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COMMUNICATION Very Important Paper

A Crystalline (Amino)(chloro)Carbene: A Platform for Nucleophilic Substitution at a Carbene Center

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ABSTRACT

Halogenocarbenes have attracted significant interest for almost a century because they combine classical singlet carbene reactivity with the presence of a readily substituted halogen group. Before this work, no halogenocarbenes had been isolated and taming their instability remained a synthetic challenge. This report describes the preparation of room temperature stable (amino)(chloro)carbenes and examples of their substitution chemistry at the carbene center, unlocking access to a wide range of acyclic carbenes.

In 1954, Doering and Hoffmann [1] reported that dichlorocarbene [2], formed by deprotonation of chloroform, adds to alkenes via a [2+1] cycloaddition (Figure 1A). Since that time, a myriad of papers have been published on cyclopropanation reactions involving a variety of chlorocarbenes [3, 4] which yield readily functionalized chlorocyclopropanes (Figure 1B) [5–10]. Transient chlorocarbenes have also found many other applications in different fields across chemistry and materials science [11–18]. In contrast, the search for stable chlorocarbenes has remained very limited due to intrinsic synthetic challenges. The difference in electronegativity between carbon and chlorine makes the C-Cl bond reactive. More importantly, the relatively small monovalent chloride does not provide steric protection and precludes cyclic structures which stabilize the carbene lone pair [19]. Indeed, it is well recognized that acyclic carbenes are generally more unstable than their cyclic counterparts due to their larger carbene bond angles, which enhance the p-character of the carbene lone pair [20]. With one exception [21, 22], all singlet carbenes isolated thus far feature an amino or phosphino substituent, the former providing superior stabilization [23]. Thus, it may be expected that an amino substituent would be ideal for stabilizing a chlorocarbene. However, it is important to note that both aminodiazo compounds and aminodiazirines, the classical carbene precursors, are not stable [24]. Thus, the first attempts to obtain amino-stabilized chlorocarbenes, which were reported by Böhme [25] involved the deprotonation of Vilsmeier reagent-like chloroiminiums (Figure 1C). This concept was later extended by the group of Meth-Cohn [26, 27]. The formation of (amino)(chloro)carbenes was indirectly confirmed by the observation of carbene dimerization products. The free carbenes were not isolable and their reactivity was poorly controlled. Beyond the inherent academic challenge, the presence of a classical leaving group at the carbene center provides strong motivation for preparing isolable chlorocarbenes. Nucleophilic substitution may provide a variety of new acyclic carbenes, some of which could rearrange into useful heterocycles. Furthermore, reduction or chloride abstraction would transform these species into hitherto unknown mono-coordinate carbon species. Therefore, developing the chemistry of stable chlorocarbenes is of clear importance for organic chemistry. In 2018, our group isolated

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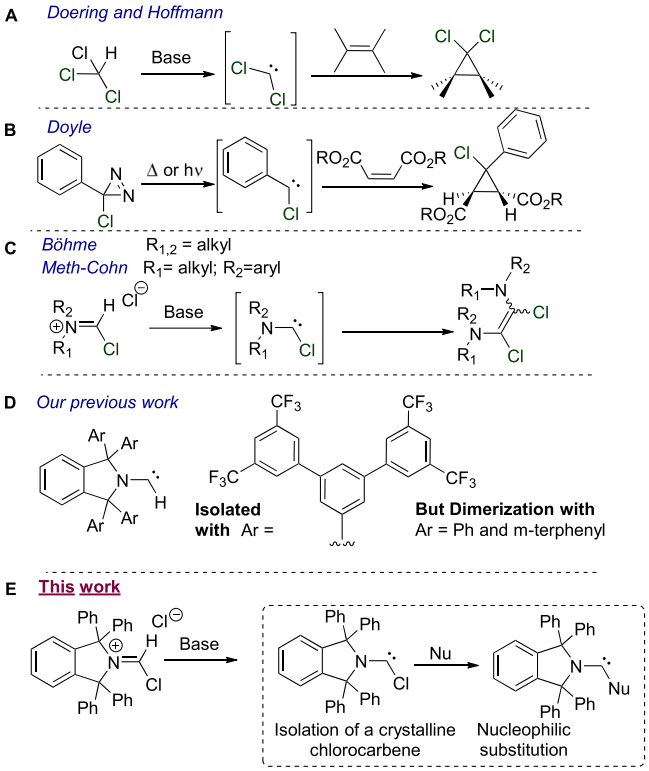


