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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Communication

A Crystalline Annelated Pyridin-1-ylidene and Its Isomerization into a Pyridin-3-ylidene

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Cite This: https://doi.org/10.1021/jacs.5c05642
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ABSTRACT: An isolable ring-fused pyridinylidene (a so-called Hammick intermediate) was synthesized from a benzo[*h*]-isoquinolinium salt, and its structure in the solid state was determined. The isolation of this first-of-its-kind pyridine-derived aromatic N-heterocyclic carbene was made possible due to the presence of an adamantyl group on nitrogen, forcing the nitrogen to be planar and enhancing both π-donation and steric protection, and to its unique polycyclic structure, which displays an intramolecular C−H···$C_{carbene}$ interaction. Additionally, an example of isomerization of a carbene into another carbene, namely, a benzo[*h*]isoquinolin-1-ylidene into a benzo[*h*]isoquinolin-3-ylidene, is reported.

The rapid growth in applications for stable carbenes,[1] spanning organic, organometallic, and medicinal chemistry, as well as in materials science,[2] has led to the development of numerous scaffolds to sustain these species.[3] Among them, those derived from aromatic N-heterocycles, especially imidazoles, 1,2,4- and 1,2,3-triazoles, have proven to be the most successful due to their stability and ease of synthesis.[4] In sharp contrast, carbenes derived from pyridine,

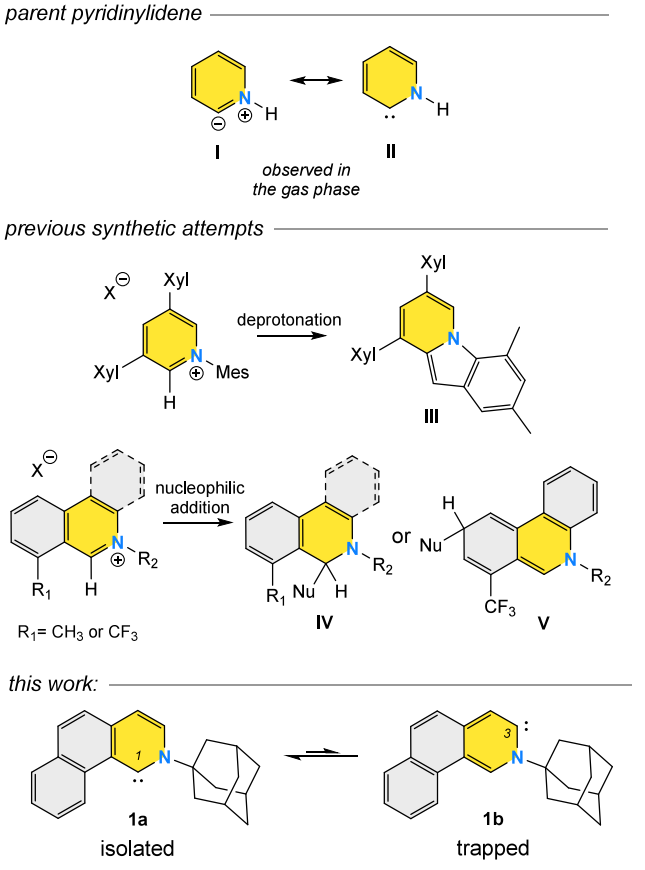
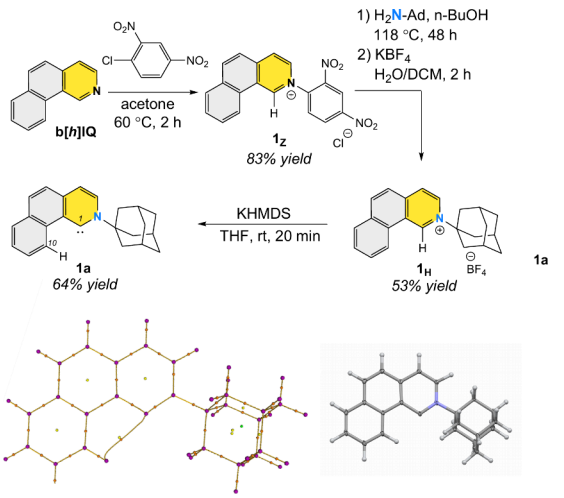


Figure 1. Observation of the parent pyridinylidene, previous attempts to synthesize some derivatives, and this work.

