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Expedient Synthesis of Thermally Stable Acyclic Amino(haloaryl)carbenes. Experimental and Theoretical Evidence of “Push-Pull” Stabilized Carbenes.

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ABSTRACT: A library of novel structurally related singlet carbenes, namely, acyclic amino(haloaryl)carbenes, were designed by a high yielding two-step procedure and their chemical stability explored both experimentally and theoretically. Thanks to a careful selection of both the amino and the aryl substitution pattern, these carbenes exhibit a wide range of stability and reactivity, spanning from rapid self-dimerization for carbenes featuring *ortho*-F substituents to very high chemical stability as bare carbenes, up to 60 °C for several hours for compounds carrying *ortho*-Br substituents. Their structure was determined through NMR and X-ray diffraction studies, whereas their reactivity was evaluated in benchmark reactions, highlighting the ambiphilic character of this novel class of singlet carbenes. In contrast with previously reported aryl substituents incorporating *o*-CF₃ and *t*-Bu groups, which were considered "spectator", the exceptional chemical stability of some of these carbenes relates to the stabilization of the σ -orbital of the carbene center by the π -accepting haloaryl substituent through delocalization. Kinetic protection of the carbene center is also provided by the *ortho*-halogen atoms, as demonstrated computationally. This push-pull stabilization effect makes acyclic amino(haloaryl) carbenes among the most ambiphilic stable carbenes reported to date, holding for some promising applications.

Introduction

The synthesis of the first stable singlet carbenes, namely phosphino(silyl)carbene **1** and imidazole-2-ylidene **2**, respectively by Bertrand in 1988¹ and Arduengo in 1991² are milestones in synthetic organic chemistry (Figure 1A). Despite their apparent structural difference, both carbenes are strongly stabilized by interaction of the carbene center with adjacent heteroatoms; they are also kinetically stabilized by the presence of bulky substituents in the vicinity of the carbene center. Apart from these similarities, **1** and **2** exhibit profound differences in terms of synthesis, structure and reactivity. In particular, **1** displays small singlet-triplet energy differences, and HOMO-LUMO gaps, with a low-lying LUMO.³ Consequently, **1** is ambiphilic and its reactivity, which notably includes migrations, C-H insertions and cyclopropanation of olefins, mimics that of transient carbenes. In sharp contrast, the peculiar structure of cyclic diaminocarbenes, commonly referred to as N-heterocyclic carbenes (NHCs), such as **2**, leads to much larger ΔG_{ST} (80 kcal/mol), important HOMO-LUMO gaps with high-lying LUMOs, favoring the singlet state of these

carbenes.⁴ Thus, **2** behaves essentially as a Lewis base, and account for the widespread use of NHCs not only as ligands for transition metals but also as organocatalysts for (macro)molecular synthesis.⁵ Since these pioneering discoveries, a myriad of stable singlet carbenes have been isolated, the vast majority being cyclic and thermodynamically stabilized by two nitrogen atoms.⁶⁻¹⁰ Bertrand *et al.* later showed that only one amino group is sufficient to stabilize the carbene, as in monoaminocarbenes (MACs), which include monosubstituted carbene,¹¹ acyclic amino(alkyl)carbene (AAAC) **3**,¹² amino(aryl)carbene (AAArC) **4**,¹³ and cyclic(alkyl)(amino)carbenes (CAACs) **5** and **6** (Figure 1A).¹⁴⁻¹⁹ MACs exhibit an intermediate ΔG_{ST} and a rather small HOMO-LUMO gap, with a low-lying LUMO. Hence, MACs are both more nucleophilic (σ -donating) and more electrophilic (π -accepting) than NHCs, *i.e.* more ambiphilic, which has enabled them to activate strong chemical bonds, such as H-H, B-H, P-H, Si-H or N-H, a difficult task that has long been exclusively reserved to transition metals.^{20,21}

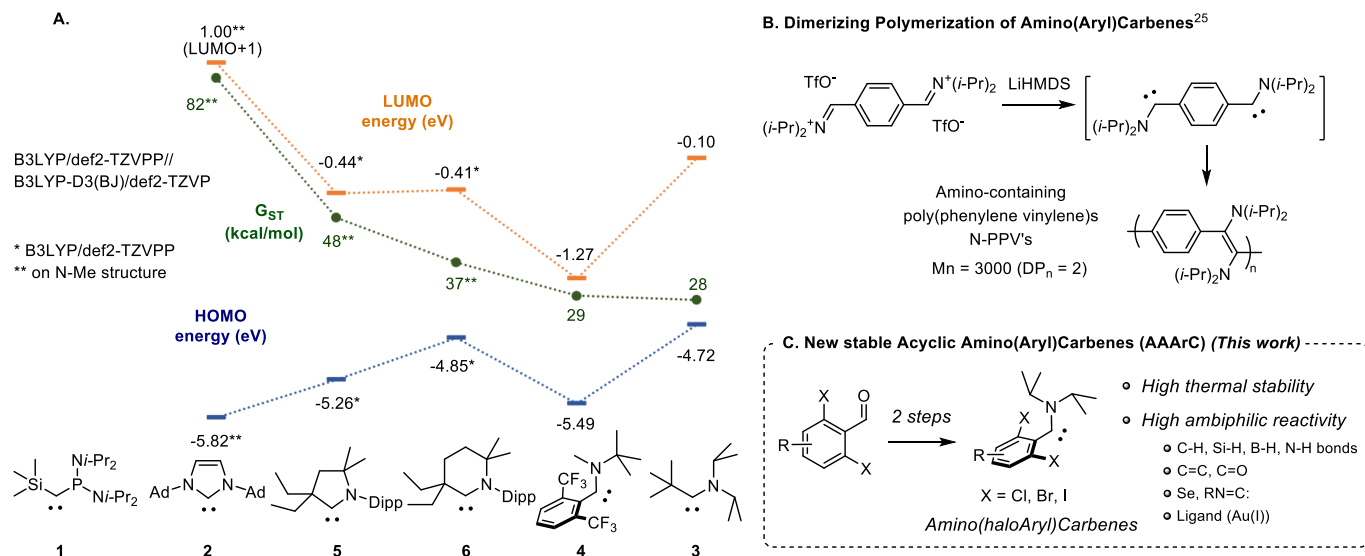


Figure 1. **A.** DFT-computed FMO energy levels and singlet-triplet gaps of representative stable aminocarbenes. **B.** Previously reported dimerizing polymerization of amino(aryl)carbenes (see ref. 25). **C.** New stable acyclic amino(aryl)carbenes (AArC) reported in this work.

The very high intrinsic reactivity of acyclic MACs contributed to a loss of interest in them, despite the fact that they are inherently more nucleophilic and synthetically more accessible than their cyclic analogues. For instance, AAAC **3** undergoes complete isomerization into imine and propene in 72 h at 25 °C, while **4** undergoes a dearomatizing ring closure via the corresponding azomethine ylide over a week at 25 °C.^{12,22,23} Noteworthy, the aryl substituent in **4**, was considered to be a spectator mesomeric group, also referred to as "π-innocent",⁸ the acute carbene angle preventing additional stabilization through overlapping between the σ orbital of the carbene center and the aryl π -system. Note finally that such amino(aryl)carbenes that are not *ortho*-substituted cannot be spectroscopically observed even at low temperature, self-dimerizing instantaneously into the corresponding diaminoalkene.^{22,24-31} On this basis, we recently designed bis-amino(aryl)carbenes, which were found to undergo spontaneous dimerizing polymerization thus leading to amino-(phenylenevinylene)s (N-PPVs), with tunable opto-electronic properties (Figure 1B).²⁵ Following these studies, we discovered that introduction of halogen substituents in the *ortho* position of the aryl moiety, efficiently prevented the self-dimerization reaction. In sharp contrast to most acyclic MACs reported to date,¹³ these new amino(haloaryl)carbenes (Figure 1C), exhibit enhanced thermal stability, and were thus isolated and characterized through X-ray diffraction studies (XRD). Furthermore, DFT calculations indicate that, the stability of these carbenes not only results from the π -donation of the amino group into the vacant orbital of the carbon, as expected, but also from the π -acceptor ability of the aryl substituent, enabling delocalization of the σ -orbital of the carbene. Through a combination of experimental and theoretical investigations, we thus evidenced the strong σ -donating properties of these amino(aryl)carbenes, as well as

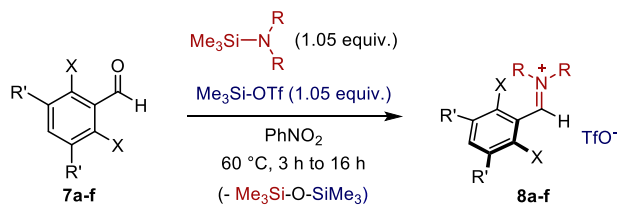
their pronounced electrophilicity. More importantly, this ambiphilic behavior, combined with their remarkable stability, allow for their use as versatile synthons in various stoichiometric transformations involving typical transient carbene reactivity, including: cyclopropanation of olefins, insertions into C(sp³)-H, C(sp²)-H, N-H, Si-H and B-H bonds. The straightforward halogenation of aromatic aldehydes, notably by electrophilic aromatic substitution, also provides an expedient route to access these stable carbenes as highlighted through the introduction of OMe substituents.