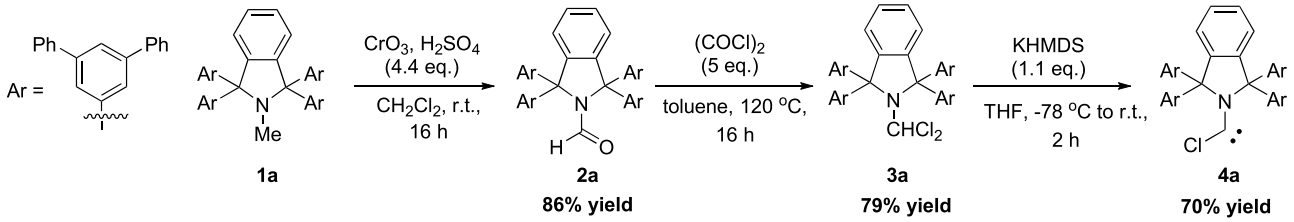
FIGURE 1 | Previous approaches for the preparation of chlorocarbenes.

a monosubstituted carbene by developing a strongly donating amino group featuring considerable steric protection provided by four *m*-terphenyl substituents decorated with trifluoromethyl groups (Figure 1D) [28]. Encouraged by this achievement, we hypothesized that a similar backbone could enable the isolation of chlorocarbenes. Herein, we report the preparation of room temperature stable (amino)(chloro)carbenes, which undergo nucleophilic substitution with soft and hard anionic nucleophiles and even neutral nucleophiles (Figure 1E).

As a potential precursor for an isolable chlorocarbene, we first targeted a chloroiminium salt derived from 2-methylisoindoline-1,3-dione and bearing four *m*-terphenyl substituents (Scheme 1). Compound **1a** [28] was prepared by a modified procedure (see Supporting Information). Oxidation with the Jones reagent yielded formamide **2a** in 86% yield. Due to the steric hindrance around the formamide, generating the corresponding chloroiminium proved more challenging than anticipated based on previous reports [25–27]. Thionyl chloride was unreactive, while only traces of the desired product **3a** were obtained with phosphorous pentachloride. However, with an excess of oxalyl chloride in refluxing toluene, **3a** was obtained in 79% yield. NMR analysis of this compound in $CDCl_3$ revealed a proton signal at 9.6 ppm which was correlated by HMQC to a ^{13}C signal at 110 ppm. The latter is strongly shielded compared to the usual chemical shift observed for iminium salts and suggests that **3a** is not a salt but rather a covalent dichloromethyl compound. We hypothesize that the covalent nature of **3a** is due to the large aromatic groups, which provide a hydrophobic environment that favors a neutral covalent form over a charged form. Similarly, pKa shifts have been observed when an acidic or basic functionality is enclosed within hydrophobic supramolecular containers [29]. Nevertheless, just as chloroform can be deprotonated to afford dichlorocarbene, the covalent nature of **3a** did not preclude deprotonation by KHMDS in THF. Gratifyingly, the desired chlorocarbene **4a** was isolated in 70% yield as an off-white solid, which is stable for weeks at room temperature in the glovebox. The ^{13}C NMR spectrum of **4a** features a characteristic carbene carbon signal at 300.2 ppm, leaving no doubt that **4a** is a carbene. For comparison, previously reported acyclic amino carbenes produce ^{13}C NMR signals in the range of 297–326 ppm which correspond to the carbene carbon [28, 30–32].

