

Toward phenanthridin-2-ylidene: electrophilicity versus acidity in planar-constrained C-aryl iminium salts

Xavier Cattoën,^{a,b} Didier Bourissou^{a,*} and Guy Bertrand^{a,b,*}

^aLaboratoire Hétérochimie Fondamentale et Appliquée du CNRS (UMR 5069), Université Paul Sabatier, 118, route de Narbonne, 31062 Toulouse Cedex 9, France

^bUCR-CNRS Joint Research Chemistry Laboratory (UMR 2282), Department of Chemistry, University of California, Riverside, CA 92521-0403, USA

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Abstract—A phenanthridinium salt was prepared in four steps, including an intramolecular CH-arylation and a hydride abstraction reaction. Treatment with sterically demanding bases does not lead to the corresponding carbene, but rather to addition products: the planar-constrained geometry significantly enhances the electrophilicity over the acidity of C-aryl iminium salts.
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Since the isolation of the first singlet carbenes **A**¹ and **B**,² the number and variety of available stable or at least persistent carbenes have considerably increased.³ We have demonstrated that the presence of a single heteroatom substituent brings substantial stabilization since various acyclic aryl- and alkyl-carbenes **C–F** have been characterized or even isolated using an amino or a phosphino group as an electron-donating substituent (Fig. 1).⁴ However, among all of the carbenes **A–F**, only the ‘pure’ σ -donor cyclic diaminocarbenes (NHCs), when used as ligands, have led to highly active and robust catalysts.⁵ Free acyclic carbenes, which include diaminocarbenes **G**⁶ are not only more fragile than NHCs, but the ensuing complexes are also less robust. Herrmann has recently suggested that the poor coordination behavior of acyclic diamino carbenes might be due to the larger N–C–N angle (121° compared to 101–106° for NHCs).⁷ Along this line, we have recently demonstrated that in contrast to their acyclic versions **F**,^{4f} cyclic amino alkyl carbenes (CAACs) **H** are strong σ -donors, and weak π -acceptors, and form highly catalytically active and robust complexes.⁸ The latter results prompted us to investigate the related cyclic amino aryl carbenes (CAArCs) **I**, and here we report surprising and

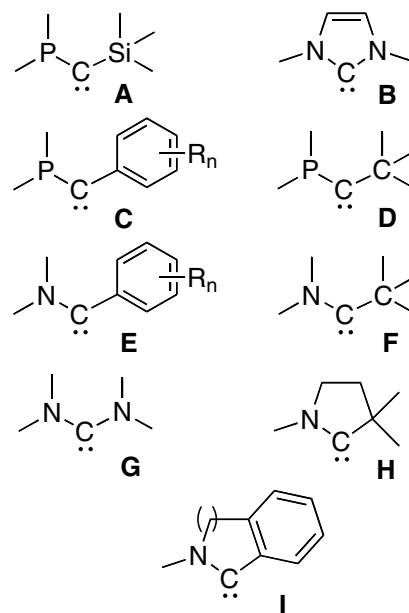


Figure 1. Known types of stable carbenes and generic formulae of CAACs (**I**).

Keywords: Carbenes; Nucleophilic addition; Deprotonation; Phenanthridinium salts; Planar-constrained geometry.

* Corresponding authors. Tel.: +33 5 61 55 77 37; fax: +33 5 61 55 82 04 (D.B.); tel.: +1 909 787 2720; fax: +1 909 787 2725 (G.B.); e-mail addresses: dbourissou@chimie.ups-tlse.fr; gbertran@mail.ucr.edu

informative results obtained during their attempted preparation.

Since the acyclic amino aryl carbene **E1**^{4b} (Fig. 2), which features the chemically inert and sterically hindered