Results and discussion

Synthesis of carbenes 9a-f

Acyclic amino(haloaryl)carbenes were synthesized by deprotonation of the corresponding iminium salt precursors in presence of a strong base. A library of such iminium salts (**8a-f**) was obtained from the corresponding *ortho*-dihalo substituted aldehydes (Scheme 1). The procedure reported by Schroth *et al.*³² was optimized to access the hindered iminium salts, using pure silylamines and TMSOTf in nitrobenzene at 60 °C. Such conditions allowed us to reach iminium salts within 16 h in high yield. The synthesis of air- and water-sensitive TMSNi-Pr₂ and TMSNi-Bu₂ was also optimized, affording the silylamines in quantitative yields (ESI).

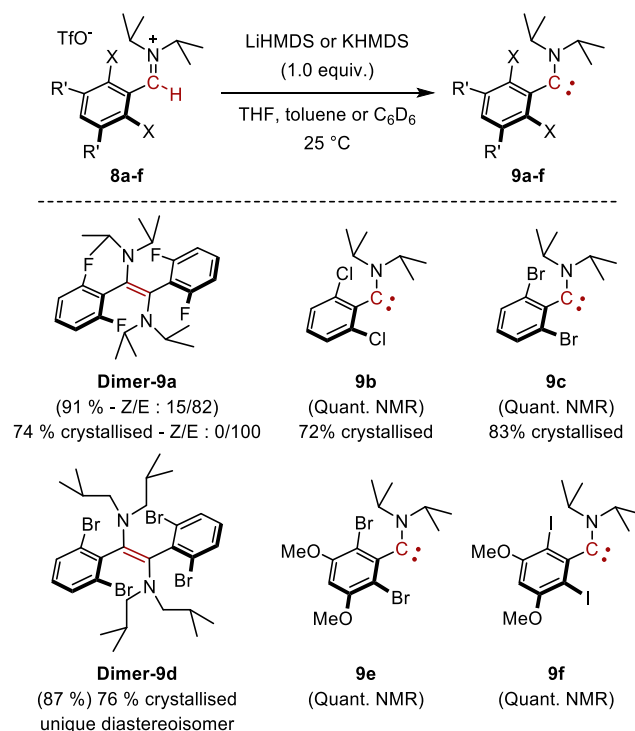
Scheme 1. Synthesis of iminium salts 8a-f from corresponding benzaldehydes 7a-f.



8a, X = F, R = *i*-Pr, R' = H (94 %) **8d**, X = Br, R = *i*-Bu, R' = H (94 %)
8b, X = Cl, R = *i*-Pr, R' = H (96 %) **8e**, X = Br, R = *i*-Pr, R' = OMe (88 %)
8c, X = Br, R = *i*-Pr, R' = H (92 %) **8f**, X = I, R = *i*-Pr, R' = OMe (83 %)

Precursors **8a-f** were then quantitatively deprotonated using either LiHMDS or KHMDS (pK_a (HMDS) = 25.8 in THF),³³ in THF, benzene or toluene as solvent. A convenient one-pot and direct synthesis of these salts followed by carbene formation, using standard Schlenk technique is also at hand. Use of weaker bases such as 1,8-Diazabicyclo[5.4.0]undec-7-ène (DBU) (pK_a = 16.9), *tert*-Butylimino-tri(pyrrolidino)phosphorane (*t*-BuP₁(pyrr)₃) (pK_a = 20.2) or 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) (pK_a = 21.0)³⁴ failed to deprotonate **8b**, suggesting a pK_a of **8b** ranging between 22 and 25 in THF. Synthesis of carbenes **9a-f** was accomplished *in situ* from LiHMDS in THF-*d*₈, showing selective and quantitative deprotonation. Depending on their substitution pattern, these carbenes exhibited distinguished reactivity, as evidenced by ¹H and ¹³C NMR spectroscopy. The fluorinated AAARc **9a** was found to spontaneously dimerize into **Dimer-9a**, while its chlorinated and brominated analogues, **9b** and **9c**, proved very stable as free singlet carbenes at 25 °C (Scheme 2). Reducing the steric hindrance on the amino group, from Ni-Pr₂ to Ni-Bu₂ in **9d**, also resulted in exclusive carbene dimerization (*i.e.* **Dimer-9d**). Both the nature of the *ortho*-halogens and the substituents on the amino group therefore appear crucial to control carbene stabilization. Thus, **9e** and **9f** proved stables as free carbenes at 25 °C, while **Dimer-9a** and **Dimer-9d** could be crystallized as single isomers. X-ray diffraction analysis of **Dimer-9a** evidenced a *E*-configuration (Scheme 2), similarly to the 1,2-bis-diisopropylamino stilbene analogues we previously reported.²⁵ On this basis, free carbenes **9b** and **9c** were prepared on larger scale, isolated in pure crystalline form after extraction with *n*-hexane and crystallization at -78 °C with respectively 72 % and 83 % yield. The NMR chemical shifts (¹H, ¹³C and ¹⁵N) of these purified carbenes in C₆D₆ were found identical to those observed for *in situ* formed carbenes using either LiHMDS/THF-*d*₈ or KHMDS/C₆D₆. The ¹³C NMR signals between 297 and 303 ppm (Figure 2) are diagnostic of the carbene center and fall in the same range as those reported for **4** and analogues.¹³ Carbene formation could also be monitored by ¹⁵N NMR spectroscopy through the appearance of the characteristic signal around -150 ppm, where precursors **8a-f** are downfield to around -120 ppm. Single crystals of carbene **9c** were grown from *n*-hexane at 0 °C, enabling further X-ray diffraction analysis (Figure 3). Thus, **9c** was shown to exhibit a planar nitrogen atom and a N-C_{carbene} bond of 1.286 ± 0.004 Å representing one of the shortest values ever reported for a

Scheme 2. Deprotonation of iminium salts 8a-f and formation of carbenes 9b-c and 9e-f and dimers 9a and 9d.



monoaminocarbene. These data mirror a strong interaction between the carbene center and the nitrogen atom, reminiscent of the strong π -donation by the nitrogen atom. The acute carbene angle of 117.88° and the C_{carbene}-C_{Ar} bond length of 1.469 ± 0.005 Å were very similar to those determined for compound **4** (Figure 3). The thermal stability of the four stable carbenes was then assessed by NMR in THF-*d*₈ (Figure 2; stack spectra also available in ESI). For the chlorinated carbene **9b**, no signs of decomposition were observed spectroscopically at 25 °C for at least 24 h. However 7% degradation was noted after 50 h and 50 % after 40 days at 25 °C. The brominated carbene **9c** proved to be more stable, as no decomposition was noted after 34 days at 25 °C in THF-*d*₈, even upon heating in a sealed NMR tube at 60 °C for 16 h. On the other hand, heating the THF solution of **9c** for 3.5 h at 100 °C caused its partial isomerization (38%) into *N*-isopropylbenzylimine and propene, full isomerization being achieved upon further heating for one hour at 120 °C (*vide infra*). Such an isomerization pathway was previously reported, for instance in the case of **3**.^{12,35} No difference in stability was noted when generating **9c** in presence of KHMDS in toluene-*d*₈, *i.e.* no solvent effect was observed. Carbene **9e** displayed a similar stability to that of **9c**. Finally, the diiodinated compound **9f** proved to be the least stable of carbenes investigated in this series, as it showed no sign of decomposition after 24 hours at 25 °C, but decomposed after a week at this temperature. Whereas *meta*-methoxy substituents in **9e-f** did not seem to play a key role on the thermal stability of these AAARc's, the nature of the halogen appeared to be decisive, with the

following order of stability: $F \ll I < Cl \ll Br$. These observations are reminiscent of the stability of triplet chlorinated and brominated diphenylcarbenes as reported by Tomioka *et al.*³⁶ Considering the large Van der Waals radius of bromine (1.85 Å) and the important C-Br bond length (1.85 Å), it may be concluded that halogen substituents provide the required

steric hindrance to enhance the carbene stability, while preventing the carbene C-H insertion. Computational studies discussed hereafter offer a more complete picture helping to rationalize the stability of our halogenated AAAC's.