Although chlorine is larger than hydrogen, the much higher stability of **4a** relative to the analogous monosubstituted carbene, which rapidly dimerizes (Figure 1D), was surprising. We thus wondered if four phenyl substituents would also be sufficient to stabilize an (amino)(chloro)carbene. The carbene precursor was prepared in three steps from the 2-methyl-1,1,3,3-tetraphenylisoindoline **1b** [33, 34] (Figure 2). Instead of using the Jones reagent, the methyl group was oxidized with an excess of bromine in basic medium to afford formamide **2b** in 80% yield. Then, treatment with an excess of oxalyl chloride in toluene at 85°C gave **3b** which was isolated in 78% yield. In contrast with the covalent nature of **3a**, **3b** is an iminium salt as indicated by a ^{13}C NMR signal at 170.1 ppm. This was confirmed by single crystal X-ray diffraction analysis (Figure 2). Lastly, deprotonation at −78°C with 1.25 equivalents of KHMDS afforded carbene **4b**, which was isolated as a beige solid in 93% yield. The ^{13}C NMR spectrum features a carbene carbon signal at 299.6 ppm. Interestingly, the two quaternary carbons α to the nitrogen give distinct signals at 89.1 and 88.7 ppm, demonstrating hindered rotation along the nitrogen-carbene bond. This is likely due to the significant double-bond character of the nitrogen-carbene bond. Single crystals of **4b** were obtained by vapor diffusion of hexane into a toluene solution. X-ray diffraction analysis reveals a 0.65-0.35 disorder in which two different C-Cl fragments were found corresponding to a 180° rotation around the N-C bond. The nitrogen-carbene bond [1.309(7) and 1.292(13) Å] was found to be slightly shorter than that observed for the monosubstituted carbene [1.325(8) Å] [28]. The C-N-C-Cl dihedral angle is close to zero [0.6(17) and 3(3)°]. Interestingly, the C-Cl bond in **4b** [1.756(14) and 1.78(2) Å] is slightly elongated compared to that in chloroiminium **3b** [1.677(3) Å], likely due to an anti-bonding interaction between a chlorine lone pair and the carbene lone pair. Lastly, the carbene bond angle [112.84(18) and 116.9(17)°] is more acute than in other acyclic carbenes such as the (amino)(alkyl)carbenes (120.5°) [32]. This could be due to the inductive effect of the chlorine, which stabilizes the σ-orbital of the carbene carbon and thus favors increased s-character in the carbene lone pair orbital.

Clearly, the distinct utility of chlorocarbenes, relative to other carbenes, stems from the presence of a leaving group, which should enable the preparation of a variety of other acyclic carbenes via nucleophilic substitution. Thus, we tested the reactivity of carbene **4b** with various nucleophiles. In toluene at low temperature, **4b** reacted with 2,6-dimethylbenzenethiolate and 2,6-dimethylphenolate, cleanly affording the corresponding amino-thio **5** and amino-oxo **6** carbenes in quantitative yield (Scheme 2). This substitution chemistry is not restricted to anionic nucleophiles. Neutral nucleophiles can also be used, as



SCHEME 1 | Preparation of (amino)(chloro)carbene **4a**.

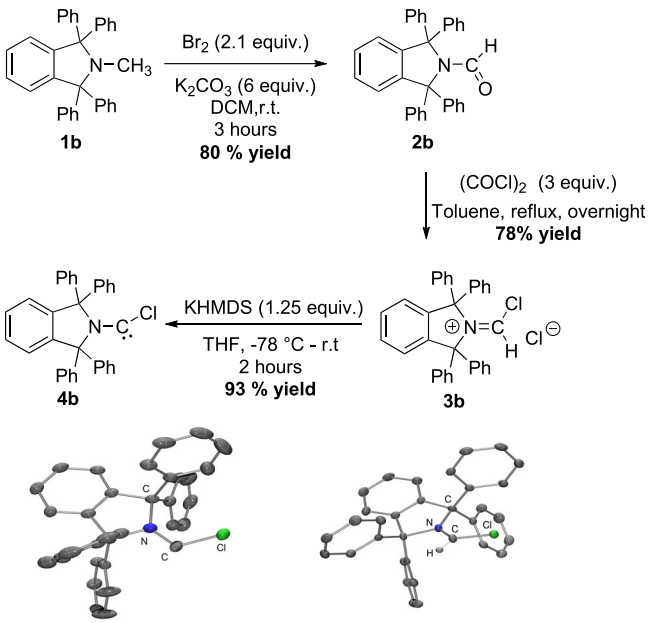


FIGURE 2 | Preparation of (amino)(chloro)carbene **4b** and solid-state structure of **3b** (the chloride ion is not shown) and **4b** [35].