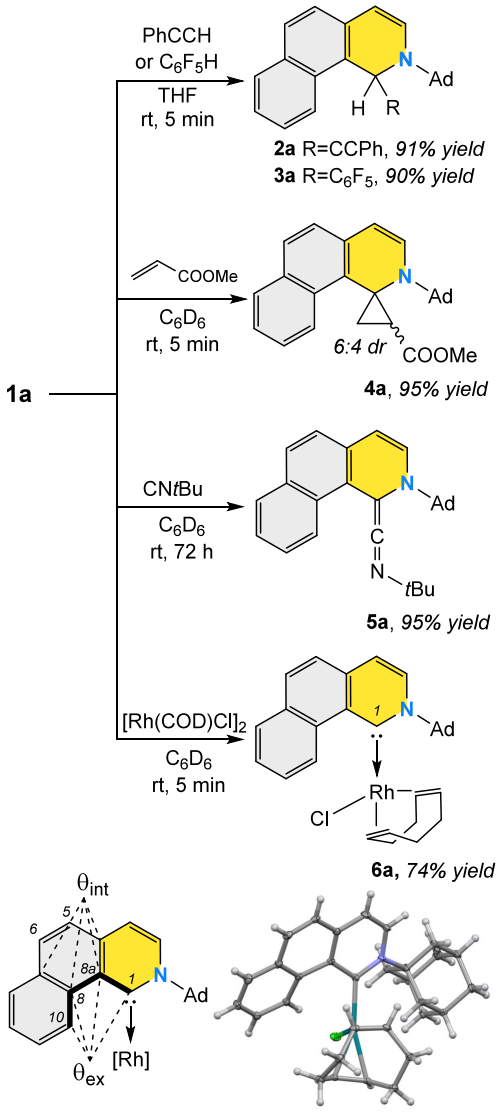
Scheme 1. Synthesis, Solid-State Structure, and QTAIM Analysis of 1a[a]



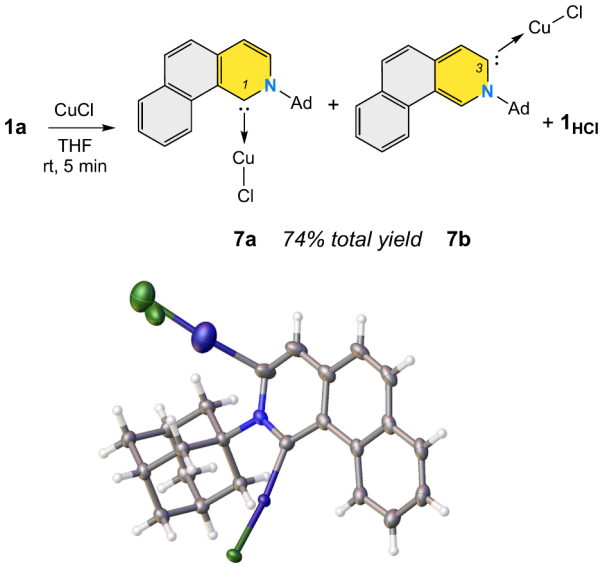
[a]Purple spheres denote attractors, brown lines denote bond paths, yellow spheres denote ring critical points, orange spheres denote bond critical points, and green spheres denote cage critical points.

Received: April 2, 2025
Revised: April 16, 2025
Accepted: April 23, 2025

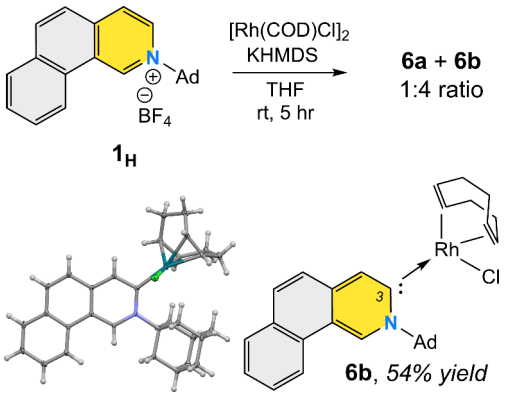
Scheme 2. Reactivity of 1a at Position 1 and Solid-State Structure of 6a



Scheme 3. Formation of a Regioisomeric Pair 7a-b and Superposition of Co-Crystal of 7a−b and 1_{HCl}



