategy and concept developed herein is applicable to higher oligopyrroles and could accelerate the development of N-confused and N-fused porphyrinoid chemistry. The formation of fascinating macrocyclic compounds by using N_2CBs can also be expected in the near future.

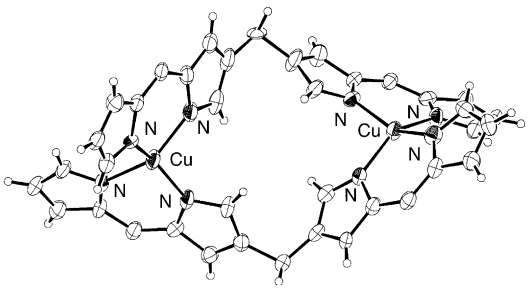


Figure 4. X-ray structure of the doubly N-confused biladiene copper(II) complex (**28**). The pentafluorophenyl groups are omitted for clarity. Thermal ellipsoids are shown at the 30% probability level.

Experimental Section

General: All reactions were performed in oven-dried reaction vessels under Ar or N_2. Commercially available solvents and reagents were used without further purification, unless otherwise stated. Dry THF (stabilizer free) was purchased from Kanto. *N*-Bromosuccinimide (NBS) was recrystallized from water. CH_2Cl_2 was distilled over CaH_2. TLC was carried out on aluminum sheets coated with silica gel 60 F_{254} (Merck). Preparative separation was performed by silica gel flash column chromatography (Kanto silica gel 60 N, spherical, neutral, 40–50 μm) and silica gel gravity column chromatography (Kanto silica gel 60 N, spherical, neutral, 63–210 μm). ^{1}H NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-AL series FTNMR (300 MHz) spectrometer at ambient temperature and chemical shifts were reported relative to the residual solvent (δ = 7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ on the same instrument and chemical shifts were reported relative to $CDCl_3$ (δ = 77.00 ppm). UV/Vis absorption spectra were recorded on a Shimadzu UV-3150PC spectrometer. Mass spectra were recorded on a Bruker Daltonics autoflex MALDI-TOF MS spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-T100CS spectrometer. Compounds **1**, **2**, **7**, and **8** were prepared as reported.[12] Synthesized tripyrrane and bilane derivatives should be a mixture of diastereomers. In addition, complicated long-range couplings existed due to ^{19}F atoms and then complete assignment of the NMR spectroscopy signals was nearly impossible, especially for ^{13}C NMR spectra. Thus, it was difficult to avoid ambiguity to some degree. Many ^{13}C NMR spectroscopy signals were observed as doublets or multiplets; hence, superscript f, d, and m are used to show the following signal patterns: f = further multiplet coupling due to remote ^{13}C–^{19}F coupling and signals were often not clear due to low intensity; thus, the chemical shift and ^1J(C,F) value would have some margin of error up to 0.2 ppm (or 15 Hz); d = double singlets, probably from the mixture of diastereomers; signal intensities were not always identical because they depended on the diastereomeric ratio; and m = multiple singlets, probably from the mixture of diastereomers.

Compound 3: Trifluoroacetic acid (TFA; 30 μL, 0.40 mmol) was added to a stirred solution of mixture containing **1** (1.0 g, 1.98 mmol) and **2** (0.828 g, 1.98 mmol) in CH_2Cl_2 under argon. The solution was stirred for 90 min and then neutralized with triethylamine. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 6:4 (v/v)), afforded **3** as a pale yellow, foamlike solid (79%, 1.42 g, 1.56 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.07 (d, J = 7.5 Hz, 9H), 1.08 (d, J = 7.5 Hz, 9H), 1.42 (septet, J = 7.5 Hz, 3H), 5.74 (s, 1H), 5.77 (s, 1H), 5.92 (s, 1H), 6.04–6.06 (m, 1H), 6.21 (s, 1H), 6.62 (s, 3H), 6.75–6.77 (m, 1H), 8.18 (brs, 1H), 9.45 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.6, 17.7, 32.3, 32.7, 106.2,[d] 110.2, 110.9, 114.0,[f] 115.5,[d]

116.2,[f] 117.7,[f] 119.4, 122.4,[d] 122.6,[d] 125.2,[d] 130.6, 132.7,[d] 137.7 (d, ^1J(C,F) = 249 Hz),[f] 140.1 (d, ^1J(C,F) = 247 Hz),[f] 142.1 (d, ^1J(C,F) = 257 Hz),[f] 144.2 (d, ^1J(C,F) = 250 Hz),[f] 143.1,[d] 144.9 (d, ^1J(C,F) = 246 Hz),[f] 171.7 ppm; IR (powder): $\tilde{\nu}$ = 1628 cm^{-1} (CO); elemental analysis calcd (%) for $C_{42}H_{32}F_{15}N_3OSi$: C 55.57, H 3.55, N 4.63; found: C 55.32, H 3.57, N 4.46.

