Communication

Synthesis of Hemilabile Cyclic (Alkyl)(amino)carbenes (CAACs) and Applications in Organometallic Chemistry

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Synthesis of Hemilabile Cyclic (Alkyl)(amino)carbenes (CAACs) and Applications in Organometallic Chemistry

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Supporting Information Placeholder

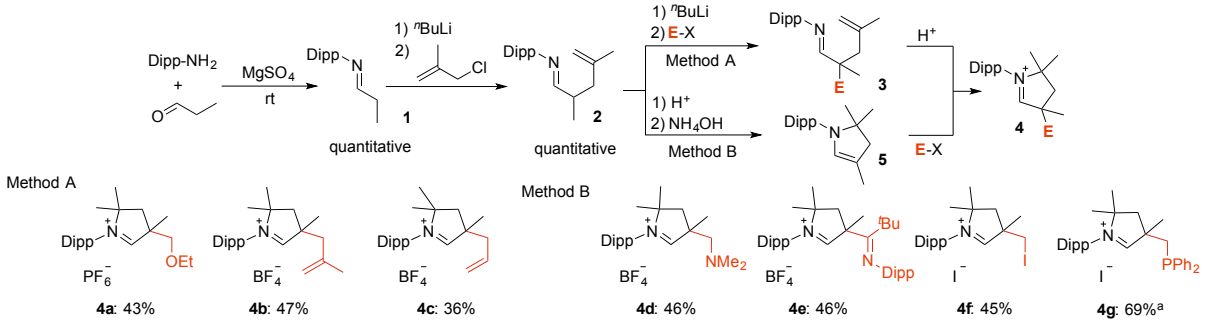
ABSTRACT: A versatile methodology, involving readily available starting materials, allows for the synthesis of stable hemilabile bidentate CAACs featuring alkene, ether, amine, imine and phosphine functionalities. The stability of the free carbenes has been exploited for the synthesis of copper(I) and gold(I) complexes. It is shown that the pendant imine moiety stabilizes the gold(III) oxidation state, and enables the C–C bond oxidative addition of biphenylene to the corresponding cationic gold(I) complex. The latter and the corresponding copper(I) complex show high catalytic activity for the hydroarylation of α-methyl styrene with *N*,*N*-dimethylaniline, and the copper(I) complex promotes the *anti*-Markovnikov hydrohydrazination of phenyl acetylene with high selectivity.

Cyclic (alky)(amino)carbenes (CAACs) have found widespread application for the stabilization of reactive intermediates, the activation of small molecules, and as ligands in organometallic chemistry.[1,2] This is due to their small HOMO–LUMO gap and their very strong σ-donor and π-accepting capabilities,[3] which considerably exceed those of conventional NHCs (*N*-heterocyclic carbenes).[4] Additionally, the steric demand of CAAC ligands is very distinct from that of NHCs.[5] The possibility of tailoring NHCs for specific tasks by attachment of ancillary functional groups has been pivotal for the success of these ligands in organometallic chemistry.[6] Chelating NHC ligands provide remarkable chemical stability to high-valent metal centers, and have found widespread application in oxidation catalysis.[7] In addition, they allow for bifunctional cooperativity including the generation of hemilabile coordination sites,[8] and some of their complexes feature luminescent and phosphorescent properties.[9]

Herein we report simple and scalable synthetic procedures allowing for the preparation of a variety of hitherto unknown hemilabile bidentate CAACs. As proof of principle for the potential of this novel type of carbenes in organometallic chemistry, we show that their coinage metal complexes can promote the oxidative addition of biphenylene (Au), the catalytic hydroarylation of alkenes (Cu and Au) and the *anti*-Markovnikov hydrohydrazination of alkynes (Cu).