Scheme 4. Synthesis and Solid-State Structure of 6b



an archetypal aromatic N-heterocycle, remain elusive, hampering their broad application.[5] Their transient existence was first postulated in 1937 by Hammick,[6] who suggested their formation as pyridine ylides (**I**) during the decarboxylation of 2-picolinic acid. This intermediate was then depicted by Breslow[7] as a singlet carbene (**II**) (Figure 1), a concept further supported by Hoffmann's[8] theoretical calculations. The parent pyridinylidene has also been detected in the gas phase by Koch and Schwarz.[9] Itami et al. attempted to synthesize a 1,3,5-triaryl-substituted pyridinylidene.[10] Although they successfully trapped it with sulfur and $(Me_2S)AuCl$, they were unable to observe the carbene by spectroscopy due to its rapid rearrangement into a pyrido[1,2-*a*]indole (**III**). Also, there are reported attempts to synthesize carbenes based on phenanthridine[11] and isoquinoline[12] cores. However, in both cases, the carbene conjugate acids were so electrophilic that even the use of bulky bases resulted in nucleophilic addition (**IV**-**V**) rather than free carbene generation. Interestingly, a theoretical paper by Hollóczki and Nyulaszi suggests that a bulky group at nitrogen, such as adamantyl, could stabilize the carbene by forcing the nitrogen to be planar, enhancing both π-donation and steric protection.[13] Herein, we show that by following this strategy and adding an additional aromatic ring to the isoquinoline core, it is possible to isolate a crystalline annellated pyridinylidene **1a**. Additionally, we report an example of isomerization of a carbene into another carbene, namely, a benzo[*h*]isoquinolin-1-ylidene **1a** into a benzo[*h*]-isoquinolin-3-ylidene **1b**.

The carbene precursor was prepared from the readily available benzo[*h*]isoquinoline **b[*h*]IQ**,[14] which features a benzo ring strategically protecting the prospective carbene center in position 1 (Scheme 1). The adamantyl substituent was then introduced by the Zincke reaction,[15] which in two steps provided the annelated pyridinium salt $\mathbf{1_H}$. To our delight, room-temperature deprotonation of $\mathbf{1_H}$ with potassium bis(trimethylsilyl)amide[16] led to the clean formation of the free benzo[*h*]isoquinolin-1-ylidene **1a**, as evidenced by the observation of a characteristic carbene signal in the $^{13}C\{^1H\}$ NMR spectrum at δ = 272.2 ppm (THF-d_8). Analytically pure carbene **1a** was isolated from a tetrahydrofuran solution by the addition of *n*-hexane, followed by azeotropic solvent evaporation, which led to the precipitation of a brick red solid that was recovered by filtration. After recrystallization by slow evaporation of a saturated benzene solution, single crystals were obtained. The structure of **1a** was confirmed by

https://doi.org/10.1021/jacs.5c05642
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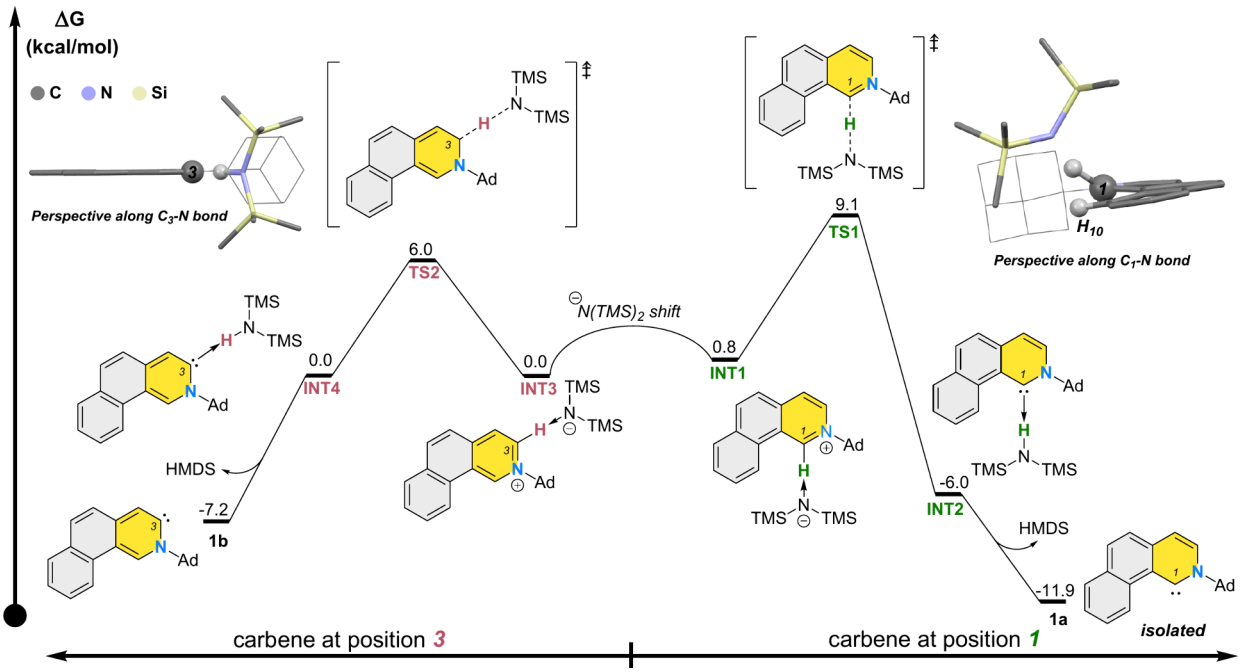

