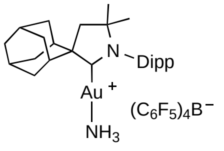
B. Progress Report

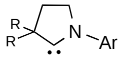
B.1. Synthesis of new types of ligands

Our proposal was based on our discovery that cationic gold(I) complexes such as **1a**, bearing cyclic (alkyl)(amino)carbenes (CAACs) **2** as the ancillary ligand, were the first homogeneous catalysts able to promote the Markovnikov addition of ammonia to non-activated alkynes and allenes.[xxii]

These reactions require high temperatures (up to 200°C), and therefore high thermally stable catalysts. The robustness of (CAAC)-gold complex **1** is largely due to the presence of a strong carbon-metal bond, but also to the peculiar electronic properties of CAACs **2**. Indeed, analogous gold(I) complexes bearing classical N-heterocyclic carbenes (NHCs) **3** as ligands, appeared to be only poor catalysts for the NH_3-hydroamination. It is clear that carbon-based ligands with various electronic properties are highly desirable, and a part of our efforts has been devoted to the search of novel κ^1C-ligands.



1a



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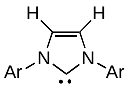
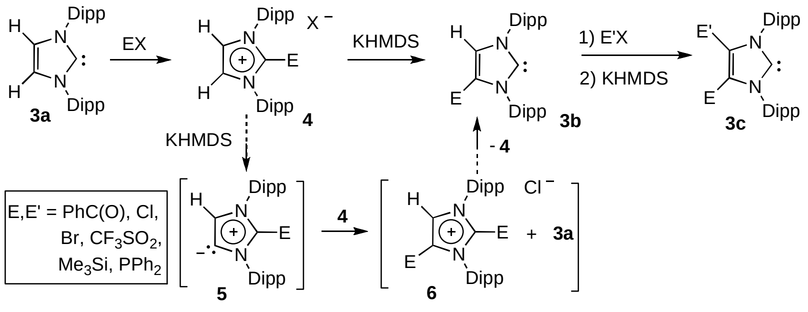


3

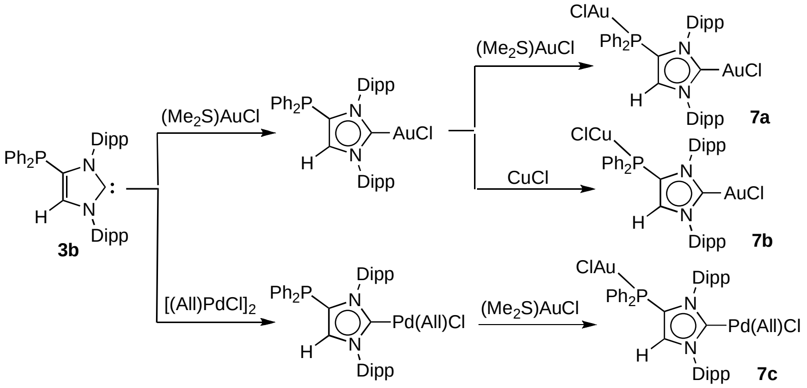
B.1.1. C4 and C4,5-functionalized NHCs[#4,#6]

It has been shown that the substituents at the carbon-carbon double bond of imidazol-2-ylidenes **3** have a dramatic influence on the electronic properties of the carbene center. For example, 4,5-dichloroimidazol-2-ylidene derivatives are exceptionally stable, and are certainly the only carbenes that can be handled in air.[xxxvi] We have serendipitously found a convenient route to a variety of these compounds from a single precursor.

With the aim of tuning the electronic properties of our newly discovered stable abnormal carbenes (*a*NHCs) **5**,[xxxiva] we wanted to vary the C2-substituent, using NHC **3a** as a starting material. As expected, the addition of one equivalent of a variety of electrophiles to **3a** cleanly afforded the corresponding adducts **4**. However, deprotonation of the latter did not lead to the expected *a*NHCs **5**, but to their isomeric NHCs **3b**, featuring the entering electrophile E at C-4. A mechanistic study demonstrated that the fate of these reactions results from the deprotonation of **4** with formation of the desired *a*NHC **5**, but only as a fleeting intermediate. The latter then acts as a nucleophile towards **4**, generating the bis-adduct **6** along with **3a**. NHC **3a** can act as a nucleophile towards the former leading to the observed 4-substituted NHC **3b**, and regenerating the starting material **4**. The same synthetic strategy can be used to place two functional groups at the carbon-carbon double bond of NHCs as shown with **3c**. Of special interest, both electron-withdrawing and -donating groups can be used to functionalize the carbon backbone of NHCs.

