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# Highly Ambiphilic Room Temperature Stable Six-Membered Cyclic (Alkyl)(amino)carbenes

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Supporting Information Placeholder

**ABSTRACT:** Cyclic (alkyl)(amino)carbenes with a six-membered backbone were prepared. Compared to their fivemembered analogues, they feature increased %V<sub>bur</sub> and enhanced donor and acceptor properties, as evidenced by the observed  $n \rightarrow \pi^*$  transition trailing into the visible region. The high ambiphilic character even allows for the intramolecular insertion of the carbene into an unactivated C(sp<sup>3</sup>)-H bond. When used as ligands, they outcompete the fivemembered analogues in the palladium-mediated  $\alpha$ -arylation of ketones with aryl chlorides.

# INTRODUCTION

Since their discovery in 2005,<sup>1</sup> five-membered cyclic (alkyl)(amino)carbenes (CAACs) have been widely used.<sup>2</sup> Similar to Arduengo N-heterocyclic carbenes (NHCs),<sup>3,4</sup> CAACs are excellent ligands for transition metals and their complexes have found applications in catalysis<sup>5</sup> and also in material science, as exemplified by the preparation of highly efficient Cu-OLED devices.<sup>6</sup> Additionally, CAACs proved to be superior to NHCs for stabilizing a variety of paramagnetic species,<sup>7,8</sup> and for activating small molecules and enthalpically strong bonds.<sup>9</sup> The advantages of CAACs over NHCs can be traced back to their higher nucleophilicity (higher HOMO, more  $\sigma$ -donating) and electrophilicity (lower LUMO, more  $\pi$ -accepting), and consequently to their smaller singlet-triplet gap ( $\Delta E_{ST}$ ). Here we report the preparation of a novel family of carbenes, namely 6-membered CAACs, which feature an even smaller  $\Delta E_{ST}$ , and consequently a higher reactivity, as shown by the intramolecular carbene insertion into an unactivated C(sp<sup>3</sup>)-H bond. Additionally, we show that these carbenes, when used as ligands, outcompete the five-membered analogues in the palladium-mediated  $\alpha$ -arylation of ketones with aryl chlorides.

It is well established that increasing the carbene bond angle of 44 NHCs induces greater p character of both the HOMO and 45 LUMO of the carbene, effectively shrinking the  $\Delta E_{ST.}$  Indeed, 46 DFT calculations at the B3LYP/def2-TZVPP level of theory 47 found that expanding the ring size of NHCs from five to six 48 decreases the HOMO-LUMO gap and  $\Delta E_{ST}$  by 0.64 eV and 49 13.3 kcal/mol, respectively (Figure 1). Similarly, the HOMO-50 LUMO gap and the  $\Delta E_{ST}$  of **CAAC-6** were found to be small-51 er than those of CAAC-5 by 0.39 eV and 11.8 kcal/mol, and 52 considerably smaller than those of NHC-6 by 0.81 eV and 53 22.9 kcal/mol. Calculations also show that CAAC-6 has a 54 smaller HOMO-LUMO gap and  $\Delta E_{ST}$  than the recently reported **BICAAC**<sup>11</sup> by 0.08 eV and 8.3 kcal/mol, respectively. 55

This can be rationalized by the accessible low energy chair conformation of the triplet **CAAC-6**, compared to the strained triplet state of **BICAAC**.



Figure 1. Calculated HOMO-LUMO gap (eV) and  $\Delta E_{ST}$  (kcal/mol) of representative carbenes at the B3LYP/def2-TZVPP level of theory.

# **RESULTS AND DISCUSSION**

The desired **CAAC-6** precursors, namely iminium salts **4a-d**, were prepared by slight modifications of the published **CAAC-5** synthesis<sup>12</sup> (Scheme 1). Condensation of aldehydes **1a-d** with 2,6-diisopropylaniline yielded imines **2a-d** in near quantitative yields. Deprotonation with *n*-BuLi followed by alkylation with 4-iodo-2-methyl-1-butene yielded imines **3a-d**, which after aqueous workup (NaHSO<sub>3</sub>/H<sub>2</sub>O), were used without further purification. Protonation of the imine with HCl in Et<sub>2</sub>O, followed by thermally induced intramolecular hydroiminiumation, resulted in the precipitation of the six-membered cationic heterocycles with Cl<sup>-</sup> or HCl<sub>2</sub><sup>-</sup> anions. After an anion exchange with NaBF<sub>4</sub> and subsequent workup, compounds **4a-d** were isolated as microcrystalline colorless solids.