Figure 2. Calculated free energy profiles (ωB97X-V/def2-mTZVPP/SMD(THF)//r^{2}SCAN-3c/CPCM(THF) level of theory) for the formation of carbenes **1a** and **1b** in the presence of HMDS as a proton shuttle. In the 3D visualizations of the calculated transition state geometries, select hydrogens are omitted and the adamantyl cages are rendered in wireframe for clarity.

single-crystal X-ray diffraction, in which we noted a distortion of the aromatic system as evidenced by the carbene bond angle of 114.2°.

Interestingly, the ^{1}H NMR spectrum of **1a** showed a distinctively downfield shifted signal at δ = 10.28 ppm (d, J = 8.0 Hz, THF-d_8), which was assigned to the C_{10}-H proton at the γ-position relative to the carbene center. Indeed, the solid-state structure of **1a** revealed that the carbene and the C_{10}-H proton are 2.49 Å apart, shorter than the sum of their van der Waals radii,[17] suggesting the possibility of a nonclassical hydrogen bonding (NCHB) interaction. To investigate this further, we conducted a quantum theory of atoms in molecules (QTAIM)[18] analysis, which revealed a bond critical point (BCP) between the carbene and the C_{10}-H proton. Using the electron density at the BCP, we calculated the binding energy magnitude to be 2.51 kcal/mol, suggesting a weak interaction.[19] Furthermore, we noted that the C_{10}-H bond length in the optimized geometry of **1a** is significantly shorter than the average C_{Ar}-H bond length (1.074 versus 1.084 Å). This shortening is characteristic of so-called "improper" hydrogen bonds, which in this case likely occurs due to the acute C_{10}–H···C_1 angle, preventing n(C_1) → σ^*(H–C_{10}) hyperconjugation.[20] Altogether, these data demonstrate that both annellation and inclusion of a bulky adamantyl substituent play crucial roles in carbene stabilization.

Next, we investigated the reactivity of **1a** toward several classical carbene-trapping agents[21] (Scheme 2). The reactions with phenylacetylene and pentafluorobenzene proceeded swiftly at room temperature, yielding carbene C–H insertion products **2a** and **3a**. Within minutes, the reaction of **1a** with methyl acrylate led cleanly to the cyclopropanation product **4a** as a mixture of diastereomers in a 6:4 ratio. In contrast, the reaction of **1a** with *tert*-butyl isocyanide required 72 h for full conversion into ketenimine **5a** as the sole product. Ketenimine formation was corroborated by a characteristic low-field ^{13}C{^{1}H} NMR signal of the central ketenimine carbon atom at δ = 187.5 ppm (C_6D_6). Notably, these results align with the reactivity observed for other highly ambiphilic carbenes.[22]

The coordination chemistry of **1a** was also examined by reaction with the dimeric rhodium complex [Rh(COD)Cl]$_2$, which selectively formed the benzo[*h*]isoquinolin-1-ylidene rhodium complex **6a**.[23] Similar to **1a**, the ^{1}H NMR spectrum of its rhodium complex **6a** displayed a distinct signal for the C_{10}–H proton at δ = 12.85 ppm (d, J = 8.1 Hz, C_6D_6), suggesting the presence of a preagostic C_{10}H---Rh interaction.[24] This was further confirmed by the solid-state structure of **6a** (Scheme 2), which revealed a short C_{10}–H---Rh distance of 2.595 Å. Notably, the coordination of **1a** to the rhodium center induces significant strain on the benzo[*h*]-isoquinoline core, leading to a helically twisted conformation. The helical deformation of the aromatic skeleton in **6a** was measured as θ_{ext} = 18.97° and θ_{int} = 11.01°, while the C_8–C_{8a} bond length in the inner helix ring is 1.453 Å, while the C_5–C_6 bond length at the periphery of the same ring is 1.342 Å. These values are comparable to those observed in other helicenes with a small number of aromatic rings[25] and suggest that metal coordination by annellated stable carbenes could serve as a new approach for synthesizing this class of compounds.