Compound 4 (including a general procedures for deprotection): Compound **3** (1.0 g, 1.1 mmol) was dissolved in dry THF at room temperature in a 100 mL round-bottomed flask and purged with argon. Then Bu_4NF (1.14 mL, 1.14 mmol, 1.0 M in THF) was added slowly for 5 min and the resulting mixture was stirred for 1 h. After deprotection was complete (as monitored by TLC), the reaction was quenched with water and the organic layer was separated, washed twice with water, and dried (Na_2SO_4). Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 7:3 (v/v)), afforded **4** as a foamlike solid (96%, 0.79 g, 1.05 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (s, 1H), 5.78 (s, 1H), 5.96 (s, 1H), 6.07–6.09 (m, 1H), 6.16 (s, 1H), 6.60–6.64 (m, 1H), 6.68 (s, 1H), 6.78–6.80 (m, 1H), 8.27 (brs, 2H), 9.66 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.2, 32.7, 106.3,[d] 108.2, 110.9, 113.9,[f] 115.7,[d] 116.1,[f] 116.5,[d] 117.5,[f] 118.8, 119.4, 120.7,[d] 122.6, 130.6, 132.3,[d] 137.7 (d, ^1J(C,F) = 249 Hz),[f] 140.2 (d, ^1J(C,F) = 247 Hz),[f] 142.2 (d, ^1J(C,F) = 257 Hz),[f] 143.1,[d] 143.8 (d, ^1J(C,F) = 250 Hz),[f] 144.9 (d, ^1J(C,F) = 247 Hz),[f] 171.7 ppm; IR (powder): $\tilde{\nu}$ = 1622 cm^{-1} (CO); elemental analysis calcd (%) for $C_{33}H_{12}F_{15}N_3O$: C 52.75, H 1.61, N 5.59; found: C 53.17, H 1.69, N 5.55.

Isomer I (including a general procedures for reduction): Compound **4** (0.75 g, 1.0 mmol) in THF (30 mL) and methanol (6 mL) in a 50 mL round-bottomed flask was treated with the portions of $NaBH_4$ (0.94 g, 25.0 mmol). After reduction was complete (as monitored by TLC), the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (20 mL) and CH_2Cl_2 (40 mL) in a 200 mL beaker. The organic layer was separated, washed twice with water, and dried (Na_2SO_4). Removal of the solvent under vacuum yielded monocarbinol **5** as a foamlike solid. Then pyrrole (1.73 mL, 25.0 mmol) was added and the reaction mixture was stirred for 5 min under argon. TFA (19 μL, 0.25 mmol) was then added and the reaction mixture was stirred for an additional 1 h and quenched with triethylamine. Removal of excess pyrrole, followed by column chromatography on silica gel (CH_2Cl_2/hexane 6:4 (v/v)), afforded isomer I as an off-white foamlike solid (72%, 0.58 g, 0.72 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.70 (s, 1H), 5.72 (s, 1H), 5.82–5.86 (m, 3H), 5.92–5.95 (m, 2H), 6.12–6.15 (m, 2H), 6.45 (s, 1H), 6.62 (s, 1H), 6.71 (d, J = 1.2 Hz, 1H), 6.78 (d, J = 2.7 Hz, 1H), 8.10–8.20 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.6, 32.8, 33.5, 106.6,[m] 107.1,[m] 107.7,[d] 108.4,[d] 108.7, 109.0,[d] 115.7,[d] 116.2,[f] 116.9,[d] 118.0,[f] 118.2,[m] 119.2, 121.3,[m] 121.7,[m] 127.4,[m] 128.6,[m] 131.6,[m] 132.3,[m] 138.1 (d, ^1J(C,F) = 251 Hz),[f] 140.6 (d, ^1J(C,F) = 244 Hz),[f] 145.3 ppm (d, ^1J(C,F) = 245 Hz)[f]; elemental analysis calcd (%) for $C_{37}H_{27}F_{15}N_4$: C 55.37, H 2.14, N 6.98; found: C 55.70, H 2.17, N 6.93.

Compound 10: A sample of 2-pentafluorobenzoyl-5-pentafluorophenyl-1-aza-10-carbadipyrromethane (1.35 g, 2.67 mmol) was reduced with $NaBH_4$ (2.52 g, 66.8 mmol), according to the general procedure, giving **9** in a quantitative manner as a pale yellow, foamlike solid. Compound **9** was treated with **8** (8.75 g, 18.7 mmol) in CH_2Cl_2 and stirred for 5 min under argon before TFA (62 μL, 0.8 mmol) was added slowly to the reaction mixture. After stirring for 1 h at room temperature, triethylamine (0.11 mL, 0.8 mmol) was added and removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 6:4 (v/v)), afforded **10** as a pale yellow foamlike solid (78%, 2.0 g, 2.09 mmol), along with recovered **8** (6.87 g, 14.7 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.05 (d, J = 7.5 Hz, 18H), 1.39 (septet, J = 7.5 Hz, 3H), 5.71 (s, 1H), 5.75 (s, 2H), 5.81 (d, J = 2.7 Hz, 1H), 5.86 (s, 1H), 5.95–6.01 (m, 2H), 6.12–6.14 (m, 2H), 6.50 (s, 1H), 6.55 (s, 1H), 6.69 (s, 1H), 6.73 (s, 1H), 7.96–8.20 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.5, 17.6, 32.3, 32.1, 106.6,[m] 106.7,[m] 107.1, 108.4,[m] 109.9,[d] 115.4,[f] 116.2, 117.0,[d] 117.8,[f] 122.0,[m] 122.4,[d] 122.7, 125.3,[d] 126.4,[m] 129.2,[m] 130.2,[d] 131.8,[m] 137.8 (d, ^1J(C,F) = 241 Hz),[f] 140.0 (d, ^1J(C,F) = 247 Hz),[f] 144.9 ppm (d, ^1J(C,F) = 242 Hz)[f]; elemental analysis calcd (%) for $C_{46}H_{37}F_{15}N_4Si$: C 57.62, H 3.89, N 5.84; found: C 57.83, H 3.98, N 5.81.