#### Scheme 1. General synthesis of CAAC-6 iminium salts 4a-c.



With iminium salts **4** in hand, we investigated whether the free carbene would be stable.  $C_6D_6$  was added to NMR tubes containing KHMDS and either **4a** or **4b**, and to our delight, we observed clean conversion of the starting materials into a single product giving a sharp <sup>13</sup>C NMR signal at 330.3 and 330.6 ppm, indicative of the formation of carbenes **5a** and **5b**, respectively (Scheme 2).

# Scheme 2. Synthesis of CAAC-6 5a-c.



These signals are slightly downfield compared to those of the analogous **CAAC-5** species (317 ppm),<sup>12</sup> and close in value to that of **BICAACs** (335 ppm).<sup>11</sup> Carbenes **5a** and **5b** are stable in solution for days without any evidence of decomposition; however, attempts to obtain single crystals failed.<sup>13</sup> In the hope of obtaining a crystalline **CAAC-6** derivative, we moved to **4c** featuring the rigid diamondoid adamantyl group. Addition of benzene to a solid mixture of **4c** and KHMDS gave a bright yellow solution containing free carbene **5c** ( ${}^{13}C_{carbene} = 345$  ppm) and imine **3c** in a 5:1 ratio.<sup>14</sup> After workup, and recrystallization from a concentrated pentane solution at -20 °C, **5c** was isolated as yellow single crystals (27 % yield) suitable for X-ray crystallography (Figure 2).



Figure 2. Solid-state structure of 5c. H-atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: N-C1 1.3101(14), C1-C2 1.5252(13), N-C1-C2 117.88(9).

The most striking structural parameter of carbene **5c** is the N-C1-C2 bond angle. Indeed, at 117.9 degrees, the carbene bond angle is 11.5 and 9.6 degrees larger than in CAAC-5 and **BICAAC**, respectively. Furthermore, acyclic (al-kyl)(amino)carbenes,<sup>15</sup> some of the most  $\pi$ -accepting singlet carbenes to date, are only 2.6 degrees more obtuse than **5c**.<sup>16</sup>

Although highly air and moisture sensitive, 5c is stable both in solution and in the solid state for weeks at room temperature, and decomposition is only observed above 50 °C in solution and 120 °C in the solid state.

Noting the yellow color of the crystals, a UV-Vis spectrum of **5c** was recorded in pentane. As shown in Figure 3, three discrete transitions exist between the visible and near-UV regions. To better understand the nature of these transitions, we simulated the spectrum of **5c** with TD-DFT. The best match between experimental and simulated UV-Vis spectra (Figure 3, top) was found using the def2-TZVPP basis set and M06-2X hybrid functional.<sup>17</sup> TD-DFT results suggest that the first peak in the UV-Vis corresponds to an  $n \rightarrow \pi^*$  transition (Figure 3, bottom), the first such transition trailing into the visible region for CAACs. The relatively low energy vertical absorption of **5c** ( $\lambda_{max} = 396$  nm) highlights the very small HOMO-LUMO gap of **CAAC-6** species. The second peak corresponds to the  $n \rightarrow \pi^*_{aryl}$ , while the third was identified as the  $\pi_{aryl} \rightarrow \pi^*_{aryl}$  transition.



Figure 3. Experimental versus simulated UV-Vis spectra (top), and molecular orbitals and corresponding electronic transitions for 5c (bottom).<sup>18</sup>

To probe the effect of the ring size on the steric environment around the carbene center, 5c was reacted with (tht)AuCl (tht = tetrahydrothiophene) which, after workup, yielded colorless crystals of complex 6c (Scheme 3). From the X-ray data, we found carbene 5c to have a percent buried volume (%V<sub>bur</sub>) of 51.2%, an increase of 3.4% from the CAAC-5 complex with identical substituents.<sup>19</sup>

Scheme 3. Comparing steric properties of CAAC-6 vs. CAAC-5.