Surprisingly, the reaction of **1a** with CuCl provided not only the expected complex **7a** but also minor side products (>5%) that showed highly shifted singlets in the ^{1}H NMR spectrum (Scheme 3). During our attempts to purify the crude reaction mixture, we received a cocrystal that revealed formation of not only **7a** but also its regioisomer **7b**, the coordination product of benzo[*h*]isoquinolin-3-ylidene, along with traces of the iminium salt $\mathbf{1}_{HCl}$ (see Supporting Information for details)

The formation of **7b** suggests that benzo[*h*]isoquinolin-1-ylidene **1a** can formally isomerize into benzo[*h*]isoquinolin-3-ylidene **1b**. Since this isomerization involves a proton transfer, we wondered if traces of HMDS, a side product formed during the generation of **1a** from iminium salt $\mathbf{1}_H$, or $\mathbf{1}_H$ itself, could serve as a proton shuttle. Therefore, we investigated the

https://doi.org/10.1021/jacs.5c05642
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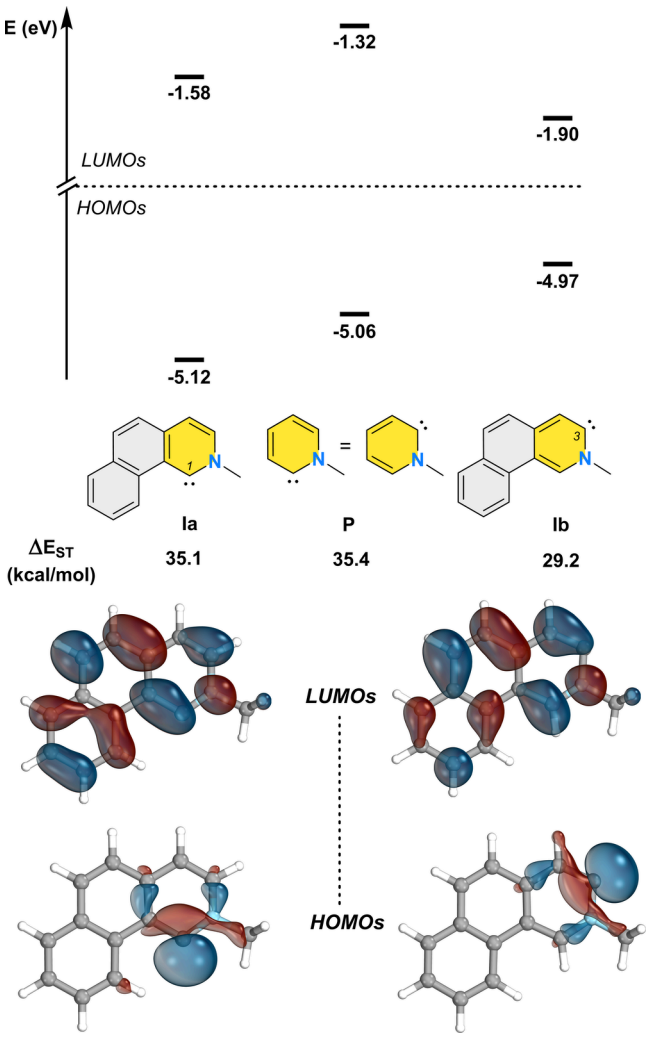

Figure 3. HOMO and LUMO eigenvalues (eV) for carbenes **Ia**, **Ib**, and **P** and their singlet−triple gaps in parentheses (kcal/mol) as well as the frontier molecular orbital isosurfaces (HOMO, LUMO) of **Ia** and **Ib** calculated at the B3LYP/def2-TZVPP level of theory.

reactivity of **1a** with the dimeric rhodium complex $[Rh(COD)Cl]_2$ in the presence of HMDS (Scheme 4). To our delight, a significant change in regioselectivity was observed compared to that of the reaction with pure **1a**. In the presence of HMDS, the major product of this reaction was **6b** (in a 4:1 ratio with **6a**), which was isolated from the reaction mixture, and the structure of which was confirmed by X-ray diffraction studies. Notably, in sharp contrast to **6a**, the solid-state structure of **6b** revealed a flat benzo[*h*]isoquinoline ring with the rhodium atom lying in the plane of the aromatic core. The lack of distortion clearly evidences the dramatic difference in steric hindrance between the two carbenes.