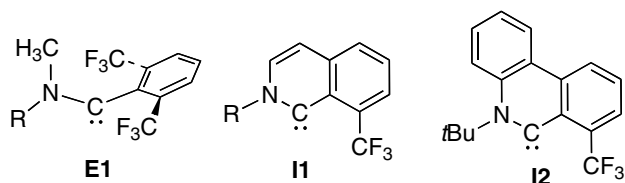


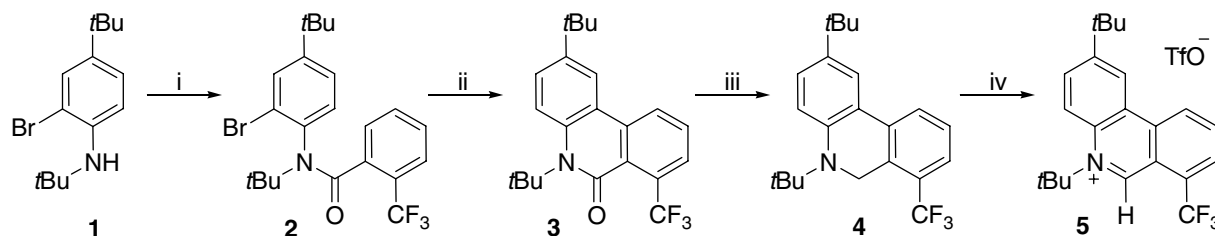
Figure 2. Design of the planar-constrained amino-aryl-carbene **12**.

2,6-bis(trifluoromethyl)phenyl group is quite stable, and easily obtained by deprotonation of the corresponding iminium salt, we envisioned the linkage of one of the ring *ortho* position to the amino substituent, such as in the isoquinolin-2-ylidene **11**. Taking into account that abnormal deprotonations might occur from the corresponding isoquinolinium precursor,^{9,10} a *tert*-butyl group was introduced at the nitrogen and the ethenyl linker was replaced by a phenyl ring, so that the phenanthridin-2-ylidene **12**¹¹ was chosen as the target compound.

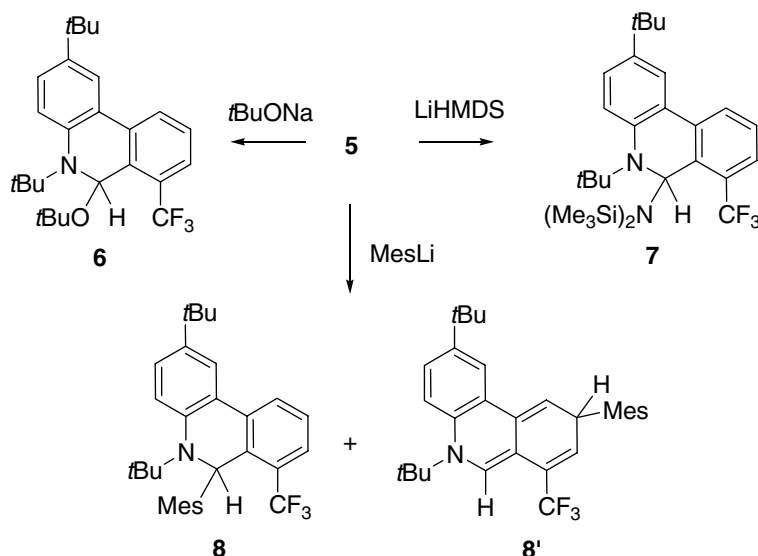
The required phenanthridinium precursor **5** was prepared in four steps in 42% overall yield (Scheme 1). Condensation of the (2-bromo-4-*tert*-butylphenyl)-*tert*-butylamine **1**¹² with 2-trifluoromethylbenzoyl chloride first led to the corresponding amide **2**, which was sub-

sequently cyclized via an intramolecular Pd-catalyzed CH-arylation reaction.¹³ Reduction of the resulting lactam **3** with LiAlH₄ afforded the dihydrophenanthridine **4**, and hydride abstraction with triphenylmethyl trifluoromethanesulfonate finally led to the desired phenanthridinium salt **5**.¹⁴ Notably, the chemical shift for the acidic proton of **5** (9.91 ppm) is in the same range as those of unconstrained *C*-aryl iminium salts (9.7–10.2 ppm), whereas the signal of the corresponding carbon atom is significantly shielded (148.0 ppm for **5** compared to 170–175 ppm).^{4b,c}

Deprotonation of the phenanthridinium salt **5** was then investigated with sterically hindered bases (Scheme 2).¹⁵ Using sodium *tert*-butoxide, the *N,O*-acetal **6** was quantitatively obtained, as deduced from the typical signals observed for the CH group at 6.39 and 75.7 ppm in ¹H and ¹³C NMR, respectively. A similar addition reaction also occurred with lithium hexamethyldisilazane, despite the severe steric hindrance in the resulting compound **7**. From a mechanistic viewpoint, the formation of adducts **6** and **7** may result from direct nucleophilic addition to the phenanthridinium salt **5**, or alternatively from deprotonation of **5** leading to the carbene followed by an OH or NH insertion reaction, respectively, as already observed.^{4c} The putative CAArC was not detected when the reactions of **5** with *t*-BuONa and



Scheme 1. Four-step synthesis of phenanthridinium salt **5**. Reagents and conditions: (i) 2-trifluoromethylbenzoyl chloride, Et₃N, CHCl₃, Δ, 48 h, 62%; (ii) Pd(OAc)₂ (5 mol %), dppp (5 mol %), Bu₃P (10 mol %), EtNi-Pr₂, DMF, Δ, 15 h, 91%; (iii) LiAlH₄, Bu₂O, Δ, 2 h, 82%; (iv) Ph₃COTf, CH₂Cl₂, –78 °C, 0.5 h, 90%.