Isomer III: Compound **10** (1.0 g, 1.04 mmol) was deprotected with Bu_4NF, according to the general procedure. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 7:3 (v/v)), afforded isomer III as a foamlike solid (97%, 0.81 g, 1.01 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.73 (s, 1H), 5.76 (s, 1H), 5.77 (s, 1H), 5.87–5.89 (m, 2H), 5.93–5.98 (m, 2H), 6.07 (s, 1H), 6.14–6.17 (m, 1H), 6.54 (s, 1H), 6.58 (s, 1H), 6.69–6.71 (m, 1H), 6.75–6.76 (m, 1H), 8.05 (brs, 1H), 8.18 ppm (brs, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.3, 33.1, 106.8,[m] 107.2, 108.0, 108.4, 115.4,[f] 116.3, 117.1,[d] 117.7,[f] 118.8, 121.0,[d] 122.0,[d] 126.5, 129.3, 130.3,[d] 131.3, 137.9 (d, ^1J(C,F) = 240 Hz),[f] 140.0 (d, ^1J(C,F) = 252 Hz),[f] 144.9 ppm (d, ^1J(C,F) = 241 Hz)[f]; elemental analysis calcd (%) for $C_{37}H_{27}F_{15}N_4$: C 55.37, H 2.14, N 6.98; found: C 55.59, H 2.26, N 6.68.

Compound 11: TFA (55.5 μL, 0.72 mmol) was added to a stirred solution of **2** (2.1 g, 4.77 mmol) and **8** (3.16 g, 4.77 mmol) in CH_2Cl_2 under argon. The solution was stirred for 90 min and then neutralized with triethylamine. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 5:95 (v/v)), afforded **11** as a fluorescent orange solid (72%, 3.0 g, 3.45 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.05 (d, J = 7.5 Hz, 36H), 1.40 (septet, J = 7.5 Hz, 6H), 5.75 (s, 2H), 5.85–5.92 (m, 2H), 6.10–6.12 (m, 2H), 6.54 (s, 2H), 6.68–6.71 (m, 2H), 8.18 and 8.31 ppm (both brs, 1H in total)* [*NH signals for each diastereomer would be observed separately]; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.7, 17.7, 32.5, 106.5, 110.1, 122.3, 123.3, 124.9, 130.0, 137.6 (d, ^1J(C,F) = 250 Hz),[f] 139.8 (d, ^1J(C,F) = 252 Hz),[f] 144.9 ppm (d, ^1J(C,F) = 241 Hz)[f]; elemental analysis calcd (%) for $C_{44}H_{53}F_{10}N_3Si$: C 60.74, H 6.14, N 4.83; found: C 60.52, H 6.15, N 4.76.

Compound 12: Compound **11** (2.22 g, 2.56 mmol) was dissolved in dry THF at room temperature and treated with Bu_4NF, according to the general procedure. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 4:6 (v/v)), afforded **12** as a foamlike solid (88%, 1.25 g, 2.24 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (s, 2H), 5.87–5.90 (m, 2H), 6.08 (s, 2H), 6.59 (s, 2H), 6.75 (d, J = 1.8 Hz, 2H), 8.15 (brs, 2H), 8.23 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.4, 106.7, 108.1, 116.2, 118.5, 121.6, 129.8, 137.6 (d, ^1J(C,F) = 253 Hz),[f] 139.9 (d, ^1J(C,F) = 253 Hz),[f] 144.8 ppm (d, ^1J(C,F) = 247 Hz)[f].