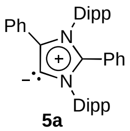


When combined with the discovery of modular syntheses of N,N'-unsymmetrically substituted imidazolium salts,[xxxvii] these results pave the way for the preparation of NHCs with virtually any substitution pattern, and therefore very different σ-donating and π-accepting properties.



Subsequently, we used the NHC of type **3b**, with E = Ph_2P, as a platform for preparing multifunctional complexes. The rare combination of a carbene and a phosphine in a single non-chelating ligand[xxxviii] could pave the way for the design of catalysts with two completely different electronic environments around metals. Since we are especially interested in gold catalysts, we synthesized several homo- and heterobimetallic complexes, such as **7a-c**. These complexes, which were isolated in good to excellent yields, remain unchanged after several days under air exposure and they are thermally stable up to 100 °C for several hours. These features make them interesting catalyst candidates for combining a hydroamination reaction with a different organic transformation in a single pot reaction. This work is under investigation.

B.1.2. Mesoionic carbenes[#2,#3,#8,#10,#11#12]

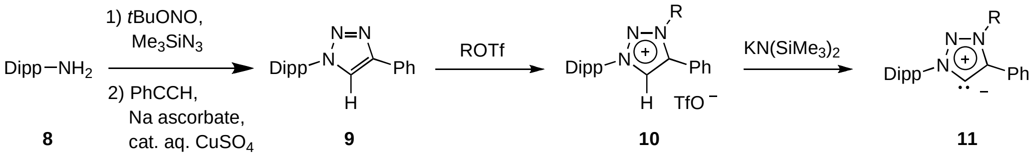


5a

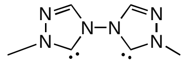
In 2009, we reported the synthesis of the first stable free imidazol-5-ylidene **5a**.[xxxiva] As a consequence of their lineage, these compounds, as ligands, were known as abnormal[xxxix] or remote carbenes.[xxxv] Since the stability of these compounds is due to their mesoionic nature,[xl] a formal positive charge is delocalized over the five ring atoms and the formal negative charge is associated with one of the ring carbon, we prefer to name them mesoionic carbenes (MICs). Free imidazol-5-ylidenes **5** possess an ensemble of features that portend to their utility. Among their most appealing properties is the lack of a dimerization pathway, in contrast with the Wanzlick equilibrium of classical carbenes,[xli] which should lead to relaxed steric requirements for their isolation. Moreover, theoretical data suggested that derivatives of type **5** are even stronger electron-donating and poorer π-accepting ligands than NHCs **3** and CAACs **2**. This opens interesting perspectives for their applications in organometallic catalysis.

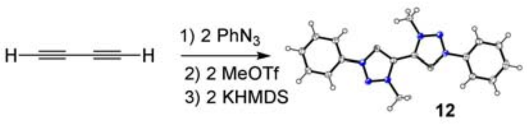
We first investigated the influence of the substituents on the electronic properties of **5**. Electron-withdrawing groups have a beneficial effect on the stability of those MICs, and although electron-donating substituents do not allow for the isolation of the free carbenes, the corresponding metal complexes can be prepared by performing the deprotonation of imidazolium salts in the presence of the metal fragment. The substituent at C-2 modestly affects the electronic properties of MICs, but the group in the 4-position does allow for significant tuning. Importantly, according to the Tolman Electronic Parameters (TEP), MICs **5** are stronger electron-donors than NHCs, even when they bear electron-withdrawing substituents.