Scheme 2. Attempted deprotonations of phenanthridinium **5**.

LiHMDS were monitored by NMR at $-78\text{ }^{\circ}\text{C}$. To definitively rule out the transient formation of the carbene, we used a sterically hindered base, whose conjugate acid is not prone to insertion reactions.¹⁶ Mesityl lithium readily reacted with **5** at $-78\text{ }^{\circ}\text{C}$, and the resulting adducts **8** and **8'**, obtained in a 4/6 ratio, were characterized by mass spectrometry, ^1H , and ^{19}F NMR spectroscopy. The minor product **8** is related to compounds **6** and **7**, whereas the major product **8'** results from conjugated nucleophilic addition with dearomatization of the planar-constrained aryl ring.¹⁷ As a result of its quinonic structure, compound **8'** proved to be rather unstable and could not be isolated.

From these results, it is clear that nucleophilic addition is strongly favored over deprotonation in the reaction of **5** with sterically demanding bases. Note that the electron withdrawing CF_3 group would be anticipated to enhance both the electrophilicity and acidity of **5**. We have verified that no significant modifications in the fate of the reactions occurred by replacing the CF_3 group by an electron-donating CH_3 group, since the addition product analogous to **7** was quantitatively obtained with LiHMDS.¹⁸

This peculiar behavior of the phenanthridinium salt **5** compared to the corresponding acyclic iminium salts might result from both steric and electronic factors. Indeed, the constrained geometry of **5** not only minimizes steric interactions with approaching nucleophiles, but also enhances its electrophilicity by enforcing the π -conjugation of the iminium fragment with the aryl ring, and thereby lowering the LUMO energy. In contrast, for the corresponding acyclic carbene **E1** and its iminium precursor,^{4b} the π -system of the aromatic ring is perpendicular to the CN π -bond.

In conclusion, the phenanthridinium salt **5** is not a suitable precursor for cyclic amino-aryl carbene **12** due to the planar-constrained geometry of **5**, which favors nucleophilic addition over deprotonation, even with sterically demanding bases. This is a strong indication that CAArCs are not obtainable by the classical deprotonation route. The preparation of free cyclic amino aryl carbenes using other potential precursors, as well as the direct synthesis of transition metal complexes featuring CAArCs as ligands^{19,20} is under active investigation in order to investigate the influence of the geometric constraints on the coordination properties of CAArCs, and on the catalytic activity of the ensuing complexes.