Compound 13: A solution of EtMgBr (7.18 mL, 7.18 mmol, 1.0 M in THF) was carefully added to a stirred solution of **12** (1.0 g, 1.79 mmol) in THF (10 mL) under argon. The mixture was stirred at room temperature for 20 min and then cooled to −78 °C. A solution of S-2-pyridyl pentafluorobenzothioate (602 mg, 1.97 mmol) in THF (5 mL) was then added over 1 min. The solution was maintained at −78 °C for 30 min and the temperature was raised to 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the mixture was allowed to warm to ambient temperature, poured into CH_2Cl_2, washed with water, and then dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure to afford a dark foam, which was purified by column chromatography on silica gel (CH_2Cl_2/hexane 7:3 (v/v)) to give **13** as a golden amorphous solid (55%, 0.74 g, 0.99 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.69 (s, 1H), 5.76 (s, 1H), 5.86–5.98 (m, 2H), 6.07 (s, 1H), 6.51 (s, 1H), 6.59 (s, 1H), 6.75–6.77 (m, 1H), 6.99–7.03 (m, 1H), 8.12 (brs, 1H), 8.22 (brs, 1H), 9.87 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.1, 32.3, 106.6, 107.9, 108.2, 113.5,[f] 116.3, 116.4,[f] 117.8,[f] 118.9, 120.1, 121.0, 126.3, 127.0,[m] 127.7, 131.1, 131.6, 137.6 (d, ^1J(C,F) = 251 Hz),[f] 140.0 (d, ^1J(C,F) = 253 Hz),[f] 142.4 (d, ^1J(C,F) = 258 Hz),[f] 143.9 (d, ^1J(C,F) = 252 Hz),[f] 144.8 (d, ^1J(C,F) = 253 Hz),[f] 172.9 ppm; IR (powder): $\tilde{\nu}$ = 1625 cm^{-1} (CO).

Isomer IV: Compound **13** (0.70 g, 0.93 mmol) was reduced with $NaBH_4$ (0.88 g, 23.3 mmol), according to the general procedure. The resulting carbinol **14** was treated with pyrrole (1.6 mL, 13.3 mmol) in the presence of TFA (14.4 μL, 0.19 mmol) for 1 h and then neutralized with triethylamine. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 6:4 (v/v)), afforded isomer IV as a pale yellow foamlike solid (76%, 0.57 g, 0.71 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.68 (s, 1H), 5.75 (s, 1H), 5.82 (s, 1H), 5.85–5.89 (m, 3H), 6.03–6.05 (m, 2H), 6.16–6.17 (m, 1H), 6.48 (s, 1H), 6.56 (s, 1H), 6.75 (s, 2H), 8.04 (brs, 1H), 8.15–8.25 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 32.3, 33.0, 106.8,[m] 107.2, 108.0,[d] 108.7, 115.3,[f] 116.3,[d] 117.7,[f] 118.4, 118.6,[m] 121.6,[d] 122.1,[d] 127.6, 129.3,[m] 129.9,[d] 137.6 (d, ^1J(C,F) = 250 Hz),[f] 140.2 (d,

^1J(C,F)=250 Hz),[f] 144.8 ppm (d, ^1J(C,F)=245 Hz)[f]; HRMS (ESI$^+$): *m/z* calcd for $C_{37}H_{17}F_{15}N_4$ [M^+]: 802.12137; found: 802.12586.

Compound 15: A solution of **7** (400 mg, 1.28 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of **2** (2.0 g, 4.77 mmol, 3.7 equiv) and CF_3CO_2H (40 μL, 0.520 mmol, 0.4 equiv) in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was warmed to ambient temperature and stirred for 12 h. Then, the reaction was quenched with an aqueous solution of NaOH and diluted with CH_2Cl_2 and water. The organic phase was separated, washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue was separated by column chromatography on silica gel using hexane/CH_2Cl_2 4:1 (v/v) as the eluent. The first fraction (R_f= 0.80, hexane/CH_2Cl_2 1:1 (v/v)) afforded **15** as a clear oil (67%, 950 mg, 0.85 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.09 (d, J=7.5 Hz, 18H), 1.10 (d, J=7.5 Hz, 18H), 1.44 (septet, J=7.5 Hz, 6H), 5.79 (s, 3H), 5.85 (d, J=3.0 Hz, 2H), 5.90 (d, J=3.0 Hz, 2H), 6.15–6.20 (m, 2H), 6.59–6.63 (m, 2H), 6.75–6.79 (m, 2H), 8.08 ppm (brs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=11.6, 17.7, 32.4, 33.3, 106.5,[d] 107.6,[d] 110.1, 122.4,[d] 122.8,[m] 125.2,[d] 127.0,[m] 131.2, 137.6 (d, ^1J(C,F)=249.1 Hz),[f] 140.0 (d, ^1J(C,F)= 252.8 Hz),[f] 144.9 ppm (d, ^1J(C,F)=241.7 Hz)[f]; HRMS (ESI$^+$): *m/z* calcd for $C_{55}H_{57}F_{15}N_4Si_2$ [M+H]$^+$: 1115.39605; found: 1115.39680.

Isomer V: Compound **15** (67 mg, 0.061 mmol) was deprotected with Bu_4NF, according to the general procedure. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane=6/4 (v/v)), afforded isomer V as a foamlike solid (99%, 49 mg, 0.061 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.75 (s, 2H), 5.78 (s, 1H), 5.86–5.91 (m, 4H), 6.08 (s, 2H), 6.59 (s, 2H), 6.75–6.77 (m, 2H), 8.11 (brs, 2H), 8.16 ppm (brs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=32.3, 33.2, 106.8,[m] 107.7,[d] 108.0,[m] 115.8,[f] 116.3, 117.7,[f] 118.7,[d] 121.0,[d] 127.1,[d] 130.9,[d] 137.6 (d, ^1J(C,F)=253 Hz),[f] 140.0 (d, ^1J(C,F)=253 Hz),[f] 144.8 ppm (d, ^1J(C,F)= 247 Hz)[f]; HRMS (ESI$^+$): *m/z* calcd for $C_{37}H_{18}F_{15}N_4$ [M+H]$^+$: 803.12919; found: 803.13118.