To support our hypothesis that the isomerization of **1a** to **1b** occurs via an intermolecular proton transfer mechanism, we performed thermochemical calculations for a possible mechanism involving HMDS.[26] The free energy profiles for the formation of carbenes **1a** and **1b** calculated at the ωB97X-V/def2-mTZVPP/SMD(THF)//r^{2}SCAN-3c/CPCM(THF) level of theory are summarized in Figure 2. In accordance with the synthetic results, we found that isolated carbene **1a** is the thermodynamic product of $\mathbf{1}_H$ deprotonation. However, deprotonation can also occur at position 3 of the benzo[*h*]-isoquinoline ring, leading to the formation of **1b**, which is only 4.7 kcal/mol less stable than its regioisomer **1a**. Notably, deprotonation at position 1 proceeds via a highly distorted transition state (**TS1**), in which the C_1−H bond is rotated 35.9° out of the benzo[*h*]isoquinoline plane. This is reminiscent of the strained geometries observed in the crystal structures of **6a**. Accordingly, **TS1** is 3.1 kcal/mol higher in energy than **TS2**, which leads to carbene **1b**. Nevertheless, the highest barrier during the **1b** → **1a** regioisomerization via an HMDS-mediated proton transfer (**1b** → **TS1**) is sufficiently low (16.3 kcal/mol) to allow for equilibration between **1a** and **1b**.

We also used density functional theory to compare the electronic structure of benzo[*h*]isoquinolin-1-ylidene **Ia**, its regioisomer benzo[*h*]isoquinolin-3-ylidene **Ib**, and nonannelated pyridinylidene **P** (Figure 3). Gas-phase calculations at the B3LYP/def2-TZVPP level of theory provided the HOMO and LUMO energies of all three carbenes as well as their adiabatic singlet−triplet gaps. We found that carbenes **Ia** and **Ib** are more electrophilic than the parent **P**, and **Ia** is in fact among the most electrophilic isolable carbenes to-date.[27] This is likely due to the delocalization of the LUMO across the entire benzo[*h*]isoquinoline π-system, which is observed for both **Ia** and **Ib** [and also in the closely related cyclic(aryl)(amino)-carbenes].[28] Interestingly, **Ia** is less nucleophilic than the parent **P**, while **Ib** is more nucleophilic. However, all three should be considered strong donor ligands, as they have higher HOMO energy levels than five-membered ring CAACs.[29] The difference between **Ia** and **Ib** can be rationalized by comparing the α-carbon substituents. Carbon, being more electronegative than hydrogen, should be relatively electron-withdrawing, slightly stabilizing the HOMO of **Ia** versus **Ib**. Altogether, our calculations show that both carbenes **Ia** and **Ib** are among the most ambiphilic carbenes yet investigated, reflected in their relatively low singlet−triplet gaps.[30]

In summary, almost nine decades after Hammick proposed their existence as fleeting intermediates, we report the isolation of a stable crystalline pyridinylidene derivative. Its isolation was enabled by annelating the pyridine core and appending a bulky adamantyl group to the nitrogen, both of which provide steric stabilization. We believe that the unique features of this benzo[*h*]isoquinoline-based carbene, such as its ability to isomerize between positions 1 and 3, form an intramolecular NCHB, and generate helicene-like structures upon coordination, can unlock new synthetic applications.

■ ASSOCIATED CONTENT

Data Availability Statement

All computational data underlying this study are openly available for download, free of charge, from the UC San Diego Library Digital Collections at DOI: 10.6075/J0CJ8DVK.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c05642.

General methods and materials, experimental procedures and characterization data, computational details and NMR spectra (PDF)

Accession Codes

Deposition Numbers 2432544−2432546 and 2440123 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge

https://doi.org/10.1021/jacs.5c05642
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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Funding

This work was supported by the NSF (CHE-2246948) (GB), the "Prematuration Program" of CNRS (MM), the Agence Nationale de la Recherche (ANR) under award #ANR-19-CE07−0017-ChiCAAC (MM, RJ), #ANR-20-CE07−0030-cResolu (MM, RJ), and #ANR-16-CE07−0019 - Hel-NHC (MM, OB).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported in part by the W. M. Keck Foundation through computing resources at the W. M. Keck Laboratory for Integrated Biology.

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https://doi.org/10.1021/jacs.5c05642
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