Acknowledgments

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References and notes

- Igau, A.; Grützmacher, H.; Baccaredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463.
- Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
- For recent reviews on stable carbenes, see: (a) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913; (b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39; (c) Kirmse, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1767; (d) Canac, Y.; Soleilhavoup, M.; Conejero, S.; Bertrand, G. *J. Organomet. Chem.* **2004**, *689*, 3857; (e) Alder, R. W.; Blake, M. E.; Chaker, M. E.; Harvey, J. N.; Paolini, F.; Schutz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896.
- (a) Buron, C.; Gornitzka, H.; Romanenko, V.; Bertrand, G. *Science* **2000**, *288*, 834; (b) Solé, S.; Gornitzka, H.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Science* **2001**, *292*, 1901; (c) Despagnet, E.; Gornitzka, H.; Rozhenko, A. B.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 2835; (d) Despagnet-Ayoub, E.; Solé, S.; Gornitzka, H.; Rozhenko, A.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *J. Am. Chem. Soc.* **2003**, *125*, 124; (e) Cattoën, X.; Gornitzka, H.; Bourissou, D.; Bertrand, G. *J. Am. Chem. Soc.* **2004**, *126*, 1342; (f) Lavallo, V.; Mafhouz, J.; Canac, Y.; Donnadiou, B.; Schoeller, W. W.; Bertrand, G. *J. Am. Chem. Soc.* **2004**, *126*, 8670.
- For recent reviews on NHCs in catalysis, see: (a) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181; (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290; (c) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951; (d) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239; (e) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247; (f) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619; (g) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534; (h) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815.
- Alder, R. W.; Allen, P. R.; Murray, M.; Orpen, A. G. *Angew. Chem., Int. Ed.* **1996**, *36*, 1121.
- Herrmann, W. A.; Ofele, K.; Preysing, D. v.; Herdtweck, E. *J. Organomet. Chem.* **2003**, *684*, 235.
- Lavallo, V.; Canac, Y.; Prasang, C.; Donnadiou, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705.
- For the generation of azomethine ylides from *N*-alkyl iminium salts, see: Cattoën, X.; Solé, S.; Pradel, C.; Gornitzka, H.; Miqueu, K.; Bourissou, D.; Bertrand, G. *J. Org. Chem.* **2003**, *68*, 911.
- A few imidazolium salts were reported to bind via C5 rather than C2 to transition metals: (a) Gründemann, S.; Kovacevic, A.; Albrecht, M.; Faller, J. W.; Crabtree, R. H. *Chem. Commun.* **2001**, 2274; (b) Chianese, A. R.; Kovacevic, A.; Zeglis, B. M.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2004**, *23*, 2461, and references cited therein.
- Similar carbenes have been postulated as intermediates in the air oxidation of quinolium salts to quinolones in the presence of bases, see: Grignon-Dubois, M.; Meola, A. *Synth. Commun.* **1995**, *25*, 2999.
- Marx, L.; Rassat, A. *Tetrahedron Lett.* **2002**, 2613.
- (a) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K. *Heterocycles* **1998**, *48*, 1989; (b) Harayama, T.; Akiyama, T.; Nakano, Y. *Chem. Pharm. Bull.* **1997**, *45*, 1723.
- For the synthesis of a related anhydrolycorinium salt by oxidation of the corresponding anhydrolycorinone, see: Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120.
- Fifty-five milligrams of the phenanthridinium trifluoromethanesulfonate **5** (0.11 mmol) was suspended in 0.3 mL of $\text{THF-}d_8$ at $-78\text{ }^{\circ}\text{C}$ in an NMR tube. A solution of the base (0.11 mmol) in 0.4 mL of $\text{THF-}d_8$ at $-78\text{ }^{\circ}\text{C}$ was slowly added. The tube was shaken until complete dissolution,

and analyzed directly by NMR. Compound **6**: ^{19}F NMR (THF- d_8): δ 17.0; ^1H NMR (THF- d_8): δ 1.07, 1.20, and 1.39 [s, 9H, C(CH₃)₃], 6.39 (s, 1H, NCHO), 7.19 (d, $^3J_{\text{HH}} = 8.4$ Hz, 1H, CH_{ar}), 7.32 (dd, $J_{\text{HH}} = 8.4$ and 2.3 Hz, 1H, CH_{ar}), 7.48 (t, $^3J_{\text{HH}} = 7.9$ Hz, 1H, CH_{ar}), 7.62 (d, $^3J_{\text{HH}} = 7.9$ Hz, 1H, CH_{ar}), 7.89 (d, $J_{\text{HH}} = 2.3$ Hz, 1H, CH_{ar}), 7.98 (d, $^3J_{\text{HH}} = 7.9$ Hz, 1H, CH_{ar}); $^{13}\text{C}\{^1\text{H}\}$ NMR (THF- d_8): δ 29.6, 29.8, and 31.9 [C(CH₃)₃], 33.7, 57.0, and 76.7 [C(CH₃)₃], 75.6 (OCN), 125.9 (q, $^1J_{\text{CF}} = 273$ Hz, CF₃), 121.7 (CH_{ar}), 125.5 (CH_{ar}), 125.5 (q, $^3J_{\text{CF}} = 7$ Hz, CHCCF₃), 128.6 (CH_{ar}), 128.9 (CH_{ar}), 130.2 (CH_{ar}), 131.1 (C_{ar}), 135.2 (C_{ar}), 135.7 (C_{ar}), 138.1 (C_{ar}), 146.9 (C_{ar}), CCF₃ not detected. Compound **7**: ^{19}F NMR (THF- d_8): δ 16.6; ^1H NMR (THF- d_8): δ -0.65 and 0.37 [s, 9H, Si(CH₃)₃], 0.93 and 1.40 [s, 9H, C(CH₃)₃], 6.14 (s, 1H, NCHN), 7.26 (br, 1H, CH_{ar}), 7.38 (br, 1H, CH_{ar}), 7.53 (br, 1H, CH_{ar}), 7.66 (br, 1H, CH_{ar}), 8.29 (br, 1H, CH_{ar}), 7.98 (br, 1H, CH_{ar}); $^{13}\text{C}\{^1\text{H}\}$ NMR (THF- d_8): δ 4.9 and 5.3 [Si(CH₃)₃], 29.6 and 31.9 [C(CH₃)₃], 35.5 and 57.5 [C(CH₃)₃], 67.1 (NCN), 122.7 (CH_{ar}), 125.8 (2CH_{ar}), 127.0 (q, $^2J_{\text{CF}} = 32$ Hz, CCF₃), 128.7 (CH_{ar}), 129.4 (CH_{ar}), 131.6 (CH_{ar}), 132.6 (C_{ar}), 137.9 (C_{ar}), 139.0 (C_{ar}), 140.4 (C_{ar}), 147.7 (C_{ar}), CF₃ not detected. Compound **8**: ^{19}F NMR (THF- d_8): δ 15.7; ^1H NMR (CDCl₃): δ 1.03 and 1.34 [s, 9H, C(CH₃)₃], 1.14, 2.10, and 2.79 (s, 3H, CH₃), 6.22 (s, 1H, NCH), 6.28 (s, 1H, CH_{Mes}), 6.81 (s, 1H, CH_{Mes}), 6.90 (d, $^3J_{\text{HH}} = 8.2$ Hz, 1H, CH_{ar}), 7.12 (dd, $J_{\text{HH}} = 8.7$ and 2.4 Hz, 1H, CH_{ar}), 7.51 (t, $^3J_{\text{HH}} = 8.2$ Hz, 1H, CH_{ar}), 7.68 (m, 2H, CH_{ar}), 7.93 (d, $^3J_{\text{HH}} = 8.2$ Hz, 1H, CH_{ar}); MS (DCI, NH₃) 480 (MH⁺). Compound **8'**: ^{19}F NMR (THF- d_8): δ 10.6; ^1H NMR (THF- d_8): δ 1.25 and 1.62 [s, 9H, C(CH₃)₃], 2.21, 2.22, and 2.35 (s, 3H,