Compound 17: TFA (7.8 μL, 0.1 mmol) was added to a stirred mixture of **4** (0.38 g, 0.51 mmol) and **16** (0.16 g, 0.61 mmol) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture was quenched with triethylamine after 1 h and evaporated in vacuo. Removal of the solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 9:1 (v/v)), afforded **17** as a pale yellow foamlike solid (24%, 0.12 g, 0.12 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.65 (s, 1H), 5.69 (s, 1H), 5.74 (s, 1H), 5.83 (s, 1H), 5.99–6.01 (m, 2H), 6.10 (s, 1H), 6.50 (s, 1H), 6.62 (s, 2H), 6.74–6.77 (m, 2H), 8.20 (brs, 2H), 8.49 (brs, 1H), 9.40 ppm (brs, 1H); HRMS (ESI$^+$): *m/z* calcd for $C_{44}H_{17}F_{20}N_{4O}$ [M+H]$^+$: 997.10830; found: 997.10804.

Compound 19: A stirred suspension of NaH (769 mg, 19.2 mmol) in THF (150 mL) was treated with 5-pentafluorophenyldipyrromethane (2.0 g, 6.4 mmol) at 0 °C. When the evolution of gas ceased, the mixture was stirred for 1 h at room temperature before being treated with *tert*-butyldimethylsilylchloride (1.93 g, 12.8 mmol). After 12 h, the reaction mixture was quenched using saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). Removal of solvent, followed by column chromatography on silica gel (CH_2Cl_2/hexane 1:9 (v/v)), afforded **19** as a white crystalline solid (79%, 2.73 g, 5.0 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.19 (s, 6H), 0.35 (s, 6H), 0.81 (s, 18H), 5.58 (s, 1H), 5.62 (brs, 2H), 6.13 (t, J= 3.0 Hz, 2H), 6.77–6.79 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= −4.6, −2.8, 19.0, 26.2, 36.6, 109.5, 113.5, 117.8,[f] 126.1, 136.8, 137.6 (d, ^1J-(C,F)=255 Hz),[f] 140.1 (d, ^1J(C,F)=253 Hz),[f] 144.8 ppm (d, ^1J(C,F)= 247 Hz)[f]; elemental analysis calcd (%) for $C_{27}H_{37}F_5N_2Si_2$: C 59.97, H 6.90, N 5.18; found: C 59.88, H 6.93, N 5.15.

Compound 20: A solution of **19** (1.5 g, 2.78 mmol) in dry THF (25.0 mL) at −78 °C under argon was treated with NBS (1.04 g, 5.83 mmol). The reaction mixture was stirred for 1 h at −78 °C and gradually warmed up to −20 °C. After adding hexane (50 mL) and water (5 mL), the mixture was warmed up to ambient temperature. The organic layer was separated, dried (Na_2SO_4), and concentrated. The resulting pale yellow solid was purified by column chromatography on alumina with hexane as the eluent to afford **20** as a white solid (49%, 0.95 g, 1.36 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.19 (s, 6H), 0.35 (s, 6H), 0.81 (s, 18H), 5.47 (s, 1H), 5.66 (s, 2H), 6.73 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= −4.4, −2.8, 18.9, 26.1, 36.4, 97.4, 116.1, 116.2,[f] 125.6, 136.9, 137.8 (d, ^1J(C,F)= 256 Hz),[f] 140.4 (d, ^1J(C,F)=253 Hz),[f] 145.2 ppm (d, ^1J(C,F)=247 Hz)[f]; elemental analysis calcd (%) for $C_{27}H_{35}Br_2F_5N_2Si_2$: C 46.42, H 5.05, N 4.01; found: C 47.13, H 5.08, N 4.01 (this compound undergoes gradual decomposition even in the solid state).