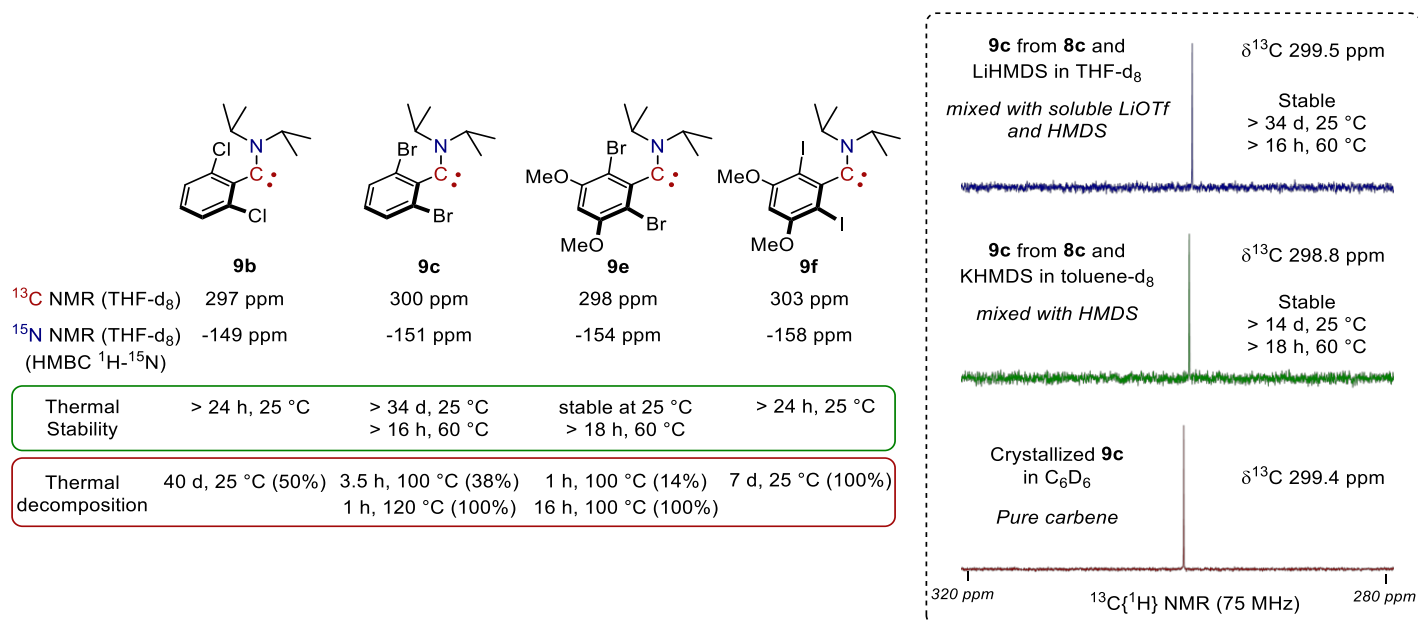


Figure 2. Thermal stability of free acyclic amino(aryl)carbenes and representative ^{13}C and ^{15}N NMR signals.

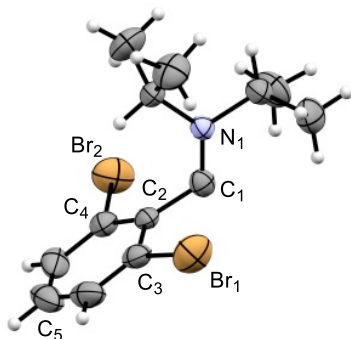


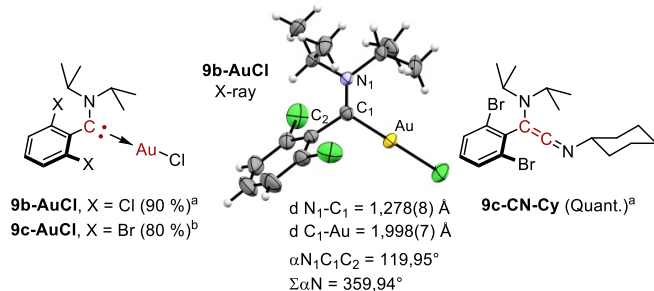
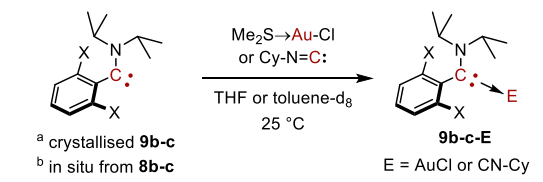
Figure 3. X-ray diffraction crystal structure of **9c** (ellipsoids are drawn at 50 % probability). N_1-C_1 1.286(4) Å, C_1-C_2 1.469(5) Å, C_3-Br_1 1.888(4) Å, C_4-Br_2 1.898(4) Å, $\alpha_{N_1-C_1-C_2}$ 117.88°, $\alpha_{N_1-C_2-C_5}$ 172.52°, torsion $N_1-C_1-C_2-C_3$ -94.92°, angles sum around N_1 360.0°

Reactivity of carbenes **9b-f**

The reactivity of carbenes **9** was first mapped through several benchmark reactions, including trapping with AuCl and isonitrile (Scheme 3). As carbene **9b** could not be crystallized as a bare carbene, its capture with AuCl(SMe₂) was explored, which led to the stable crystalline gold(I) chloride complex **9b-AuCl**. The structure of **9b-AuCl**, as determined through

X-ray diffraction analysis, is characterized by a long C_1-Au bond (2 Å) and an almost linear environment around the metallic center, similar to that reported for CAACs gold(I)chloride complexes.³⁷ The ^{13}C NMR signal of the carbene center at 229 ppm appeared upfield compared to the free carbene **9b**, as usually observed for such complexes.³⁷ As only ambiphilic carbenes with a low-lying LUMO are known to react with isonitriles, reaction of AAAC **9c** with *c*-hexylisocyanide was investigated at room temperature. This yielded the corresponding keteneimine **9c-CN-Cy**, quantitatively, according to ^1H , ^{13}C and ^{15}N NMR analysis.

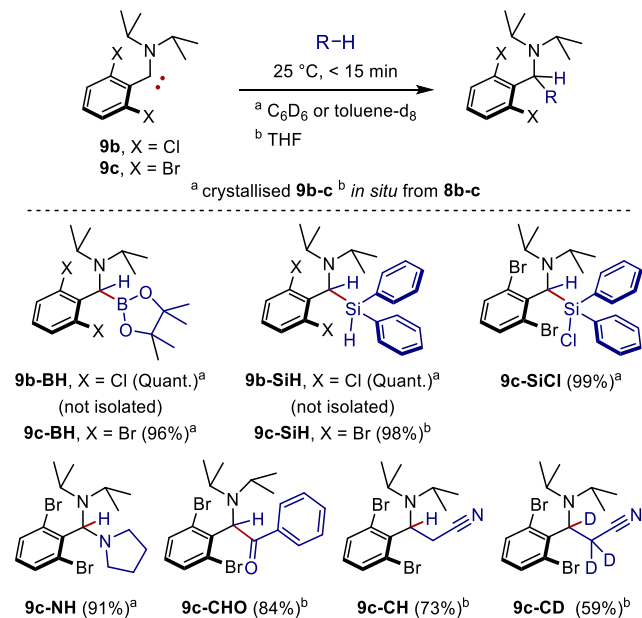
Scheme 3. Trapping reactions of carbenes **9b-c**.



As mentioned, both AAARCs and CAACs exhibit ambiphilic character, in contrast to widespread NHCs, which primarily behave as nucleophilic species. Only one insertion reaction involving an AAARC onto the O-H bond of *tert*-butanol was reported to date.³⁸ Insertion reactions of **9** into C-H, N-H, Si-H and B-H bonds were thus studied in order to assess the synthetic potential of these underexplored class of carbenes (Scheme 4). Carbenes **9b-c** proved to selectively and quantitatively insert into a variety of polarized bonds in less than 15 min. For instance, insertion into the B-H bond of pinacolborane, as well as into the Si-H bond of both diphenylsilane and chlorodiphenylsilane were evidenced to proceed in excellent yield, leading to **9-BH**, **9-SiH** and **9-SiCl**, respectively. Of particular interest, AAARC **9c** selectively inserted into the Si-H bond of chlorosilane to provide **9c-SiCl**, *i.e.* leaving the Si-Cl unchanged.³⁹ In contrast, no reaction was observed using PhMe₂SiH or (Me₂HSi)₂O, suggesting a mechanism involving a pentacoordinated silicon intermediate.⁴⁰ The latter would be generated upon reaction between the nucleophilic carbene and the electrophilic silicon center, followed by a 1,2-migration of the resulting hydride onto the electrophilic iminium. A similar mechanism may be expected for the insertion into the B-H bond of Lewis acidic boranes. In contrast, **9b** proved to be inert toward the phenylpinacol borane, and no Lewis pair adduct was detected by NMR, likely owing to steric reasons. Noteworthy, reaction products **9-BH**, **9-SiH** and **9-SiCl** could only be handled under an inert atmosphere, as the resulting C-B and C-Si bonds rapidly underwent fragmentation into the corresponding benzylamine under exposure to air. Insertion of **9c** into the polar N-H bond of pyrrolidine (pK_a 44 in DMSO) led to the air-sensitive aminal adduct **9c-NH**, attesting to the strong ambiphilic character of **9c**, similarly to that of the most efficient CAACs.²¹ We then turned our attention to the synthetically important activation of polarized C-H bonds. Insertion into the aldehydic C-H bond of benzaldehyde thus led to the formation of the stable ketone **9c-CHO**, a known reactivity of CAACs occurring through the Breslow intermediate.³⁸ Carbenes **9b-c** were also shown to efficiently insert into polarized C-H bonds of acetonitrile (pK_a 31.3 in DMSO) leading to adducts **9c-CH** and **9c-CD**. Insertion into acetonitrile-d₃ from the *in situ* generated carbene in THF

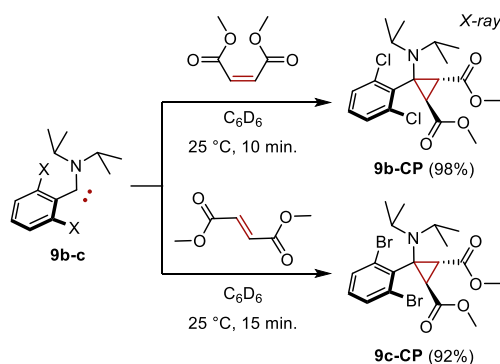
showed no proton deuterium exchange with HMDS, confirming that there was no need to isolate the bare carbene to achieve the inserted reaction product.