One of the drawbacks of imidazol-5-ylidenes **5** is their rather tedious preparation. Therefore, we investigated the possibility of synthesizing other types of MICs, which could be readily prepared in large quantities. We targeted 1*H*-1,2,3-triazol-5-ylidenes **11**, and by analogy with the synthetic route used for preparing NHCs and CAACs, 1,2,3-triazolium salts **10** were chosen as precursors. 1,2,3-Triazoles **9** were obtained in up to 83% yield by the Cu-catalyzed cycloaddition of aryl azides and terminal alkynes (CuAAC, "click chemistry"). Since the purification of aryl azides can be cumbersome, and presents safety risks when performed on large scales, the one-pot conversion of aniline **8** to the desired aryl azide, followed by in-situ CuAAC was found to be especially convenient. Alkylation with methyl or isopropyl trifluoromethanesulfonate afforded the corresponding triazolium salts **10** in moderate to excellent yields. A simple deprotonation with either potassium bis(trimethylsilyl)amide or even potassium *tert*-butoxide in an ethereal solvent gave rise to the corresponding MICs **11** as stable compounds.

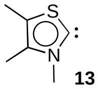


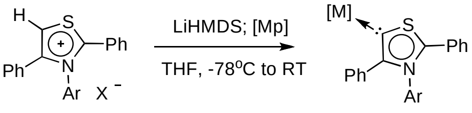
According to the CO vibration frequencies of $[(\mathbf{11})Ir(CO)_2Cl]$ complexes, it can be concluded that the donor properties of **11** are superior than those of NHCs **3** but lesser than those of MICs of type **5**, as expected due to the presence of three nitrogens.


"bitz"



The simplicity of the synthetic route to MICs **11** prompted us to prepare MIC-based bidentate ligands **12**. The latter are analogous to the "bitz" ligands developed by Crabtree and Peris[xlii] as N-heterocyclic carbene equivalents of 2,2'-bipyridines. Bis(triazole) precursors were obtained in good yields in one pot, by reacting an arylazide and a bis(alkyne) via double 1,3-dipolar cycloaddition. After alkylation with methyl triflate and subsequent deprotonation with KHMDS, bisMICs, such as **12**, were isolated as free species in good yields (note that "bitz" cannot be isolated).

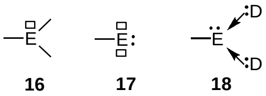

13



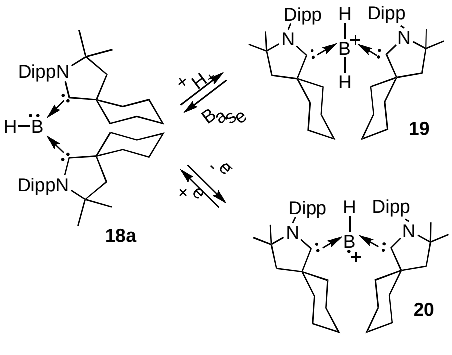
14 **15**

This year, we have expanded the family of MIC ligands to 1,3-thiazol-5-ylidenes **15**. It is noteworthy that the isomeric 1,3-thiazol-2-ylidenes **13** have been used for decades as organocatalysts,[xliii] beginning with the seminal work by Breslow,[xliv] before their isolation by Arduengo.[xlv] The thiazolium salt precursors **14** are conveniently prepared in two steps from thioamides. So far, we have not been able to isolate the corresponding free MICs. However, when salts **14** were treated at −78 °C with an equimolar amount of LiHMDS, in the presence of (THT)AuCl or other metal precursors [Mp], the corresponding thiazol-5-ylidene transition metal complexes **15** were obtained and isolated in moderate to good yields (51 to 90%), and appeared to be thermally- and air-stable. Research in our laboratory is currently underway to explore the catalytic activity of the gold and rhodium complexes for the NH_3- and NH_2NH_2-hydroamination.

B.1.3. Neutral tricoordinate organoboron isoelectronic with amines [#9,#13]


16 **17** **18**
E = B, Al, Ga

For many years the "directing" neutral two-electron donor ligands were based on the elements of groups 15 and 16. The organometallic community was concerned with optimizing catalysts only by fine-tuning the structure of amines, phosphines, ethers, thioethers, etc. The introduction of NHCs, and therefore of ancillary ligands based on a group 14 element, has generated many breakthroughs.[xlvi] This is mostly the result of the strong σ-donating properties of NHCs, which are due to the lower electronegativity of carbon compared to group 15 and 16 elements. This analysis prompted us to attempt the preparation of neutral two-electron donor ligands based on group 13 elements, which are even less electronegative than carbon. This was a paradigm-shifting proposal since trivalent boron, aluminum and gallium compounds **16** are usually regarded as the prototypical Lewis acids.