The most convenient synthesis of the conjugate acid of CAACs relies on the condensation of an aniline derivative with 2,2-dialkyaldehydes, followed by deprotonation with LDA, alkylation with 3-chloro-2-methylpropene, and cyclization under acidic conditions.[1b-d] We generalized this reaction sequence to unbranched aldehyde. Deprotonation of **1** with ^{n}BuLi followed by alkylation with 3-chloro-2-methylpropene gave imine **2** in quantitative yield on a 55 g scale. A second deprotonation with ^{n}BuLi and alkylation with an alkyl halide bearing a functional group, followed by cyclization of the resulting imine **3** under acidic conditions (HCl) afforded the desired cyclic iminium salts **4** (Scheme 1, method A). Alternatively, proton induced cyclization of **2** followed by treatment with aqueous ammonia led to the cyclic enamine **5**, which upon reaction with electrophiles gave rise to salts **4** (Scheme 1, method B). With method A, cyclic iminium salts **4a-c** were synthesized with chloromethoxy ethyl ether, methallyl chloride, and allyl chloride as alkylating agents in moderate to good overall yields (43%, 47% and 36% yield, respectively, from the aniline). Base sensitive functionalities can be introduced using method B, which does not require deprotonation with strong bases. Cyclic iminium salts **4d-f** were prepared through enamine alkylation with *N*-methylene-*N*,*N*-dimethylammonium chloride (Böhme's salt),[10] *N*-di*iso*propylphenyl pivalimidoyl chloride, and methylene diiodide, respectively (**4d**: 46%; **4e**: 46%; **4f**: 45% yield from the aniline). The methylene iodide substituted salt **4f** can be further

Scheme 1. Synthesis of functionalized CAAC precursors 4a-g.



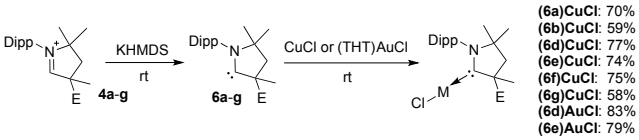
Dipp: 2,6-diisopropylphenyl. [a]Yield from **4f**.

derivatized as shown by the substitution reaction with $HPPh_2$ in the presence of Hünig's base, which afforded **4g** in 69%.

To our delight the deprotonation of all cyclic iminium salts **4a-g** afforded cleanly the corresponding free carbenes **6a-g** (Scheme 2). Carbene **6f** was found to be the least stable at room temperature decomposing after only a few hours, whereas the methylene ethoxy substituted carbene **6a** was found to be indefinitely stable in the solid state and was therefore isolated.

A series of the corresponding copper **(6)CuCl** and gold **(6)AuCl** complexes were easily synthesized in good yields by addition of a solution of carbene to copper chloride and (tetrahydrothiophene)gold chloride, respectively (Scheme 2). The connectivity of the coinage metal complexes **(6d)CuCl**, **(6f)CuCl** and **(6e)AuCl** (Scheme 3) was confirmed by single crystal X-ray crystallography. They are mononuclear complexes that do not show any interaction of the tethered functional groups with the metal center (See Supporting Information).

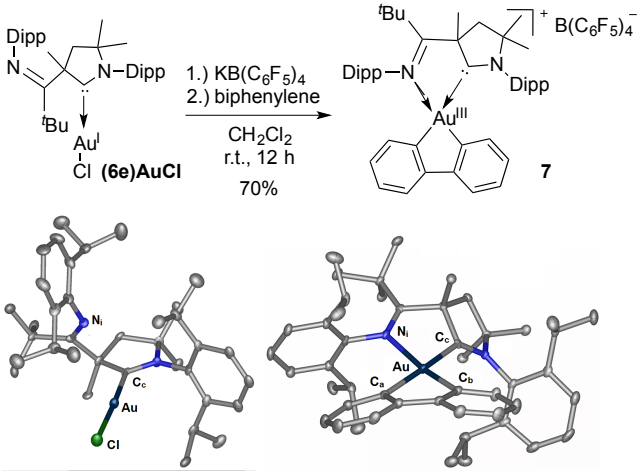
Scheme 2. Synthesis of free carbenes 6a-g and of their copper and gold complexes.