Scheme 4. Insertion reactions involving carbenes **9b-c**.



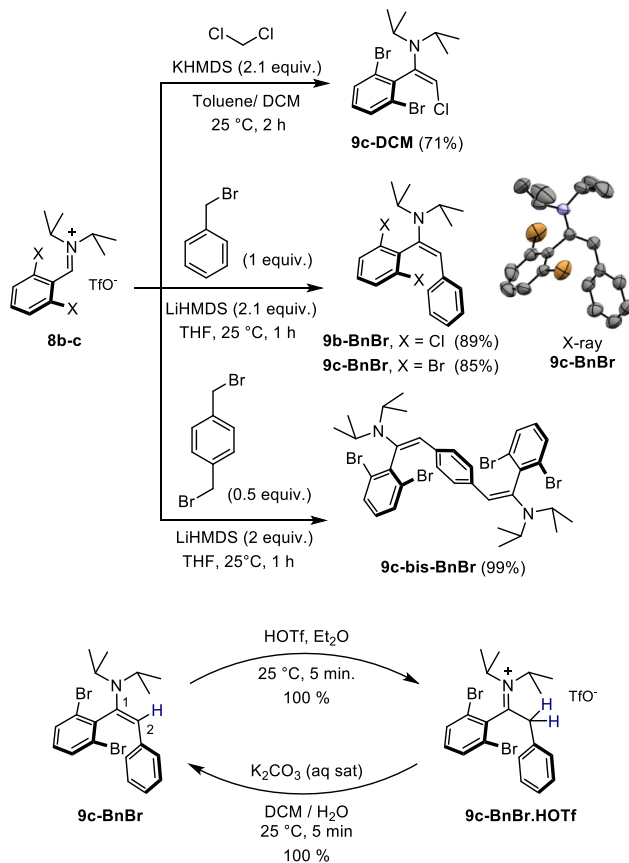
Cyclopropanation reactions in the presence of activated alkenes were also investigated, as these reactions are also diagnostic of the reactivity of ambiphilic singlet carbenes. Cyclopropanation of carbenes **9b-c** in the presence of maleate and fumarate esters was thus successfully carried out, giving high yields of reaction products **9-CP** (Scheme 5). The cyclopropanation reaction employing maleate ester and **9b** led to the cyclopropane **9b-CP** as a single diastereoisomer, with the *trans*-relative configuration as shown by X-ray diffraction analysis (ESI). The cyclopropanation of the fumarate ester also produced the *trans*-isomer **9c-CP**, indicative of a two-step process, involving a nucleophilic 1,4-addition of the carbene, followed by cyclization of the resulting enolate, yielding the thermodynamically more stable isomer.³⁸

Scheme 5. Cyclopropanation of activated olefins with **9b-c**.



Besides the electrophilicity, the nucleophilicity of these carbenes was also examined, notably to access conjugated amino stilbene-type structures (Scheme 6) in a one-pot fashion. Reaction of iminiums **8b-c** with benzyl bromide, in the presence of two equivalents of a base, thus led to the formation of **9-BnBr**. X-ray diffraction analysis of **9c-BnBr** indicated the formation of the isomer with the *Z*-stilbene-configuration (ESI). The complete *Z*-stilbene-selectivity is noteworthy and contrasts with the dimerization of AAACs, which generally affords predominantly *E*-stilbene-selectivity (*Z/E* ~ 20:80).²⁵ In addition, reversible protonation of **9c-BnBr** was successfully performed using triflic acid under anhydrous conditions (Scheme 6). Protonation occurred regioselectively at the C₂ center forming the iminium **9c-BnBr.HOTf**. This iminium can be regarded as a likely intermediate in the formation of **9-BnBr** from benzyl bromide under basic conditions. This is further supported by the quantitative deprotonation of **9c-BnBr.HOTf** back to **9c-BnBr**, using aqueous potassium carbonate, which occurred without hydrolyzing the iminium. The presence of protonated-**9c-BnBr** as an intermediate also justifies the use of two equivalents of strong and non-nucleophilic base to form **9c-BnBr**, avoiding the deprotonation of protonated-**9c-BnBr** by the carbene. This strategy was then successfully extended to the synthesis of the conjugated bright yellow compound **9c-Bis-BnBr**. The same reactivity was observed using dichloromethane as substrate, leading in this case to the chloro-enamine **9c-DCM** (Scheme 6).

Scheme 6. Synthesis of enamines 9c-DCM, 9c-BnBr and 9c-Bis-BnBr from iminiums 8b-c.

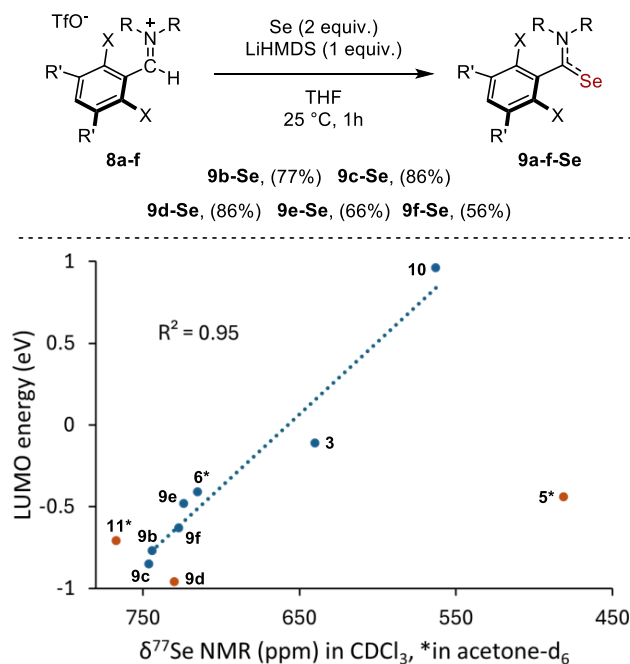


Electronic properties of amino(haloaryl)carbenes – Experimental studies

The π -accepting properties of amino(haloaryl)carbenes **9b-f** were assessed from ⁷⁷Se Chemical shifts of selenoamides **9b-Se** prepared from *in situ* generated **9b-c** and **9e-f** (Scheme 7 and Figure 4).^{41–43} Adducts **9b-Se** and **9c-Se** were analyzed in both acetone and chloroform, while **9e-Se** and **9f-Se** were characterized in CDCl₃ only, due to their solubility. Selenoamides **9b-Se** and **9c-Se** exhibited nearly the same chemical shift in both solvents. A 20 ppm downfield shift was noted in acetone-d₆, as compared to CDCl₃, which is rather low considering the magnitude of the measured chemical shifts. Compounds **9e-Se** and **9f-Se** were found about 20 ppm upfield compared to **9b-Se** and **9c-Se** (in CDCl₃). This is consistent with their aromatic ring substituted by two electron-donating MeO groups, increasing the electron-density on the carbene π -system, the latter becoming less π -accepting. All AAACs showed ⁷⁷Se chemical shifts in a narrow 723–765 ppm window, making them of comparable π -accepting properties to those of CAAC-6 **6** and AAAC **11**.¹⁵ However, carbenes **9** generating selenoamides **9-Se** exhibited a more electrophilic character than ADAC **10** and AAAC **3**; they also proved even more electrophilic than CAAC-5 **5** (although for some unknown reason the latter is outside the correlation). Comparison between **9b-f** and the structurally similar **3** is enlightening, as it evidences the increasing π -acceptor character brought by the aryl substituent. The LUMO energies calculated at the B3LYP-D3(BJ)/def2-TZVP level of theory for the parent carbenes associated to **9-Se**, **3-Se**,¹⁶ **6-Se**,⁴³ and **10-Se**³⁵ are

linearly correlated to their experimental ^{77}Se chemical shifts in CDCl_3 (Scheme 7).¹¹ A non-linear behavior from non-classical $\text{C}(\text{sp}^3)\text{H}-\text{Se}$ hydrogen bonds was shown to cause major deviations in ^{77}Se NMR shifts.³⁷

Scheme 7. Synthesis of 9b-f-Se. Linear correlation between ^{77}Se chemicals shifts of Se-adducts 9b-f-Se, 3-Se, 5-Se, 6-Se, 10-Se, 11-Se and the LUMO energy of their respective associated carbenes. (in orange compounds excluded from the correlation).