Isomer VIII: *n*BuLi (5.38 mL, 3.44 mmol, 4.0 equiv) was added dropwise to a stirred solution of **20** (600 mg, 0.86 mmol) in anhydrous THF at −78 °C and the resulting mixture was stirred for 1 h at −78 °C. Pentafluorobenzaldehyde (265 μL, 2.15 mmol, 2.5 equiv) in THF (15 mL) was added slowly and stirring was continued for an additional 1 h at −78 °C. The cooling bath was removed and the mixture was allowed to warm to room temperature. Then a saturated aqueous solution of NH_4Cl was added and the mixture was diluted with Et_2O. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting pale yellow oil, including **21**, was used for the next step without further purification. Pyrrole (3.7 mL, 53.4 mmol) was added to the above oil and stirred under argon for 5 min. Then TFA (10 μL, 0.13 mmol) was added and the solution was stirred for an additional 2 h. The reaction was quenched with triethylamine and excess pyrrole was removed under vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/hexane 6:4 (v/v)) to afford isomer VIII as a pale yellow foamlike solid (33%, 0.228 g, 0.284 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.73 (s, 2H), 5.78 (s, 1H), 5.92 (s, 2H), 5.98 (s, 2H), 6.13–6.16 (m, 2H), 6.55 (s, 2H), 6.67–6.71 (m, 2H), 8.06 (brs, 2H), 8.18 ppm (brs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=32.3, 33.1, 106.8,[d] 107.8, 108.4, 114.9,[f] 116.7, 117.2, 117.5,[f] 122.2,[d] 128.6,[d] 130.1,[d] 137.7 (d, ^1J(C,F)=251 Hz),[f] 140.0 (d, ^1J-(C,F)=253 Hz),[f] 144.8 ppm (d, ^1J(C,F)=242 Hz)[f]; HRMS (ESI$^+$): *m/z* calcd for $C_{37}H_{17}F_{15}N_4$ [M]$^+$: 802.12137; found: 802.12383.

Compound 22: A solution of EtMgBr (5.0 mL, 5.0 mmol, 1.0 M in THF) was added dropwise to a stirred solution of isomer III (1.0 g, 1.25 mmol) in THF (10 mL) under argon. After stirring at room temperature for 20 min, a solution of *S*-2-pyridyl pentafluorobenzothioate (382 mg, 1.25 mmol) in THF (5 mL) was added over 1 min at −78 °C. The temperature was raised to 0 °C after stirring the resulting mixture at −78 °C for 30 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the mixture was allowed to warm to ambient temperature, poured into CH_2Cl_2, washed with water, and then dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure to give a dark foam, which was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc=98/2 (v/v)), to give **22** as a pale yellow solid (38%, 0.45 g, 0.45 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.69 (s, 1H), 5.72 (s, 1H), 5.77 (s, 1H), 5.89–5.99 (m, 4H), 6.14–6.18 (m, 1H), 6.49 (s, 1H), 6.53 (s, 1H), 6.70–6.71 (m, 1H), 6.97–6.99 (m, 1H), 8.04 (brs, 2H), 8.18 (brs, 1H), 9.80 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=32.1, 32.3, 33.1, 106.9,[d] 107.5,[m] 108.0,[m] 108.4, 113.4,[f] 115.1,[f] 116.0,[f] 116.6, 117.2,[d] 117.5,[f] 119.6, 122.4,[m] 125.5,[d] 126.5,[d] 128.1,[m] 128.8,[m] 129.4, 130.1,[d] 131.7, 137.7 (d, ^1J(C,F)=250 Hz),[f] 140.1 (d, ^1J(C,F)=240 Hz),[f] 142.5 (d, ^1J-(C,F)=258 Hz),[f] 143.9 (d, ^1J(C,F)=255 Hz),[f] 144.8 ppm (d, ^1J(C,F)= 244 Hz)[f]; IR (powder): $\tilde{\nu}$=1634 cm^{-1} (CO); elemental analysis calcd (%) for $C_{44}H_{16}F_{20}N_{40}$: C 53.03, H 1.62, N 5.62; found: C 53.11, H 1.66, N 5.95.

Compound 28: A solution of isomer VII (50 mg, 62 μmol, 1 equiv) in CH_3CN (50 mL) was added dropwise over 5 min to DDQ (50 mg, 220 μmol, 3.5 equiv) in CH_3CN (50 mL) at ambient temperature. After stirring for 10 min, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). $NaOAc{\cdot}3H_2O$ (85 mg, 620 μmol, 10 equiv) and $Cu^{II}(OAc)_2{\cdot}H_2O$ (62 mg, 310 μmol, 5 equiv) were added and the mixture was stirred at ambient temperature for 2 h. The resulting mixture was passed through a pad of alumina and the filtrate was evaporated to give **28**, which was further purified by recrystallization from CH_2Cl_2/hexane (30 mg, 17 μmol, 56% yield). The copper(II) complex **28** was NMR silent.

Calculation details: Conformational search was performed with the Spartan′10 program package. DFT calculations were performed with the Gaussian 09 program package[20] without symmetry assumption. The geometries were fully optimized at the Becke's three-parameter hybrid functional[21] combined with the Lee–Yang–Parr correlation functional,[22] abbreviated as the B3LYP level of DFT. Stationary points were confirmed by frequency analysis, in which no imaginary frequency was found.

X-ray crystallography: X-ray analysis of N,N′-protected doubly N-confused dipyrromethane was performed on a SMART APEX diffractometer equipped with a CCD detector (Bruker AXS) using $Mo_{K\alpha}$ (graphite, monochromated, $\lambda = 0.71069$ Å) radiation. X-ray analysis of **28** was performed on a Saturn diffractometer equipped with a CCD detector (Rigaku) using $Mo_{K\alpha}$ (graphite, monochromated, $\lambda = 0.710747$ Å) radiation. The structure was solved by the direct method of SHELXS-97 and refined by using the SHELXL-97 program.[23] The positional parameters and thermal parameters of non-hydrogen atoms were refined anisotropically on F^2 by the full-matrix least-squares method except for disordered positions of **28**. Hydrogen atoms were placed at calculated positions and refined riding on their corresponding carbon atoms.