How did we design neutral compounds with a group 13 element possessing a lone pair? Borylenes and their higher homologues **17** have a lone pair but they are extremely unstable, mainly because of the presence of two vacant orbitals.[xlvii] We reasoned that appending two neutral Lewis bases to the group 13 element center of **17** will make the corresponding adducts **18** stable. Indeed, we found that derivative **18a,** featuring two CAACs as the donor groups D, can be isolated and is stable at room temperature under argon for several months, both in solution and in the solid state (m.p.: 328 °C).

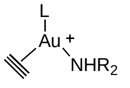
Ab initio calculations showed that the HOMO is essentially a pair of electrons in the p(π)-orbital of boron. Derivative **18a,** being isoelectronic to amines and phosphines, behaves as a base giving **19** and can readily be oxidized into the stable radical cation **20**, as usually observed for amines and phosphines. However, the reactivity of **18a** with metal centers is hampered by the bulkiness of the carbenes, and we currently are in the process of preparing analogues of **18a** with smaller donor substituents and also other group 13 elements.

Some twenty years after the successful introduction of N-heterocyclic carbenes as ancillary ligands for transition metal catalysts, it is reasonable to predict that ligands based on group 13 elements will lead to numerous breakthroughs. As soon as they are available, gold complexes of boron derivatives of type **18** will be tested in hydroamination reactions. Note that our calculations predict that the gold-boron bond in these complexes is extremely strong.

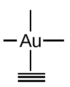
B.2. Catalysis

B.2.1. Discovery of the Novel Hydroammoniumation and Methylamination Reactions[#1]

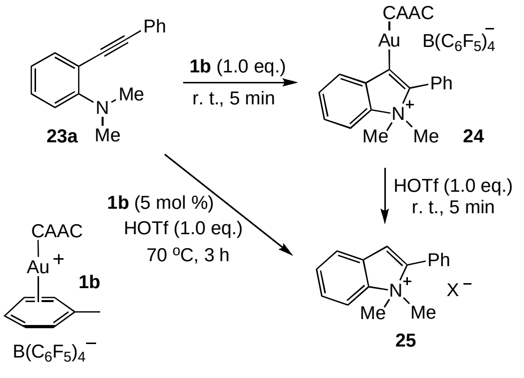
Based on preliminary mechanistic studies of the gold(I) catalyzed NH_3-hydroamination reaction,[xxii,] we postulated that the key step of the catalytic cycle was the formation of a tricoordinate gold complex **21** (R=H) which was followed by *inner-sphere* C-N bond formation, as first hypothesized by Tanaka *et al.*,[xlviii] and Nishina and Yamamoto for other amines.[xlix,l] However, Che *et al.*[li] and Li *et al.*[lii] postulated, for gold(III) catalysts, an *outer-sphere* nucleophilic trans-attack of the amine to the alkyne complex **22**, a mechanism well accepted for palladium[liii] and platinum complexes.[liv] In an attempt to confirm the formation of a tricoordinate gold complex of type **21**, we chose to use the 2-alkynyl-*N*,*N*-dimethylbenzenamine **23a**. Indeed, the rigidity of the phenyl spacer places both the amino group and the alkyne in perfect positions to coordinate the metal center, and the absence of NH-bonds prevents the hydroamination process. A stoichiometric amount of cationic (CAAC)gold(I) complex **1b** was added at room temperature to a solution of **23a**, and we observed the instantaneous formation of a new complex, which was not the desired tricoordinate gold complex of type **21,** but a rare example[lv] of gold(I)(η^1-alkene) complex **24**, resulting from the trans-addition of the tertiary amino group to the coordinated alkyne.