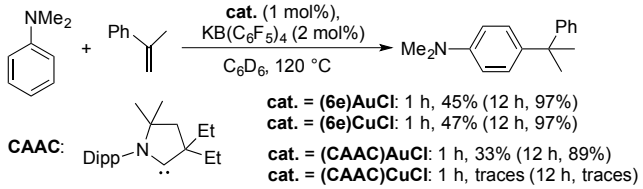
To demonstrate the potential of these novel carbenes in organometallic chemistry, we selected the gold complex **(6e)AuCl**, which features the imine functionality. Whereas CAAC ligands support low oxidation states, their propensity to stabilize high-valent complexes has rarely been explored.[11] Although it is very well-known that oxidative addition on gold(I) is kinetically challenging,[12] it was very recently shown by Bourissou[13] and Toste[14] that the metal center of some cationic gold(I) complexes could undergo oxidative addition of biphenylene. We reasoned that the imine moiety of **(6e)AuCl**, which does not coordinate the soft gold(I) (Au-N_i > 3.39 Å), should be able to help stabilize the gold center in the +III oxidation state.[15] Indeed, monitoring the room temperature reaction of **(6e)AuCl** with biphenylene in presence of $KB(C_6F_5)_4$ by ^{13}C NMR spectroscopy revealed a shift of the carbene signal from 231.7 to 251.0 ppm and of the imine carbon from 177.3 to 196.1 ppm. An X-ray diffraction study confirmed the activation of a C–C bond and the formation of the cationic gold(III) complex **7** in which the imine ligand coordinates to the gold center (Au-N_i = 2.246(3) Å) (Scheme 3). Note that with (CAAC)AuCl complexes without functional groups on the side-chain, the oxidative addition does not occur even upon heating to 80 °C in the presence of $KB(C_6F_5)_4$. These results demonstrate that the pendant imine strongly stabilizes the gold(III) center, and suggest that such hemilabile bidentate ligands should be suitable for catalysis involving high oxidation states.

We reasoned that a basic moiety on the side-chain of the CAAC ligands should also assist reactions involving a formal proton transfer. We therefore evaluated the potential of the gold imine complex **(6e)AuCl** for the hydroarylation of α-methyl styrene with *N*,*N*-dimethyl aniline. We had previously reported that *anti*-Bredt NHC gold complexes promote this reaction with excellent conversion but upon heating at 135 °C for 24 hours.[16] We found that the reaction proceeds much faster with **(6e)AuCl**, a 97% conversion was observed after only 12 hours at 120 °C (Scheme 4). Encouraged by the high catalytic activity of this gold complex, we wondered whether the corresponding copper complex **(6e)CuCl** could also promote the hydroarylation reaction. We were pleased to also observe a 97% conversion after 12 h. Interestingly, under

Scheme 3. Oxidative addition of biphenylene to (6e)AuCl. Solid-state structure of (6e)AuCl (bottom left) and of 7 (bottom right). X-ray crystal structure with thermal ellipsoids (30% probability); solvent molecules, hydrogen and anion were omitted for clarity. Selected bond lengths (Å): (6e)AuCl (left): Au-C_c 1.984(8), Au-N_i 3.391(7); 7 (right): Au-C_c 2.077(3), Au- N_i 2.246(3), Au-C_a 2.051(3), Au-C_b 2.091(3).



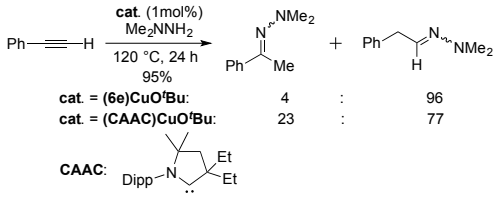
Scheme 4. Gold and copper complexes with imine functionality in the side chain of the CAAC ligand lead to high catalytic activity for the hydroarylation reaction.



the same experimental conditions, the monodentate CAAC gold complex appeared to be also efficient (89 % conversion) but the corresponding copper complex gave only traces of the hydroarylation product. Note that the copper catalyzed intermolecular[17] hydroarylation of alkenes had not yet been reported.