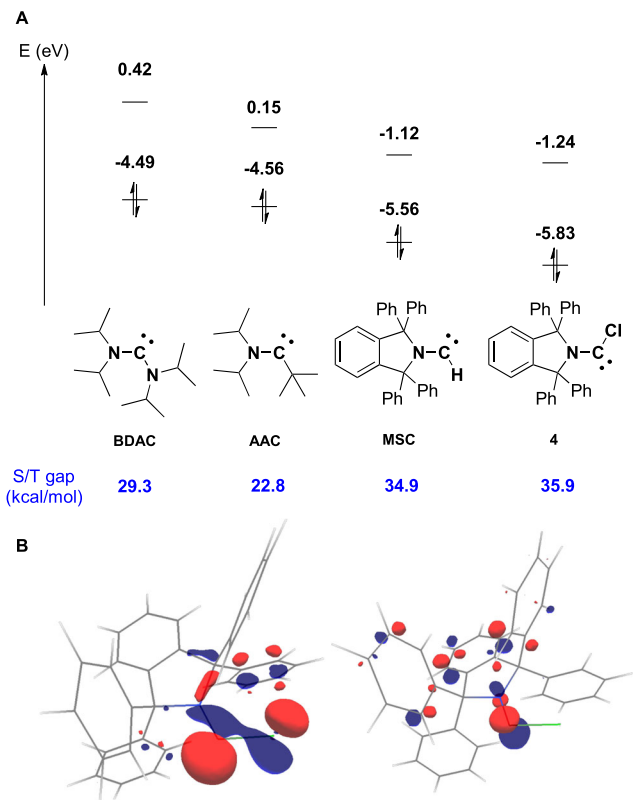
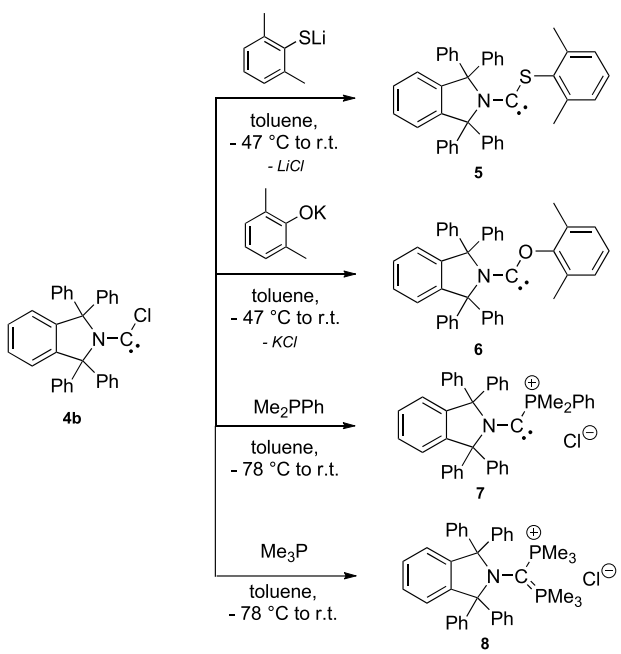


FIGURE 3 | DFT analysis of acyclic aminocarbenes. A: HOMO-LUMO energies and singlet-triplet gap; B: HOMO (left) and LUMO (right) of carbene **4**.



SCHEME 2 | Nucleophilic substitution reactions.

shown by the reaction with dimethylphenylphosphine to afford **7**. Notably, the smaller trimethylphosphine adds twice, whatever the stoichiometry of the reaction, to form the bis(adduct) **8**. Note that the coupling of phosphines with electrophilic carbenes has already been reported [36].

We investigated the electronic structure of several carbenes at the ωb97X-V/def2-mTZVPP/SMD(benzene)//r^{2}SCAN-3c/CPCM(benzene) level of theory [32, 37, 38]. Comparison with other acyclic aminocarbenes (Figure 3 and Supporting Information) revealed that the adiabatic singlet-triplet gap of (amino)(chloro)carbene **4** (35.9 kcal/mol) is similar to that of other acyclic aminocarbenes such as the **BDAC** [39], **AAC** [32], and **MSC** [28]. As expected given the chloride substituent, **4** appears slightly less nucleophilic and more electrophilic than the other acyclic aminocarbenes. Analysis of the frontier molecular orbitals of **4** reveals that the HOMO is the carbene lone pair with a significant antibonding σ-interaction with the 3p chlorine

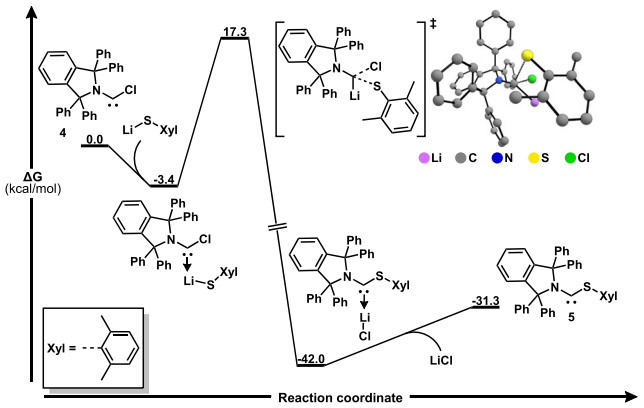


FIGURE 4 | Calculated free energy diagram for the substitution reaction with an anionic nucleophile as exemplified by the process leading to **5**. In the transition state structure, hydrogen atoms have been removed for clarity.