21

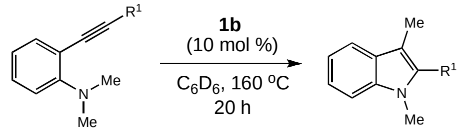


22



Not surprisingly, treatment of complex **24** with one equivalent of trifluoromethane-sulfonic acid instantaneously induced the proto-deauration,[lvi] affording the corresponding gold-free cyclic ammonium salt **25**. The stoichiometric two-step transformation of **23a** into **25** led to the question whether this process could be catalytic for gold, or if the presence of triflic acid would induce the protonation of the basic tertiary amine,[lvii] preventing the cyclization process. We were pleased to observe that in the presence of 5 mol% of **1b**, the desired cyclization occurred; **25** was obtained in 98% yield after only 3 h at 70 °C. We briefly explored the scope of this novel reaction that we named *hydroammoniumation reaction*, and found that aryl and alkyl groups are tolerated on the alkyne, and that the cyclization process occurs under milder conditions when a weak basic amine was used. For example, the hydroammoniumation of 2-alkynyl-*N*-methyl-*N*-phenylbenzenamine readily occurs in a few minutes at room temperature.

There are some reports concerning the direct carboamination of alkynes, the formal insertion of a carbon-carbon triple bond into a carbon-nitrogen bond.[lviii] Although, the cleavage of a relatively weak carbon-nitrogen bond was involved, these results prompted us to investigate the related *methylamination* reaction. In the presence of 10 mol% of **1b**, 2-alkynyl-*N*,*N*-dimethylbenzenamines **23a-d** were transformed into 2,3-disubstituted indoles **26a-d** in good to excellent yields after 20 h at 160 °C. This



R^1 = Ph **23a**	**26a** (90%)
R^1 = *p*-Me-C_6H_4 **23b**	**26b** (78%)
R^1 = *p*-MeO-C_6H_4 **23c**	**26c** (78%)
R^1 = ^{n}Bu **23d**	**26d** (84%)

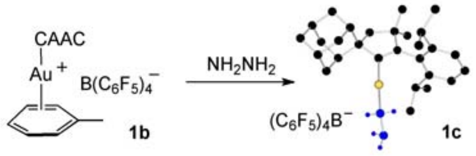
rearrangement tolerates aryl, as well as alkyl substituents on the alkyne.

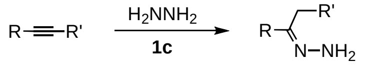
In summary, our results demonstrate that the gold-catalyzed hydroamination of alkynes does not involve a tricoordinate gold complex of type **21**, but an activation of the alkyne, followed by a trans-addition of the amine. More importantly, cationic gold(I) complexes supported by CAAC ligands allow for the intramolecular hydroammoniumation and methylamination reactions of alkynes, two catalytic transformations that have no precedent.

B.2.2. Gold-Catalyzed Hydroamination of Alkynes and Allenes with Parent Hydrazine[#7]

As mentioned in the Background and Significance section, although many homogeneous catalysts are efficient to promote the hydroamination reaction of unactivated carbon-carbon multiple bonds with aryl amines, and to a lesser extent with primary and secondary alkyl amines, no hydroamination reactions involving the parent hydrazine had been reported before our work.

Our discovery that gold(I) complexes, featuring a bulky CAAC as an ancillary ligand, are very robust and efficiently promote the intermolecular addition of NH_3 to alkynes and allenes[xxii] prompted us to investigate whether these catalysts would also tolerate the parent hydrazine. Since gold-hydrazine complexes were not described, we first checked the compatibility of our gold complex **1b** with H_2NNH_2, and found that the latter cleanly coordinates to gold producing complex **1c** in excellent yield. The X-ray diffraction study showed that only one amino group binds to the cationic gold(I) center, giving an η^1-Werner complex. This result is striking since examples of formation of gold particles by reduction of gold chloride with hydrazine have been reported,[lix] and cationic trinuclear phosphine-gold complexes of type $[(LAu)_3(O)]^+X^-$ have been shown to promote the dehydrogenation of H_2NNH_2, leading to N_2-complexes $[(LAu)_6(N_2)]^{2+}$.[lx]