The σ -donor properties, *i.e.* the nucleophilicity, of carbenes **9a-f** were next experimentally evaluated by measuring $^1J(^{13}\text{C}-^1\text{H})$ coupling constants from ^1H NMR spectra of iminium precursors **8a-f** (Figure 5A).^{42,44-45} Ganter *et al.* showed that the $^1J_{\text{CH}}$ coupling constant of aminocarbenes iminium salts precursors correlates with the HOMO orbital energy of the corresponding carbenes.⁴¹ This methodology was later applied to other aminocarbenes by Nolan *et al.*, who underlined the existence of the NMR empirical relation: $^1J_{\text{CH}} = S \cdot 500$ Hz, where S is the percentage of s -character of the corresponding $\sigma_{\text{C-H}}$ orbital.^{44,46} Thus, the lower the coupling constant, the more

σ -donating the carbene is, due to a decreased s -character of the C-H bond. This coupling constant is conveniently determined from carbenic precursors as satellites around the acidic proton signal on high sensitivity ^1H spectra. Coupling constants of **8a-f** were thus determined in dry acetonitrile- d_3 (ESI). A linear correlation was observed between coupling constants of 2,6-dihaloaryl **8a-d** and the HOMO energies (B3LYP-D3(BJ)/def2-TZVP level of theory) of the corresponding carbenes (Figure 5B). An alternative linear correlation was observed for 3,5-dimethoxylated **8e-f** as well as CAAC **5-Cy** and AAAC **11**.^{26,44} The comparison with other carbenes revealed that **9b-f** were much more nucleophilic than widespread NHCs such as SIMes and IMes, but less than Alder's ADAC **3**. Compared to **5-Cy** and **11**, **9b-f** showed a similar nucleophilic character (Figure 5A).

Analysis by ^{15}N HMBC NMR spectroscopy (2D NMR based on $^3J(^{15}\text{N}-^1\text{H})$ correlation) was then implemented to estimate the nitrogen π -donation for carbene **9c** derivatives. This analysis is based on the method developed by Roesky *et al.* for CAAC **5**.⁴⁷ If a carbene only acts as a σ -donor with a species **E**, the formally empty $2p^\pi(\text{C})$ orbital is only stabilized by nitrogen π -donation, resulting in an electron-poorer nitrogen and a low field ^{15}N NMR signal (Figure 6). Conversely, when the carbene forms an adduct with a σ -accepting and π -donating species, the latter will also interact with the empty $2p^\pi(\text{C})$ orbital through π -back donation, resulting in a weaker π -donation by the nitrogen and a higher field ^{15}N signal. Strong HMBC correlations were observed, owing to the presence of Ni-Pr_2 substituent, evidencing a similar trend between **9c** and CAAC-**5**. Since the carbene may be regarded as a strong σ -donor toward the proton, iminium **8c** nitrogen being found at -122 ppm, the resulting carbene logically exhibited an upfield ^{15}N chemical shift (-151 ppm). The gold(I) complex **9c-Au** displays an electron-poorer nitrogen (-144 ppm) than in **9c**, indicating that there was no π -back donation by the metal. A signal significantly downfield for selenoamide **9c-Se** is illustrative of the π -back donation of selenium. However, based on Roesky's scale, it is clear that the carbene σ -donation is stronger than selenium π -back donation. Finally, as expected for trapping products **9c-CN-Cy**, **9c-bis-BnBr**, **9c-NH** and **9c-CHO** the nitrogen shift appeared around -300 ppm, showing no more π -donation by the pyramidalized nitrogen atom (sp^3 -hybridized and electron richer) (Figure 6).

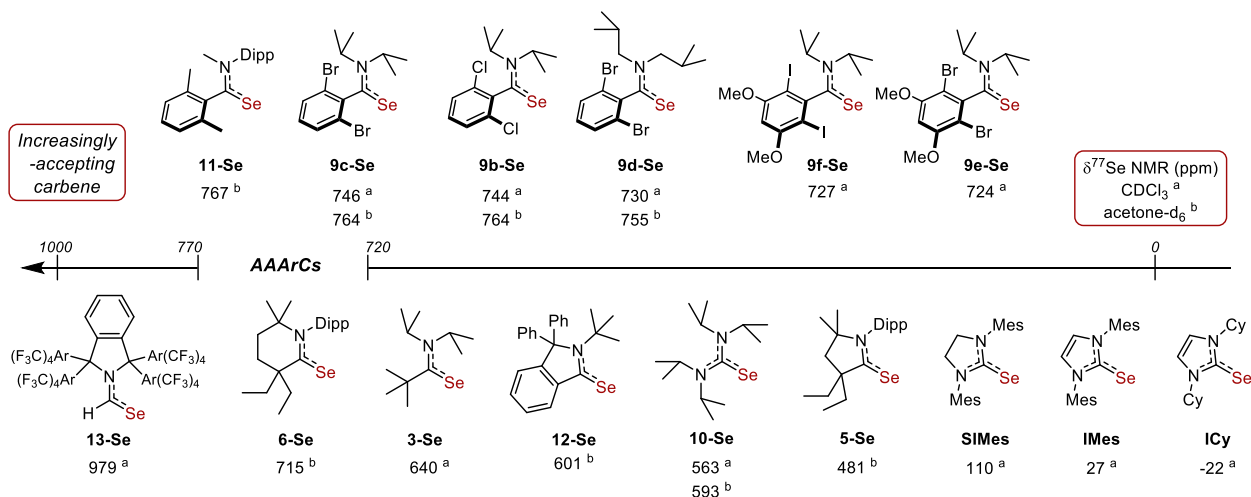


Figure 4. ^{77}Se Chemical shifts of Se-adducts **9b-f-Se** and comparison with representative literature examples of aminocarbenes.

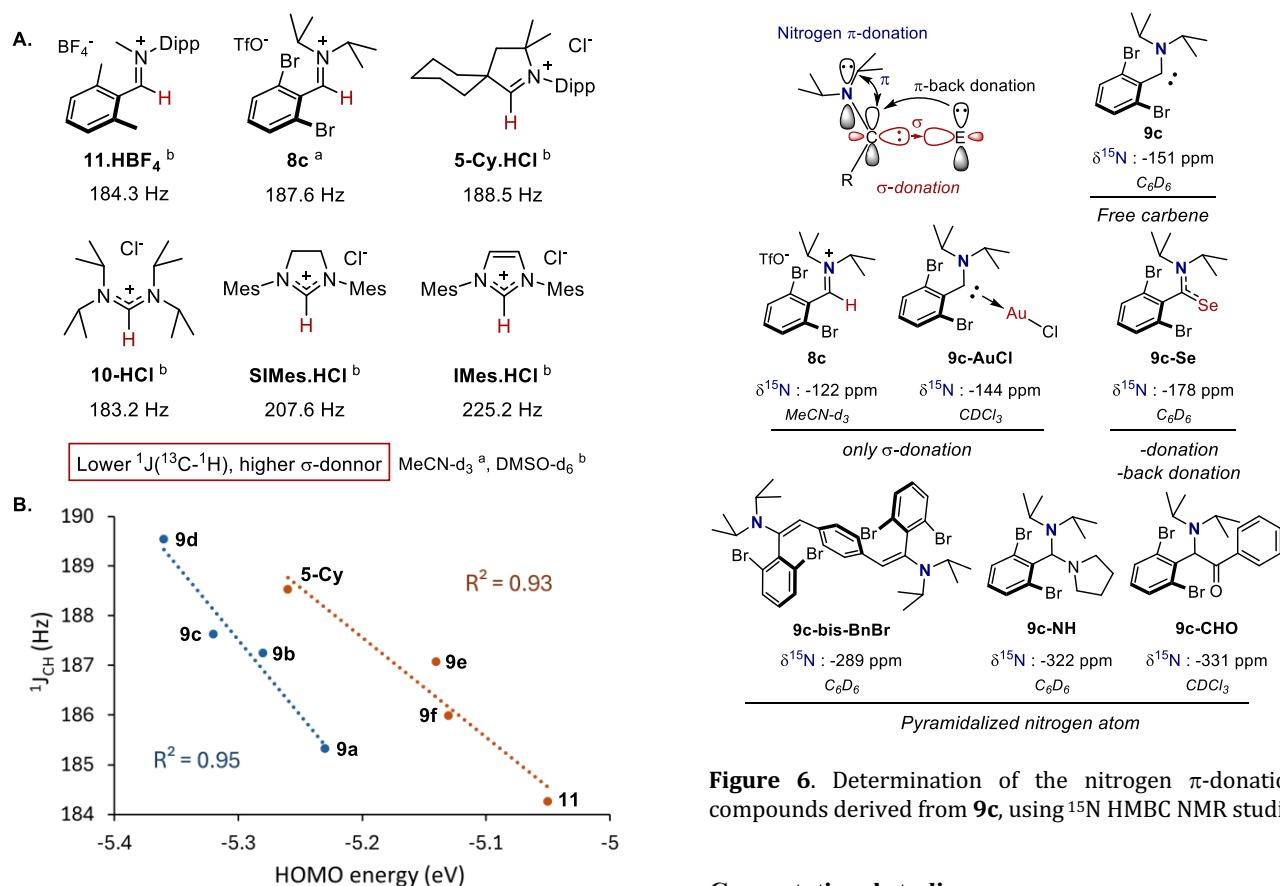


Figure 5. **A.** $^1J_{\text{CH}}$ coupling constant of carbene precursors **8a-f** and representative iminium salts **B.** Correlation between $^1J_{\text{CH}}$ and HOMO energies (nucleophilicity).