CH₃), 5.18 (b, 1H, CH), 5.38 (s, 1H, CH), 5.84 (s, 1H, CH), 6.80 (CH_{Mes}), 6.90 (CH_{Mes}), 7.17 (m, 2H, CH and CH_{ar}), 7.27 (d, $^3J_{\text{HH}} = 8.7$ Hz, 1H, CH_{ar}), 7.48 (d, $J_{\text{HH}} = 2.4$ Hz, 1H, CH_{ar}).

16. So far, diamino-carbenes have been reported to insert only into activated C–H bonds [(a) Arduengo, A. J., III; Calabrese, J. C.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Krafczyk, R.; Marshall, W. J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta* **1999**, *82*, 2348; (b) Nyce, G. W.; Csihony, S.; Waymouth, R. M.; Hedrick, J. L. *Chem. Eur. J.* **2004**, *10*, 4073] and only intramolecular CH-insertion has been observed with mono-amino-carbenes.^{4b}
17. Dearomatization has already been observed with amino-aryl-carbenes in an abnormal cyclopropanation reaction: Solé, S.; Cattoën, X.; Gornitzka, H.; Bourissou, D.; Bertrand, G. *Tetrahedron Lett.* **2004**, 5391.
18. The related phenanthridinium salt featuring a CH₃ group was prepared following the same strategy. Reaction with LiHMDS under the same conditions afforded an adduct analogous to **7**: ^1H NMR (THF- d_8): δ -0.62 and 0.39 [s, 9H, Si(CH₃)₃], 0.92 and 1.38 [s, 9H, C(CH₃)₃], 2.41 (s, 3H, CH₃), 5.80 (s, 1H, NCHN), 7.1–7.3 (m, 4H, CH_{ar}), 7.56 (d, $^3J_{\text{HH}} = 7.6$ Hz, 1H, CH_{ar}), 7.76 (d, $^3J_{\text{HH}} = 2.3$ Hz, 1H, CH_{ar}).
19. W(CO)₅ and Cr(CO)₅ complexes of mono-amino-carbenes have recently been prepared by generation of the N-heterocyclic carbene in the coordination sphere of the metal: Fischer, H., private communication.
20. Pd complexes of mono-amino-carbenes have recently been prepared by oxidative addition of C-chloroiminium salts: Kremzow, D.; Seidel, G.; Lehmann, C. W.; Fürstner, A. *Chem. Eur. J.* **2005**, *11*, 1833.