The intermolecular hydroamination reaction of alkynes and alkenes involves the transfer of a proton as well. The synthesis of the *anti*-Markovnikov product remains a challenge.[18] Recently, we reported that ancillary ligand-free copper catalysts afford solely the Markovnikov addition product in the reaction of phenylacetylene with dimethylhydrazine.[19] Monnier *et al.* showed that copper(I) with a cyanide anion leads to 90% selectivity for the *anti*-Markovnikov product with di*n*propylamine as the reaction partner.[20] We found that the *tert*-butoxide analogue of the copper chloride complex, namely **(6e)CuO^{t}Bu**, promotes at 120 °C the addition of dimethylhydrazine to phenyl acetylene. A 95% conversion was observed after 24 h and the *anti*-Markovnikov product was obtained with 96% selectivity (Scheme 5). It is important to note that under the same experimental conditions, the **(CAAC)CuO^{t}Bu** complex is much less selective, demonstrating again the prominent role played by the imine functionality.

Scheme 5. (6e)CuOtBu catalyzes the *anti*-Markovnikov addition of dimethylhydrazine to phenyl acetylene.



The versatile methodology discussed in this paper should allow for the preparation of a variety of hemilabile bidentate CAACs, which will expand the number of applications of this class of carbenes.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, catalytic experiments, NMR spectra, solid-state structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) For the synthesis of CAACs, see: (a) Lavallo, V.; Canac, Y.; Präsang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 5705. (b) Jazzar, R.; Dewhurst, R. D.; Bourg, J. B.; Donnadieu, B.; Canac, Y.; Bertrand, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2899. (c) Jazzar, R.; Bourg, J. B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492. (d) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand G. *J. Am. Chem. Soc.* **2009,** *131*, 8690.

(2) For reviews on CAACs, see: (a) Martin, D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2011**, *2*, 389. (b) Martin, C. D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2013**, *4*, 3020. (c) Soleilhavoup, M.; Bertrand, G. *Acc. Chem. Res.* **2015**, *48*, 256. (d) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010,** *49*, 8810. (e) Martin, D.; Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Organometallics* **2011**, *30*, 5304. (f) Roy, S.; Mondal, K. C.; Roesky, H. W. *Acc. Chem. Res.* **2016**, *49*, 357.

(3) (a) Back, O.; Henry-Ellinger, M.; Martin, C. D.; Martin, D.; Bertrand, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 2939. (b) Lavallo, V.; Canac, Y.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Angew. Chem. Int. Ed.* **2006**, *45*, 3488.

(4) For thematic issues and books on NHCs, see: (a) Rovis, T.; Nolan, S. P. *Synlett* **2013**, *24*, 1188. (b) Arduengo, A. J.; Bertrand, G. *Chem. Rev.* **2009**, *109*, 3209. (c) Diez Gonzalez, S. *N-Heterocyclic Carbenes : From Laboratory Curiosities to Efficient Synthetic Tools* Royal Society of Chemistry: Cambridge, 2010. (d) Nolan, S. P. *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*; Wiley-VCH: Weinheim, 2014.

(5) (a) Droege, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940. (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.

(6) (a) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109*, 3677. (b) Schaper, L. A.; Hock, S. J.; Herrmann, W. A.; Kuhn, F. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 270. (c) Liddle, S. T.; Edworthy, I. S.; Arnold, P. L. *Chem. Soc. Rev.* **2007**, *36*, 1732. (d) Kuhl, O. *Chem. Soc. Rev.* **2007**, *36*, 592. (e) Normand, A. T.; Cavell, K. J. *Eur. J. Inorg. Chem.* **2008**, *2008*, 2781. (f) Waters, J. B.; Goicoechea, J. M. *Coord. Chem. Rev.* **2015**, *293–294*, 80. (g) Corberán, R.; Mas-Marzá, E.; Peris, E. *Eur. J. Inorg. Chem.* **2009**, 1700.