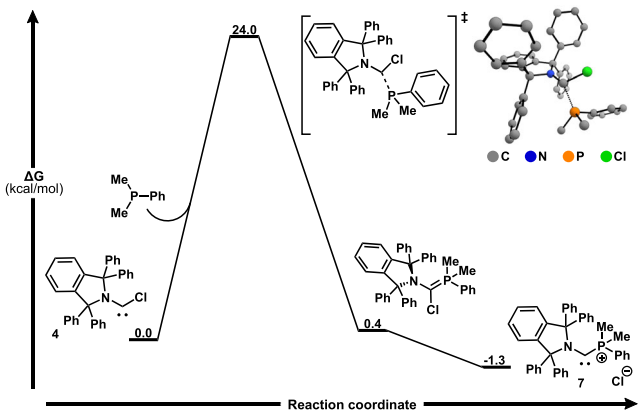


FIGURE 5 | Calculated free energy diagram for the substitution reaction with a neutral nucleophile as exemplified by the process leading to **7**. In the transition state structure, hydrogen atoms have been removed for clarity.

orbital in line with the C-Cl bond (see Figure 3B left). The LUMO is best described as a combination of the carbene empty orbital (N-C π^*) and the aromatic Ψ_3 orbitals of the phenylene moiety (see Figure 3B right).

At the same level of theory, we also studied the mechanism of the substitution reactions by an anionic and a neutral nucleophile using the formation of carbenes **5** and **7** as examples (Figures 4, 5). For **5**, the reaction begins by the association of the chlorocarbene carbon with the lithium cation of the thiolate salt to form a complex. Chloride substitution proceeds through a single transition state ($\Delta G^{\ddagger}$ = 20.7 kcal/mol) featuring a tetrahedral geometry at the carbene carbon (see Figure S32). This transition state leading to the LiCl adduct of carbene **5** corresponds to the concomitant disassociation of Cl^- from the carbene with the nucleophilic attack by ArS^-. In the final step, the LiCl disassociates from the thiocarbene **5**. Note, our calculations model solvation for benzene, which cannot solubilize LiCl. Furthermore, the lattice energy of crystalline LiCl is not accounted for; this would almost certainly make the final step exergonic. No four-coordinate carbenoid intermediate could be identified as a minimum, and thus the mechanism is distinct from a two-step addition-elimination process.

The mechanism of the reaction leading to **7** is slightly different (Figures 5, S33). The first step is the coupling of the amino(chloro)carbene **4** with the phosphine via a non-least motion pathway ($\Delta G^{\ddagger}$ = 24.0 kcal/mol) giving rise to a neutral phosphorous ylide. The transition state resembles addition of the phosphine lone pair to the empty orbital of the carbene, which has significant N-C π^* character. Subsequent elimination of chloride produces the amino(phosphonio)carbene **7**. While ylide formation is slightly endergonic (ΔG = 0.4 kcal/mol), subsequent elimination of chloride to form **7** renders the overall reaction slightly exergonic (ΔG = -1.3 kcal/mol). Thus, in contrast with the case of anionic nucleophiles, substitution of chloride by phosphines proceeds through a two-step associative process. This difference is likely a reflection of the high stability of phosphorous ylides compared to tetracoordinate metal-halogen carbenoids.

In summary, we have described the first examples of room temperature stable chlorocarbenes. Interestingly, their isolation does not require excessive steric protection, and thus many different (amino)(chloro)carbenes should be available. They constitute an unprecedented platform for accessing a myriad of acyclic carbenes through substitution reactions with anionic and neutral nucleophiles. We are currently exploiting the presence of the reactive carbon-chlorine bond to widen the chemical space offered by carbene chemistry [40, 41].

Author Contributions

Guy Bertrand conceptualized this work. Wenyi Dong, Mohand Melaimi, Daniel Chan, François Vermersch and Michèle Soleilhavoup performed the synthetic work. Mohand Melaimi performed X-Ray diffraction analysis. Mehdi Abdellaoui, Mohand Melaimi and Patrick Yorkgitis performed the DFT studies. The manuscript was written by all the authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article

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35. Deposition numbers 2523210 (**3b**), 2523209 (**4b**), and 2524849 (**8**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: anie72740-sup-0001-SuppMat.pdf.