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We then explored the overall donor capabilities of **CAAC-6** (Scheme 4). A stirred THF solution of carbene **5c** and [Rh(cod)Cl]<sub>2</sub> led to the formation of the corresponding (**5c**)Rh(cod)Cl complex. Subjecting a THF solution of this complex to a CO atmosphere afforded **7c** whose IR spectrum (KBr, DCM solution) showed two CO stretching frequencies at 2067 and 1990 cm<sup>-1</sup> ( $v^{av}_{CO} = 2029$  cm<sup>-1</sup>). The average value is red-shifted from both **CAAC-5** ( $v^{av}_{CO} = 2036$  cm<sup>-1</sup>) and **BICAAC** ( $v^{av}_{CO} = 2032$  cm<sup>-1</sup>) proving that **5b** is by far the most overall electron-donating CAAC to date.

Scheme 4. Probing steric and electronic properties of CAAC-6.



Comparing the <sup>31</sup>P NMR signals of carbenephenylphosphinidene adducts has been shown to be a useful method for assessing the  $\pi$ -accepting properties of a carbene.<sup>16a-c</sup> Although **5c** proved to be too sterically demanding,

**8a** could be generated *in situ* by heating a mixture of **5a** and (PhP)<sub>5</sub> at 60 °C for 3h. The <sup>31</sup>P NMR signal of **8a** appears at 103 ppm, downfield shifted compared to those of **CAAC-5** and **BICAAC**, by 34 and 13 ppm, respectively, suggesting that **CAAC-6** is extremely electrophilic. To confirm the  $\pi$ -accepting properties of **CAAC-6**, the Se adduct **9a** was synthesized, <sup>16d,e</sup> and gave a <sup>77</sup>Se NMR signal at 715 ppm, downfield of both **CAAC-5** (492 ppm) and **BICAAC** (645 ppm). From these results as a whole, it can be concluded that **CAAC-6** species are highly ambiphilic.

In the hope of preparing an enantiomerically pure CAAC-6, we turned our attention to the deprotonation of 4d (Scheme 5). Upon addition of KHMDS, complete consumption of the starting material resulted in a 10:1 mixture of two products. The minor product was easily identified as imine 3d,<sup>14</sup> while, surprisingly, the major product was not carbene 5d as no <sup>13</sup>C NMR signal could be found downfield of those of the aromatic carbons. Furthermore, DEPT-90 and DEPT-135 experiments revealed the presence of two additional CH groups and one fewer CH<sub>2</sub> group than would have been expected for carbene 5d. These data suggested that a carbene C-H insertion occurred.

Scheme 5. Formation of the carbene C-H insertion product 10.



Indeed, an X-ray diffraction study of single crystals, grown from a concentrated pentane solution at room temperature, unambiguously identified the product as the tricyclic compound **10** (Figure 4). The latter clearly results from the insertion of the carbene into the  $\alpha$ -CH<sub>2</sub> group of the menthyl substituent.



Figure 4. Solid-state structure of 10. Hydrogen atoms except H1 and H2 were removed for clarity. Selected bond lengths [Å] and angles  $[\degree]$ . N-C1 1.4378(18), C1-C2 1.508(2), C1-C3 1.524(2), N-C1-C2 120.85(13), N-C1-C3 121.53(13) C2-C1-C3 60.19(10).

This is the first example of a CAAC inserting into an unactivated  $C(sp^3)$ -H bond, and a further indication of the highly

ambiphilic nature of **CAAC-6**. Note that since such a C-H insertion was not observed in the case of **5a**, it is likely due to the rigidity of the menthyl substituent, which brings the methylene group in close proximity to the carbene center.