(7) (a) Cramer, S. A.; Jenkins, D. M. *J. Am. Chem. Soc.* **2011**, *133*, 19342. (b) Klawitter, I.; Anneser, M. R.; Dechert, S.; Meyer, S.; Demeshko, S.; Haslinger, S.; Pöthig, A.; Kühn, F. E.; Meyer, F. *Organometallics* **2015**, *34*, 2819. (c) Rogers, M. M.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *21*, 21. (d) Kaufhold, S.; Petermann, L.; Staehle, R.; Rau, S. *Coord. Chem. Rev.* **2015**, *304–305*, 73. (e) Munz, D.; Strassner, T. *Inorg. Chem.* **2015**, *54*, 5043. (f) Strassner, T. *Top. Organomet. Chem.* **2007**, *22*, 125.

(8) a) Kuwata, S.; Ikariya, T. *Chem. Commun.* **2014**, *50*, 14290. (b) Jahnke, M. C.; Hahn, F. E. *Coord. Chem. Rev.* **2015**, *293–294*, 95. (c) Braunstein, P.; Naud, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 680.

(9) (a) Visbal, R.; Gimeno, M. C. *Chem. Soc. Rev.* **2014**, *43*, 3551. (b) Fung, S. K.; Zou, T.; Cao, B.; Chen, T.; To, W.-P.; Yang, C.; Lok, C.-N.; Che, C.-M. *Nat. Commun*. **2016**, 7:10655. (c) Ai, P.; Mauro, M.; De Cola, L.; Danopoulos, A. A.; Braunstein, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 3338. (d) Lee, J.; Chen, H.-F.; Batagoda, T.; Coburn, C.; Djurovich, P. I.; Thompson, M. E.; Forrest, S. R. *Nat. Mater*. **2016**, *15*, 92. (e) Mercs, L.; Albrecht, M. *Chem. Soc. Rev.* **2010**, *39*, 1903.

(10) Böhme, H.; Mundlos, E.; Otto-Erich Herboth, O.-E. *Chem. Ber.* **1957***, 90,* 2003.

(11) Romanov, A. S.; Bochmann, M. *Organometallics* **2015**, *34*, 2439.

(12) (a) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; De Buck Becker, J.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133. (b) Livendahl, M.; Goehry, C.; Maseras, F.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 1533.

(13) (a) Joost, M.; Estévez, L.; Miqueu, K.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 5236. (b) Joost, M.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 15022.

(14) Wu, C.-Y.; Horibe, T.; Jacobsen, C. B.; Toste, F. D. *Nature* **2015**, *517*, 449.

(15) a) Huang, L.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2016**, 55, 4808. (b) Huang, L.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2016**, *52*, 6435.

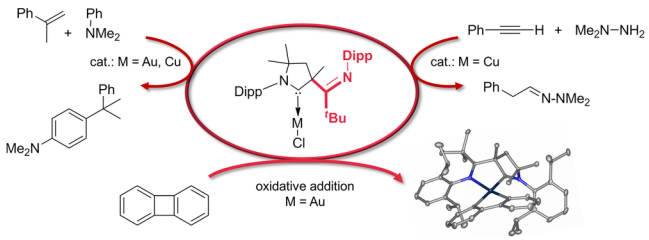
(16) Hu, X.; Martin, D.; Melaimi, M.; Bertrand, G. *J. Am. Chem. Soc.* **2014**, *136*, 13594.

(17) For intramolecular examples of hydroarylation of alkenes, see: Reichart, B.; Guedes de la Cruz, G.; Zangger, K.; Kappe, C. O.; Glasnov, T. *Adv. Synth. Catal.* **2016**, *358*, 50.

(18) For reviews on hydroamination (a) Huang, L.; Arndt, M.; Goossen, K.; Heydt, H.; Goossen, L. J. *Chem. Rev.* **2015**, *115*, 2596. (b) Thomas E. Müller; Kai C. Hultzsch; Miguel Yus; Francisco Foubelo; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (d) Hartwig, J. F. *Nature* **2008**, *455*, 314.

(19) Peltier, J. L.; Jazzar, R.; Melaimi, M.; Bertrand, G. *Chem. Commun.* **2016**, *52*, 2733.

(20) Bahri, J.; Blieck, R.; Jamoussi, B.; Taillefer, M.; Monnier, F. *Chem. Commun.* **2015**, *51*, 11210.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