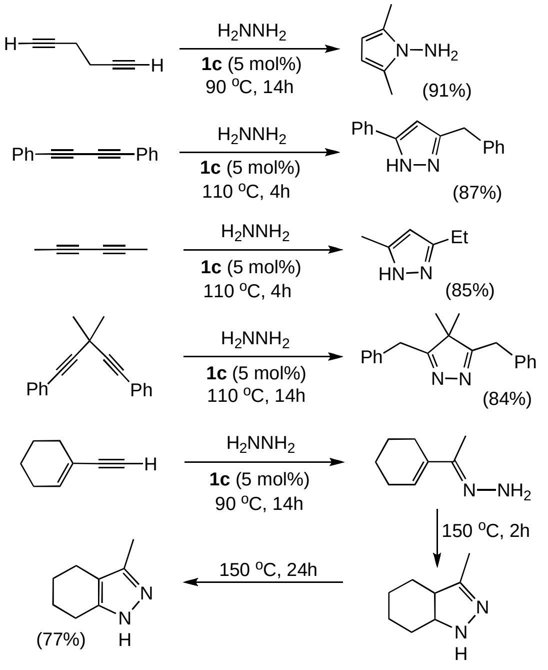




R	R'	**1c** [mol%]	t [h]	T [°C]	Conv. [%]
4-MeOPh	H	5.0	0.5	100	95
		1.0	2	100	95
		0.1	5	100	32
		0.1	6	150	95
nBu	H	5.0	3	100	89
$PhCH_2$	H	5.0	3	100	95
cHex	H	5.0	3	100	92
Ph	Ph	5.0	14	90	93

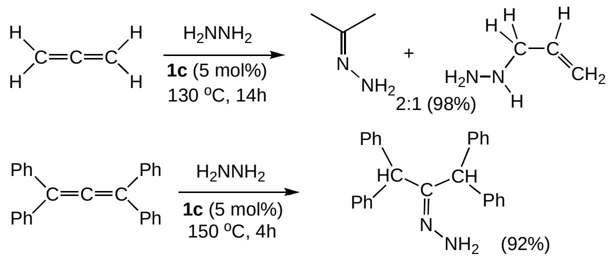
We investigated the catalytic hydroamination of a series of internal and terminal alkynes using excess anhydrous hydrazine and various amounts of catalyst **1c** in chloroform or benzene. Upon heating at 90-150 °C for 30 minutes to 14 hours, clean addition of H_2NNH_2 was observed, which afforded hydrazones, the expected tautomer of the "enamines" resulting from a Markovnikov addition. In the absence of catalyst, or in the presence of AuCl, AuCl/KB$(C_6F_5)_4$, and even [(CAAC)AuCl] no reaction occurred. Therefore, as previously observed with ammonia, the gold center can only catalyze the hydroamination reaction ith hydrazine when it is cationic and coordinated by the CAAC ligand.

Then, we turned our attention to the direct synthesis of heterocycles from diynes, and were pleased to observe that all the tested reactions worked extremely well. From 1,5- hexadiyne, a 1-



aminopyrrole derivative arising from two consecutive Markovnikov hydroaminations, involving a single NH_2 group, followed by aromatization, was isolated in up to 91% yield. When 1,4-diphenylbuta-1,3-diyne and 1,4-dimethylbuta-1,3-diyne were used, the two amino groups of hydrazine were involved, giving rise to pyrazole derivatives in greater than 80% yield. Similarly, 1,5-diphenyl-3,3-dimethylbuta-1,4-diyne reacts with hydrazine to produce a 4*H*-pyrazole (84% yield). As expected, these results show that the formation of five-membered heterocycles is largely favored over their six-membered ring isomers. Lastly, we expanded the scope of these cyclization processes to an ene-yne. The first step, a Markovnikov hydroamination of the triple bond, took place at 90 °C yielding the corresponding hydrazone, which can be thermally converted (150 °C, 2 h) into an indazole derivative. Interestingly, even without adding an external oxidant,[lxi] further heating at 150 °C for 24 h induced the aromatization by dehydrogenation, and afforded 4,5,6,7-tetrahydro-3-methyl-1*H*-indazole, which was isolated in 77% yield.