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We previously demonstrated that the enhanced electronic properties of CAAC-5 compared to NHCs could significantly benefit the palladium-mediated  $\alpha$ -arylation of ketones,<sup>20</sup> allowing for the first  $\alpha$ -arylation of propiophenone with aryl chlorides at room temperature.<sup>1</sup> We also reported that specific CAAC-5 frameworks were required in order to tailor the reactivity of the catalyst to the steric demand of the substrates. While the unhindered (ethyl-CAAC-5)Pd(Allyl)Cl 11a proved to be inefficient in this process, the bulky (menthyl-**CAAC-5**)Pd(Allyl)Cl **11b** achieved the complete  $\alpha$ -arylation of propiophenone with chlorobenzene within 1 h; however it displayed much less reactivity with more sterically hindered arvl chlorides such as o-chlorotoluene (36 h. 82% vield) and 2-chloro-m-xylene (20 h, 0% yield). For the latter substrate, complex **11c**, featuring a flexible cyclohexyl substituent gave the best results (Scheme 6). We reasoned that the enhanced donating properties and flexibility of the CAAC-6 backbone, over the more rigid CAAC-5, should improve the catalytic efficiency and broaden the scope of applications. To test this hypothesis we first compared the steric influence of the previously reported (menthyl-CAAC-5)Pd(allyl)Cl complex 11b,<sup>1</sup> with complexes 11a and 12 bearing less bulky ethyl substituents at the  $\alpha$ -carbon (Figure 5). Complexes **11a** and **12** were prepared in high yields by addition of [Pd(allyl)(Cl)]<sub>2</sub> to the corresponding free carbenes, and were characterized by X-ray crystallography. The solid-state structure confirmed the larger steric environment around the palladium center for 12 compared to both 11a (+4.7% buried volume) and even 11b (+1.9% buried volume) (Figure 5).<sup>1</sup>



Figure 5. X-ray crystal structures and  $%V_{bur}$  of [(CAAC)Pd(allyl)Cl] complexes 11a, 11b<sup>1</sup> and 12.

We next performed kinetic experiments (Figure 6), using insitu <sup>1</sup>H NMR spectroscopy, to compare the catalytic activity of **11a**, **11b** and **12** in the  $\alpha$ -arylation of propiophenone with chlorobenzene [1:1 (0.5 mmol) mixture of aryl chloride and propiophenone, 1 mol% catalyst, 1.1 equivalent of sodium tert-butoxide in 0.7 mL of THF-d<sup>8</sup> at room temperature]. To our delight we found that CAAC-6 complex 12 dramatically outperforms CAAC-5 complex 11a, and is even slightly better than **menthyl-CAAC-5** complex 11b, our previously best reported catalyst for this transformation.<sup>1</sup>



Figure 6. Comparative kinetics in the palladium-mediated α-arylation of propiophenone with chloro-benzene.

We then compared the activity of CAAC-5 (11a-c) and CAAC-6 (12) complexes towards different aryl chlorides. Scheme 6 clearly shows that CAAC-6 complex 12 outperforms CAAC-5 complexes of varying steric profiles with all substrates.





In summary, when compared to CAAC-5, CAAC-6 feature increased %V<sub>bur</sub>. Several indicators, including the observed n  $\Rightarrow \pi^*$  transition trailing into the visible region, show their en-

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hanced donor and acceptor properties. The high ambiphilic character allows for intramolecular carbene insertion into an unactivated  $C(sp^3)$ -H bond. Since such a process does not occur in the cases of **5a** and **5b**, it will not preclude the synthetic availability of a wide variety of **CAAC-6** derivatives. Our results demonstrate the superiority of **CAAC-6** over their **CAAC-5** counterparts in the  $\alpha$ -arylation of ketones with aryl chlorides. Other catalytic chemical transformations are under current investigation, since it is safe to predict that the peculiar electronic properties of **CAAC-6** will result in very strong metal-carbene bonds, which will allow for catalysis at high temperatures. This novel family of carbenes should also be useful for stabilizing electron-poor and paramagnetic species.

# ASSOCIATED CONTENT

# Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxxxxxxx

General methods and materials, experimental procedures and characterization data, X-ray crystal structure determination, computational section, and NMR spectra (PDF) Crystallographic data for **5c** (CCDC 1580015), **6c** (CCDC 1580016), **7c** (CCDC 1580013), **10** (CCDC 1580014), **11** (CCDC 1845430), **12a** (CCDC 1837571) (CIF).

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