Figure 6. Determination of the nitrogen π -donation for compounds derived from **9c**, using ^{15}N HMBC NMR studies.

Computational studies

Electronic properties of amino(haloaryl)carbenes – Theoretical studies

DFT calculations were conducted at the B3LYP-D3(BJ)/def2-TZVP level of theory on **9a-f** as well as on non-halogenated analogue diisopropylamino(phenyl)carbene (Ph-C-Ni-Pr_2) **9g**, **3** and **4** for comparison purpose.⁴⁸⁻⁴⁹ Optimized geometry of **9c** perfectly matches the experimental X-ray diffraction structure, further supporting the validity of the selected computational level (Table S1). The frontier molecular orbitals (FMOs) of carbene **9c** are graphically depicted in Figure 7, as a

representative example. As expected, the HOMO is mainly located on the $n_{\sigma}(C)$ non-bonding orbital of the carbene center with some delocalization over the aromatic ring through the $\pi_1^*(Ar)$ orbital of correct symmetry. The LUMO involves the unoccupied $\pi_{C=N}^*$ orbital, typically associated to the nitrogen π -donation into the vacant orbital of the carbene, in combination with the $\pi_2^*(Ar)$ orbital of the dibromo-phenyl ring. The FMOs energy and the singlet-triplet gap for **9a-g**, **3** and **4** were also calculated (Table 1). A good correlation was observed between the calculated singlet-triplet gap (ΔG_{ST}) and the stability of the free carbene observed experimentally. Stable free carbenes thus exhibit $\Delta G_{ST} \geq 6.9$ kcal/mol, with the exception of **9d** ($\Delta G_{ST} = 27.9$ kcal/mol). In the latter case, it can be hypothesized that the origin of the dimerization is due to a lower steric protection provided by the isobutyl groups, compared to that provided by isopropyl groups (*vide infra*). By comparing data in Table 1 for carbenes with identical structure, but involving different *ortho*-substituents, it can be observed that: (i) both FMOs are stabilized in the order: H (**9g**) < F (**9a**) < Cl (**9b**) < Br (**9c**) and (ii) the ΔG_{ST} follows the opposite trend, increasing from **9g** to **9c**. Carbenes **9e-f** have

both higher FMOs and singlet-triplet gaps compared to carbene **9c**, as expected, due to the donating effect of methoxy groups on the aryl ring. In comparison, AAAC **4** exhibits the lowest FMOs of all considered carbenes but displays a similar ΔG_{ST} to **9b-c**. It is finally worthy of note that stable carbene **3**, *i.e.* featuring the same *i*-Pr₂N substituent as **9a-g** but a σ -donor *t*-Bu instead of an aryl, exhibits destabilized FMOs, but higher ΔG_{ST} compared to dimerizing carbenes **9a** and **9g**.

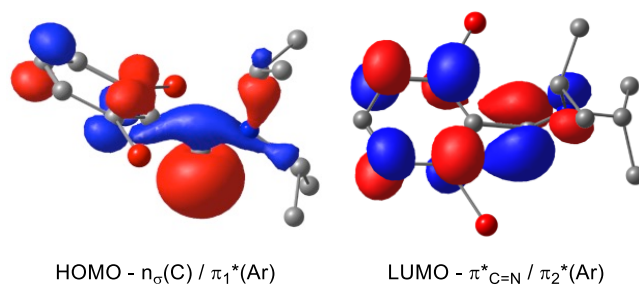
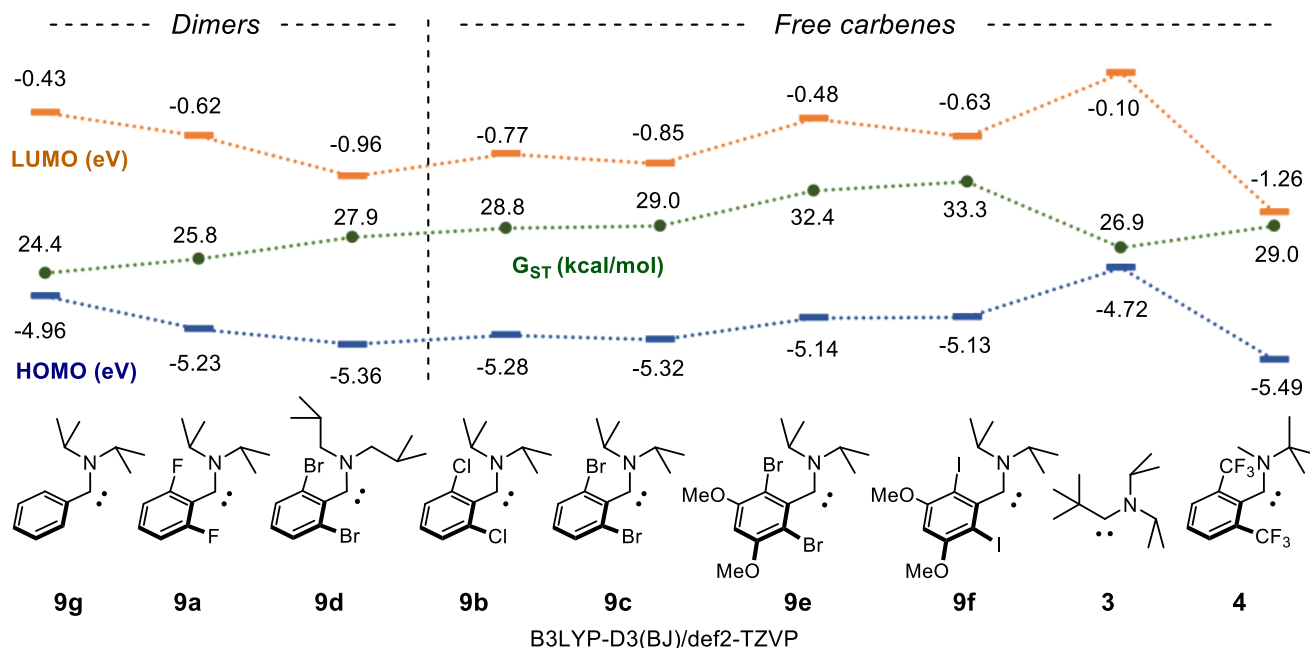


Figure 7. Plot of the HOMO and LUMO for carbene **9c**. Isosurface cutoff: 0.05.

Table 1. FMO energies (in eV) and Singlet-Triplet gap ΔG_{ST} (in kcal/mol), computed at B3LYP-D3(BJ)/def2-TZVP level of theory for **9a-g**, **3** and **4**.



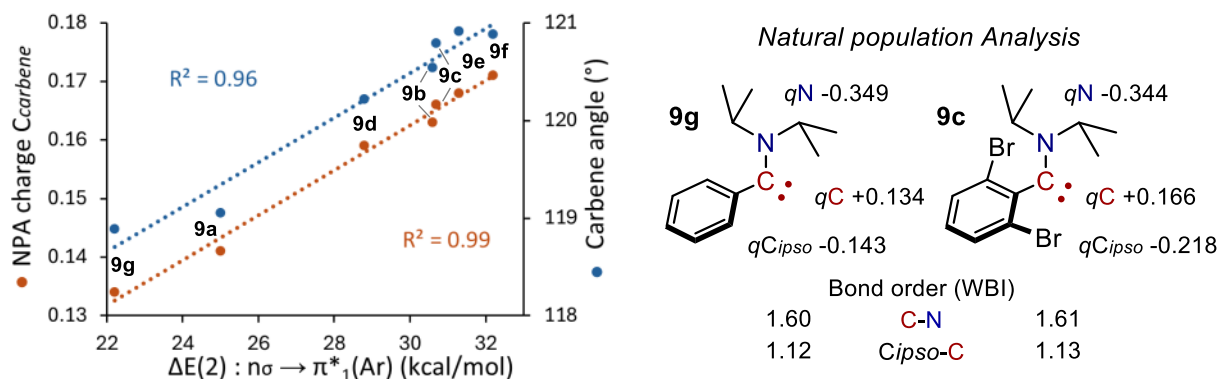


Figure 8. Correlation between NPA charges (q_C) on the carbene center, carbene bond angle (in $^\circ$) and the donor-acceptor $n_\sigma(C) \rightarrow \pi_1^*(Ar)$ stabilizing interaction in kcal/mol ($\Delta E(2)$). Comparison of the NPA charge distribution and bond order (WBI : Wiberg Bond Index) of the carbene center of **9g** and **9c**.