We also investigated the hydrazine-hydroamination reaction of allenes. When 1,2-propadiene was reacted with H_2NNH_2, the formation of a 2:1 mixture of hydrazone and allylhydrazine was observed (98% conversion after 14 h at 130 °C). The addition of hydrazine to 1,2-dienes is not restricted to the parent allene. Tetraphenyl-1,2-propadiene undergoes hydroamination, affording the hydrazone derivative in more than 90% isolated yield after 4 h at 150 °C. The observed regioselectivity is probably due to steric factors.



Since gold complexes display excellent functional group tolerance, as well as low air and moisture sensitivity, these reactions should be ideal initial steps for the synthesis of acyclic and heterocyclic bulk chemicals. This study conquers the difficulties associated with the use of hydrazine, and will open the avenue for extensive applications, which are part of our renewal proposal.

B.3. Summary

During the current funding period, we have uncovered several novel types of neutral L ligands. Among them, the mesoionic carbenes, such as 1*H*-1,2,3-triazol-5-ylidenes **11**, feature very appealing properties; i) they are readily available in large quantities; ii) multidentate ligands based on these scaffolds are accessible; iii) there is no dimerization pathway in contrast with the Wanzlick equilibrium of classical carbenes, which leads to relaxed steric requirements for their isolation; iv) theoretical and experimental data suggest that they are even stronger electron-donating ligands than NHCs **3**. We have also reported the preparation of the first neutral tricoordinated boron derivative, isoelectronic with amines. It represents the first neutral base centered on a group 13 element. Because of the lower electronegativity of boron, compared to those of nitrogen and carbon, these compounds are potentially stronger electron-donor ligands than amines and even carbenes.

In addition, we discovered two catalytic reactions, namely the hydroammoniumation and methylamination of alkynes, which have no precedent in the literature. Furthermore, we have shown that cationic gold(I) complexes tolerate parent hydrazine, and promote the NH_2-NH_2 hydroamination of alkynes and allenes. Prior to our work, the recently disclosed[xiv] palladium-catalyzed C-N bond formation of aryl chlorides and tosylates with hydrazine was the only example of transition metal-catalyzed functionalization of H_2NNH_2.

Collectively, these results have so far been published in 12 papers, with an additional one already accepted for publication (see next page).

Publications resulting from the funding period.

#1 X. Zeng, R. Kinjo, B. Donnadieu, G. Bertrand, “Serendipitous Discovery of the Catalytic Hydroammoniumation and Methylamination of Alkynes” **Angew. Chem. Int. Ed. 2010**, *49*, 942-945.

#2 G. Guisado-Barrios, J. Bouffard, B. Donnadieu, G. Bertrand, “Crystalline 1*H*-1,2,3- Triazol-5-ylidenes: New Stable Mesoionic Carbenes (MICs)” **Angew. Chem. Int. Ed. 2010**, *49*, 4759-4762.

#3 M. Melaimi, M. Soleilhavoup, G. Bertrand, “Stable Cyclic Carbenes and Related Species beyond Diaminocarbenes” **Angew. Chem. Int. Ed. 2010**, *49*, 8810-8849.

#4 D. Mendoza-Espinosa, B. Donnadieu, G. Bertrand, “Synthesis of 4- and 4,5-Functionalized Imidazol-2-ylidenes from a Single 4,5-Unsubstituted Imidazol-2-ylidene” **J. Am. Chem. Soc. 2010**, *132*, 7264-7265.

#5 D. Martin, M. Soleilhavoup, G. Bertrand “Stable Singlet Carbenes as mimics for Transition Metal Centers” **Chem. Sci. 2011**, *2*, 389-399.

#6 D. Mendoza-Espinosa, B. Donnadieu, G. Bertrand “Facile Preparation of Homo- and Hetero-dimetallic Complexes with a 4-Phosphino Substituted NHC Ligand. Toward the Design of Multifunctional Catalysts” **Chem. Asian J. 2011**, *6*, 1099-1103.

#7 R. Kinjo, B. Donnadieu, G. Bertrand “Gold-Catalyzed Hydroamination of Alkynes and Allenes with Parent Hydrazine” **Angew. Chem. Int. Ed. 2011**, *50*, 5560-5563 (Hot Paper).

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