CCDC-843906 (N,N′-protected doubly N-confused dipyrromethane) and CCDC-843907 (**28**) 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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[1] a) F. J. Leeper, *Nat. Prod. Rep.* **1989**, *6*, 171–203; b) R. J. Porra, *Photochem. Photobiol.* **1997**, *65*, 492–516; c) B. Franck, A. Nonn, *Angew. Chem.* **1995**, *107*, 1941–1957; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1795–1811; d) T. D. Lash, U. N. Mani, M. A. Drinan, C. Zhen, T. Hall, M. A. Jones, *J. Org. Chem.* **1999**, *64*, 464–477; e) T. D. Lash, U. N. Mani, E. A. Lyons, P. Thientanavanich, M. A. Jones, *J. Org. Chem.* **1999**, *64*, 478–487.

[2] a) S. J. Vigmond, M. C. Chang, K. M. R. Kallury, M. Thompson, *Tetrahedron Lett.* **1994**, *35*, 2455–2458; b) J.-W. Ka, C.-H. Lee, *Tetrahedron Lett.* **2000**, *41*, 4609–4613; c) J.-W. Ka, W.-S. Cho, C.-H. Lee, *Tetrahedron Lett.* **2000**, *41*, 8121–8125; d) B. Koszarna, D. T. Gryko, *J. Org. Chem.* **2006**, *71*, 3707–3717.

[3] a) C.-H. Lee, F. Li, K. Iwamoto, J. Dadok, A. A. Bothner-By, J. S. Lindsey, *Tetrahedron* **1995**, *51*, 11645–11672; b) R. Guilard, D. T. Gryko, G. Canard, J.-M. Barbe, B. Koszarna, S. Brandès, M. Tasior, *Org. Lett.* **2002**, *4*, 4491–4494; c) C. V. Asokan, S. Smeets, W. Dehaen, *Tetrahedron Lett.* **2001**, *42*, 4483–4485; d) R. P. Briñas, C. Brückner, *Synlett* **2001**, *3*, 442–444; e) D. K. Dogutan, S. H. H. Zaidi, P. Thamyongkit, J. S. Lindsey, *J. Org. Chem.* **2007**, *72*, 7701–7714.

[4] a) A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, G. W. J. Matcham, E. McDonald, *J. Chem. Soc. Chem. Commun.* **1979**, 1155–1158; b) A. R. Battersby, C. J. R. Fookes, P. S. Pandey, *Tetrahedron* **1983**, *39*, 1919–1926; c) C. Pichon, A. I. Scott, *Tetrahedron Lett.* **1994**, *35*, 4497–4500; d) P. C. Anderson, A. R. Battersby, H. A. Broadbent, C. J. R. Fookes, G. J. Hart, *Tetrahedron* **1986**, *42*, 3123–3135; e) C. Pichon-Santander, A. I. Scott, *Tetrahedron* **1999**, *55*, 5719–5732.

[5] B. Jolicoeur, E. E. Chapman, A. Thompson, W. D. Lubell, *Tetrahedron* **2006**, *62*, 11531–11563.

[6] a) M. Toganoh, H. Furuta, *Chem. Commun.* **2012**, *48*, 937–954; b) M. Toganoh, H. Furuta, in *Handbook of Porphyrin Science, Vol. 2* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), World Scientific, Singapore, **2010**, pp. 295–367; c) M. Pawlicki, L. Latos-Grażyński, in *Handbook of Porphyrin Science, Vol. 2* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), World Scientific, Singapore, **2010**, pp. 104–192; d) J. D. Harvey, C. J. Ziegler, *J. Inorg. Biochem.* **2006**, *100*, 869–880; e) P. J. Chmielewski, L. Latos-Grażyński, *Coord. Chem. Rev.* **2005**, *249*, 2510–2533; f) A. Srinivasan, H. Furuta, *Acc. Chem. Res.* **2005**, *38*, 10–20.

[7] a) Z. Xiao, B. O. Patrick, D. Dolphin, *Chem. Commun.* **2002**, 1816–1817; b) X. Li, B. Liu, P. Yi, R. Yi, X. Yu, P. J. Chmielewski, *J. Org. Chem.* **2011**, *76*, 2345–2349.