The Natural Bond Orbital (NBO)⁴⁸ method was used to gain further insight into the stabilization of carbenes **9a-g**. To this end, we assessed the role of the aryl group at accepting electron density from the carbene center, namely by analyzing the stabilizing donor-acceptor interaction between the $n_\sigma(C)$ orbital of the carbene moiety and the $\pi_1^*(Ar)$ orbital of the aryl group. Our study reveals a strong $n_\sigma(C) \rightarrow \pi_1^*(Ar)$ interaction, with a stabilizing energy $\Delta E(2)$ ranging between 22 and 32 kcal/mol (Figure 8) from (**9a**) to (**9e**), which can be visualized in the associated Natural Localized Molecular Orbital (NLMO) in Figure 9A. This is in line with the orientation of the aryl group with respect with the carbene fragment ($\sim 92^\circ$, see Table S2), which allows a good overlap between $n_\sigma(C)$ and $\pi_1^*(Ar)$ orbitals. The magnitude of this stabilizing energy clearly depends on the *ortho*-substituents of the aryl group and follows the order: H (**9g**) < F (**9a**) < Cl (**9b**) < Br (**9c**). These results are fully consistent with experimental observations regarding the stability of the different carbenes. This interaction has also been confirmed and quantified with the EDA-ETS/NOCV⁴⁸ method, by analyzing the charge flow density from the carbene center to the aryl group in **9c** (Figure 9B and figure S1 in ESI). The NBO analysis of **9c** reveals a hybridization of the lone pair of the carbene of $sp^{1.64}$ (38% s-character and 62% p-character). As a consequence of this $n_\sigma(C) \rightarrow \pi_1^*(Ar)$ interaction, electron occupancy of the σ -orbital is lowered, *i.e.* 1.73 to 1.77 electrons instead of 2, leading to a positive Natural Population Analysis (NPA) charge on the carbene center (Figure 8). Interestingly, we found that the $n_\sigma(C) \rightarrow \pi_1^*(Ar)$ stabilization energy is linearly correlated ($R^2 = 0.99$) with the singlet-triplet gap, except for carbenes **9e-f** featuring *meta*-OMe substituents, which seemed to follow a different trend (Figure S2). Importantly, and as shown in Figure 8, the $n_\sigma(C) \rightarrow \pi_1^*(Ar)$ energy also correlated with the calculated carbene bond angle ($R^2 = 0.96$) as well as with the NPA charge on the carbene center ($R^2 = 0.99$) for all substrates (specific values in Table S2). Consequently, the stronger the stabilization energy, the wider the angle and the more electropositive the carbene is. This may be explained by a better π -orbital overlap resulting

from an enhanced parallel alignment between the $n_\sigma(C)$ -orbital, which presents a higher p-character, and the π -aryl system (Figure S3). In contrast, halogen non-bonding orbitals ($n_{X^{\pi}}$) only provide very weak interaction, *i.e.* 0.59 to 1.89 kcal/mol, with the $\pi_{C=N}^*$ orbital and do not bring much stabilization to the carbene.

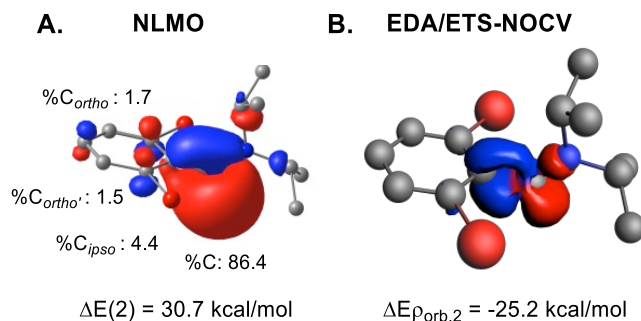


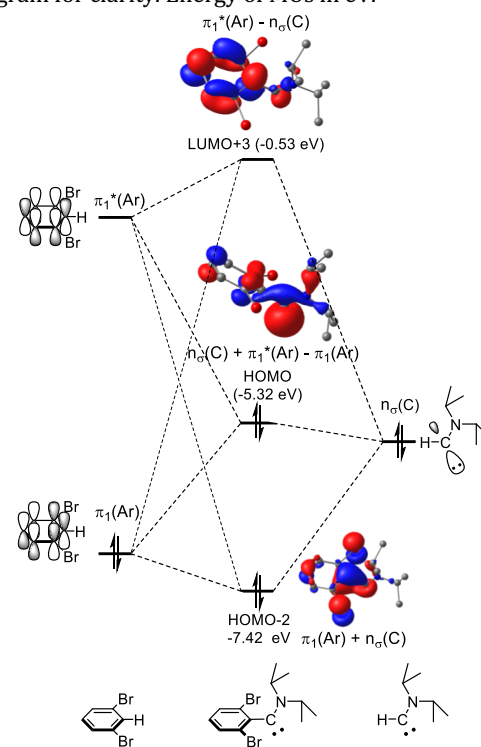
Figure 9. Visualization of the $n_\sigma(C) \rightarrow \pi_1^*(Ar)$ delocalization using NBO and EDA/ETS-NOCV analyses. A) Plot of the NLMO (cut-off 0.03) and contributions of main atoms in %. Stabilizing interaction $\Delta E(2)$. B) Plot of the contour of deformation density contribution $\Delta \rho_{orb,2}$ of the main pairwise orbital interaction involving the carbene center and associated orbital interaction energy contribution ($\Delta E_{orb,2}$). The charge flow is red \rightarrow blue ($\Delta \rho < 0$ in red and $\Delta \rho > 0$ in blue). The contour value for density is 0.001 a.u.

Complementing the NBO analysis, the molecular orbitals (MO) perturbation diagram of carbene **9c** was constructed in order to further understand the different orbital interactions and mainly those involving the $n_\sigma(C)$ -orbital of the carbene center. For a MO diagram involving the C=N π -orbitals see figure S4. Monosubstituted diisopropylamino carbene and 1,3-dibromobenzene fragments interactions were considered (Figure 10). Multiple interactions involving the $n_\sigma(C)$ -orbital or the $\pi_{C=N}$ -system of the carbene and the bromo-aryl π -system and the bromo lone pairs are observed. The HOMO and LUMO+3 of **9c** mainly originates from the bonding and

antibonding combination between the $n_{\sigma}(\text{C})$ orbital of the carbene and the $\pi_1^*(\text{Ar})$ orbital of the aryl group (similar symmetry), with a weak participation of the $\pi_1(\text{Ar})$ orbital. These MOs are consistent with the above-commented NBO and EDA analyses, where a $n_{\sigma}(\text{C}) \rightarrow \pi_1^*(\text{Ar})$ interaction was highlighted. The combination between the acceptor character of the aryl group and the classical push effect of the amino substituent makes carbenes **9b**, **9c**, **9e** and **9f** “push-pull” carbenes, contrasting with previously reported carbene **4**,¹² featuring an aryl group described as a spectator substituent. The HOMO-2 of **9c** similarly results from a bonding π -overlap mainly between the $n_{\sigma}(\text{C})$ and the $\pi_1(\text{Ar})$ orbital. The $\pi_{\text{C}=\text{N}}$ orbital appears in the HOMO-6 and the $\pi_{\text{C}=\text{N}}^*$ in the LUMO and LUMO+1 (Figure S4). A similar MO diagram was obtained for model compound **9g** (featuring a phenyl substituent), albeit showing significantly weaker orbital stabilizations (Figure S5). The main difference in the case of **9g** is that the occupied and unoccupied π -orbitals in the phenyl rings are higher in energy than those of the 2,6-dibromophenyl ($\pi_1^*(\text{ArH})$ -0.39 eV, $\pi_1^*(\text{ArBr})$ -1.14 eV and $\pi_1(\text{ArH})$ -7.06 eV, $\pi_1(\text{ArBr})$ -7.39 eV). Consequently, the interaction between $n_{\sigma}(\text{C})$ and $\pi_1^*(\text{ArH})$ orbital is stronger and the $n_{\sigma}(\text{C}) \rightarrow \pi_1^*(\text{ArH})$ stabilization is weaker, leading to the HOMO of **9g** being thus higher in energy compared to **9c**. *The dihaloaryl is therefore bringing an important electronic stabilization through the $n_{\sigma}(\text{C}) \rightarrow \pi_1^*(\text{Ar})$ delocalization.* This is a general trend with all dihaloarenes fragments considered here, the lower the $\pi_1^*(\text{ArX})$ of the arene, the higher π -overlap with $n_{\sigma}(\text{C})$ (Figure S6). The influence of the *ortho*-substituents on the MOs was also examined by comparing the MOs in carbenes **9a** (F), **9b** (Cl) and **9c** (Br) (see Table S3). Whereas the position of the $n_{\sigma}(\text{C})$ is only slightly influenced by *o,o'*-substitution, the LUMO orbital (π_{CN}^*) was found to be more stabilized upon Br substitution. The potential influence of the amino group on the delocalization of the $n_{\sigma}(\text{C})$ lone pair of the carbene into the aromatic ring was finally examined further through a comparative analysis of the electronic delocalization in carbenes **9c** and **9d**, having different amino substituents ($\text{N}(i\text{-Pr})_2$ and $\text{N}(i\text{-Bu})_2$, respectively). Additionally, we modeled a “parent” carbene, where the amino group was replaced by a

hydrogen atom, and the dihedral angle $\text{N-C-C}_{\text{ispo-C}_{\text{ortho}}}$ fixed to the same value as in **9c** (94.098°) to maintain the same orientation of the aryl group with respect to the $n_{\sigma}(\text{C})$ lone pair. The Natural Bond Orbital (NBO) analysis revealed that the delocalization of the $n_{\sigma}(\text{C})$ lone pair of the carbene was significantly influenced by the presence of the donating amino group, thereby reinforcing the stabilization effect. Consequently, the so-called “push-pull” effect should be regarded as a synergistic stabilization resulting from the combined effects of the donor and electron-withdrawing groups on the carbene center.