[8] a) M. Toganoh, Y. Hihara, H. Furuta, *Inorg. Chem.* **2010**, *49*, 8182–8184; b) M. Toganoh, T. Kimura, H. Furuta, *Chem. Eur. J.* **2008**, *14*, 10585–10594; c) M. Toganoh, T. Kimura, H. Furuta, *Chem. Commun.* **2008**, 102; d) I. Gupta, A. Srinivasan, T. Morimoto, M. Toganoh, H. Furuta, *Angew. Chem.* **2008**, *120*, 4639–4643; *Angew. Chem. Int. Ed.* **2008**, *47*, 4563–4567; e) A. Srinivasan, T. Ishizuka, H. Furuta, *Angew. Chem.* **2004**, *116*, 894–897; *Angew. Chem. Int. Ed.* **2004**, *43*, 876–879; f) H. Furuta, T. Ishizuka, A. Osuka, T. Ogawa, *J. Am. Chem. Soc.* **2000**, *122*, 5748–5757; g) H. Furuta, T. Ishizuka, A. Osuka, T. Ogawa, *J. Am. Chem. Soc.* **1999**, *121*, 2945–2946.

[9] a) Y.-S. Xie, K. Yamaguchi, M. Toganoh, H. Uno, M. Suzuki, S. Mori, S. Saito, A. Osuka, H. Furuta, *Angew. Chem.* **2009**, *121*, 5604–5607; *Angew. Chem. Int. Ed.* **2009**, *48*, 5496–5499; b) M. Toganoh, T. Kimura, H. Uno, H. Furuta, *Angew. Chem.* **2008**, *120*, 9045–9048; *Angew. Chem. Int. Ed.* **2008**, *47*, 8913–8916; c) D.-H. Won, M. Toganoh, Y. Terada, S. Fukatsu, H. Uno, H. Furuta, *Angew. Chem.* **2008**, *120*, 5518–5521; *Angew. Chem. Int. Ed.* **2008**, *47*, 5438–5441; d) A. Srinivasan, T. Ishizuka, H. Maeda, H. Furuta, *Angew. Chem.* **2004**, *116*, 3011–3015; *Angew. Chem. Int. Ed.* **2004**, *43*, 2951–2955; e) H. Maeda, A. Osuka, H. Furuta, *J. Am. Chem. Soc.* **2003**, *125*, 15690–15691; f) A. Srinivasan, T. Ishizuka, A. Osuka, H. Furuta, *J. Am. Chem. Soc.* **2003**, *125*, 878–879; g) H. Furuta, H. Maeda, A. Osuka, *J. Am. Chem. Soc.* **2000**, *122*, 803–807.

[10] a) J. Wojaczyński, L. Latos-Grażyński, *Chem. Eur. J.* **2010**, *16*, 2679–2682; b) R. K. Pandey, S. H. Leung, T. P. Forsyth, K. M. Smith, *Tetrahedron Lett.* **1994**, *35*, 8995–8998; c) C.-H. Hung, C.-C. Liaw, W.-M. Chin, G.-F. Chang, C.-H. Chuang, *J. Porphyrins Phthalocyanines* **2006**, *10*, 953–961.

[11] M. Toganoh, Y. Kawabe, H. Furuta, *J. Org. Chem.* **2011**, *76*, 7618–7622.

[12] K. Fujino, Y. Hirata, Y. Kawabe, T. Morimoto, A. Srinivasan, M. Toganoh, Y. Miseki, A. Kudo, H. Furuta, *Angew. Chem.* **2011**, *123*, 6987–6991; *Angew. Chem. Int. Ed.* **2011**, *50*, 6855–6859.

[13] G. P. Moss, *Pure Appl. Chem.* **1987**, *59*, 779–832.

[14] B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, J. M. Muchowski, *J. Org. Chem.* **1990**, *55*, 6317–6328.

[15] a) S. H. Leung, L. T. Nguyen, K. M. Smith, *Heterocycl. Commun.* **1996**, *2*, 9–12; b) Z. Zhang, J.-Y. Shin, D. Dolphin, *J. Org. Chem.* **2008**, *73*, 9515–9517.

[16] L. F. Tietze, H. Geissler, *Angew. Chem.* **1993**, *105*, 1090–1091; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1040–1042.

[17] a) H. Furuta, H. Maeda, A. Osuka, *J. Org. Chem.* **2000**, *65*, 4222–4226; b) H. Furuta, H. Maeda, A. Osuka, *J. Org. Chem.* **2001**, *66*, 8563–8572.

[18] H. Furuta, H. Maeda, A. Osuka, *J. Am. Chem. Soc.* **2001**, *123*, 6435–6436.

[19] a) Y. Zhang, A. Thompson, S. J. Rettig, D. Dolphin, *J. Am. Chem. Soc.* **1998**, *120*, 13537–13538; b) Z. Zhang, D. Dolphin, *Inorg. Chem.* **2010**, *49*, 11550–11555; c) T. E. Wood, A. C. Ross, N. D. Dalgleish, E. D. Power, A. Thompson, X. Chen, Y. Okamoto, *J. Org. Chem.* **2005**, *70*, 9967–9974; d) A. Thompson, D. Dolphin, *J. Org. Chem.* **2000**, *65*, 7870–7877; e) T. E. Wood, N. D. Dalgleish, E. D. Power, A. Thompson, X. Chen, Y. Okamoto, *J. Am. Chem. Soc.* **2005**, *127*, 5740–5741.

[20] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E.

Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[21] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.

[22] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.

[23] G. M. Sheldrick, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997**.

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