Figure 10. Molecular orbitals perturbation diagram of **9c**. Only the most important orbitals involving $n_{\sigma}(\text{C})$ are represented in the diagram for clarity. Energy of MOs in eV.



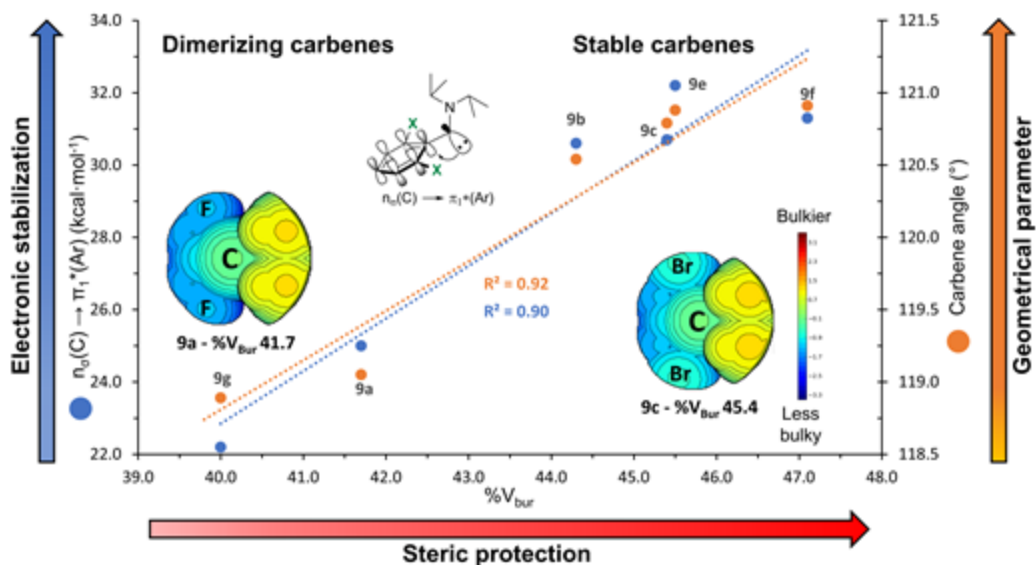


Figure 11. Plot of the steric hindrance (percentage of buried volume at 2Å) versus the electronic stabilization ($n_{\sigma}(C) \rightarrow \pi_1^*(Ar)$) (blue line) and versus the calculated carbene angle (orange line) for carbenes **9a-c** and **9e-g**. Steric maps at 2 Å for **9a** and **9c**. Calculations carried out at B3LYP-D3(BJ)/Def2-TZVP level.

Halogens steric effects in amino(haloaryl)carbenes **9**

Since it is well-known that carbenes can be stabilized by both electronic and steric effects, we computationally explored steric hindrance in free carbenes **9a-g** to get insight into the role of halogenated aryl groups on the kinetic protection of the carbenes. To this end, the SambVca 2.1 tool was employed to compute the respective percentage of buried volume values (%V_{bur}) and steric maps of the considered carbenes (See details in the ESI).⁵⁰ In order to support the selected methodology, a comparison was performed between the %V_{bur} of crystal and DFT-computed structures of **9c**, for which less than 3 % deviation was found (Figure S7-8). After validation of the methodology, the respective %V_{bur} and steric maps of DFT-structures for carbenes **9a-g**, **3** and **4** including those that dimerize were computed. Our study revealed that the steric hindrance is affected by the *ortho*-substituents for carbenes **9a-g** with the %V_{bur} values following the order: H (**9g**) 40.0 % < F (**9a**) 41.7 % < Cl (**9b**) 44.3 % < Br (**9c**) 45.4 % < I (**9f**) 47.1 %. Carbenes **9c** and **9e** (%V_{bur}: 45.4 % vs 45.5 %) present similar buried volumes percentages, indicating a negligible steric effect coming from the methoxy groups at *meta* positions. Carbene **9d** exhibits the lowest %V_{bur} (39.8 %) of all considered carbenes, as expected due to the lower steric protection of isobutyl chains compared to that provided by isopropyl chains. By comparison with **9c**, this reduced steric protection may be the primary factor responsible for the experimentally observed dimerization of carbene **9d**. Finally, **4** exhibits a %V_{bur} of 46.4 %, halfway between **9c** and **9f**, and **3** is the most hindered of all considered cases (%V_{bur} = 49.6 %), due mainly to the bulky *ortho*-trifluoromethyl substituents. Remarkably, as illustrated in Figure 11, we observed a linear correlation ($R^2 = 0.90$) between the %V_{bur} and the stabilization energy associated with the $n_{\sigma}(C) \rightarrow \pi_1^*(Ar)$ interaction in carbenes featuring Ni-Pr₂

amino groups. Additionally, it was found that the %V_{bur} is also strongly correlated with the carbene angle ($R^2 = 0.92$). It may thus be concluded from above-commented theoretical study that both steric (i.e., kinetic) and electronic (i.e., thermodynamic) effects act synergistically in the stabilization of the presented carbenes.

Conclusion

New acyclic amino(haloaryl)carbenes showing exceptionally high thermal stability were designed and their structure clearly established through X-ray diffraction analysis. These carbenes are among the most ambiphilic stable singlet carbenes reported to date, as evidenced by spectroscopic and computational studies. Their thermodynamic stabilization arises from the strong π -accepting *ortho*-dihaloaryl substituent, providing a unique push-pull stabilization. The steric hindrance of the dihaloaryl fragment also affords a kinetic protection to the carbene center, the latter yet retaining a remarkable ambiphilic character. Thus, instead of spontaneously dimerizing like their counterparts deprived of *ortho*-halogen atoms on the aryl ring, acyclic amino(haloaryl)carbenes can, not only be isolated and spectroscopically characterized, but can also react with a range of substrates. This was showcased through their reaction with gold (Au), chalcogen (Se), isonitrile as well as their insertion into Si-H, B-H, N-H and C-H bonds. All these observations led us to reconsider previous conclusions about the role of spectator of the arene moiety in amino(aryl)carbenes, acting as an attractive substituent which stabilizes the carbene through a push-pull effect. The steric hindrance of the substituents in the *ortho* position contributes strongly to the stabilization of these carbenes, nonetheless without compromising their reactivity. These stable carbenes, whose

reactivity is very similar to that of CAACs, are however more easily available using a high-yield two-step process, holding promising applications in synthesis and catalysis.

ASSOCIATED CONTENT

The supporting Information material is available free of charge via the Internet at <http://pubs.acs.org>.
Experimental procedures, ¹H, ¹³C NMR spectra, X-ray diffraction studies data.

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Author Contributions

The manuscript was written with the contribution of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

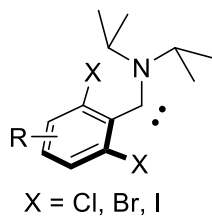
ADAC, acyclic diaminocarbene; AAAC, acyclic amino(alkyl)carbene; AAAC, acyclic amino(aryl)carbene;

CAAC, cyclic amino(alkyl)carbenes; NHC, N-heterocyclic carbene.

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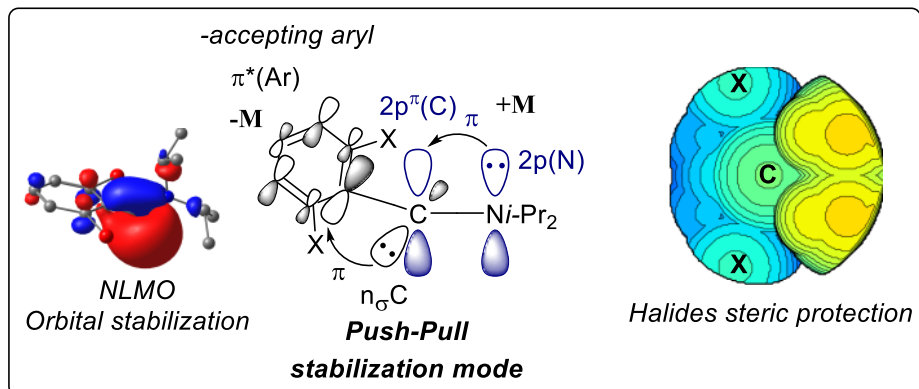
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- High thermal stability
- High ambiphilic reactivity

Amino(halo-Aryl)Carbenes



→ Thermodynamic and Kinetic cooperative stabilization