ACES Asian Chemical Editorial Society

DOI: 10.1002/asia.201500353

CHEMISTRY AN ASIAN JOURNAL Communication

Carbenes

Facile Synthesis of Functionalized Carbene Metal Complexes from Coordinated Isonitriles

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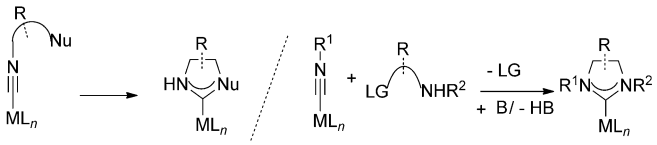
Abstract: The scope and limitations of the isonitrile-based NHC template synthesis were investigated with a series of precursors containing a nucleophilic amine in combination with tethered electrophiles. In the case of alkynes and phosphonic esters as electrophiles no ring closure was observed and new functionalized NAC gold complexes were obtained. By the use of unsaturated esters and phosphonic esters as Michael acceptors in the amine precursors, ester-modified gold and palladium NHC complexes were accessible in high efficiency.

Introduction

In 1915 Chugaev and co-workers[1] conducted a very interesting experiment. By treating a platinum isonitrile compound with hydrazine, they synthesized the first metal carbene complex. Naturally, at that time they could not assign the correct structure and thus they assumed a hydrazine bridged dimeric platinum compound. Interestingly, it took almost 60 years until Shaw and co-workers[2] were able to correct this misinterpretation. Today, in modern organometallic chemistry, carbenes play an intriguing role as ligands in metal complexes spanning a large part of the periodic table of elements.[3]

The high impact of these ligands is owing to the groups of Arduengo,[4] Herrmann,[5] Bertrand,[6] Organ,[2h] Nolan,[7] Grubbs,[8] Glorius[9] and many others, who introduced carbenes, especially *N*-heterocyclic carbenes (NHCs), as ligands for catalysts.

In many cases the synthesis of NHCs is not trivial,[10] requiring several steps executed as a linear sequence with the coordination of the metal as the final step. A much shorter route was reported in a pioneering work of Fehlhammer, Hahn and co-workers.[11] That route relies on the intramolecular nucleophilic attack at the carbon atom of a metal-coordinated isonitrile as the basic principle (Scheme 1, left). Only the coordination of the functionalized isonitrile activates the carbon atom for the intramolecular attack by the nucleophile and thus enables the ring closure in this template synthesis. A drawback is the limitation that only one nitrogen atom of the NHC in these metal complexes is substituted, whereas the former isonitrile nitrogen atom always bears a proton. This restricts the versatility and the use of this method for the preparation of catalysts. In addition, an intramolecular mode of cyclization does not allow a convergent synthesis of the carbenes and combinatorial approaches for the installation of screening libraries are not possible.



Scheme 1. Different template strategies towards NHC complexes from isonitrile precursors.

A different approach of the groups of Saegusa, Michelin, Pombeiro and Fehlhammer[12] is based on the nucleophilic addition of amines with tethered electrophiles/leaving groups (Scheme 1, right). Thus, after an initial attack onto the isonitrile carbon atom, the former isonitrile nitrogen can act as a nucleophile and close the cycle to form the heterocyclic carbene. The advantage of this methodology is the intermolecular process that enables fast and modular approaches by combining three components in a template synthesis. Interestingly, despite the early reports on this simple strategy, no reports on the synthesis of complexes bearing *N*,*N*′-disubstituted NHCs were reported and all of the examples delivered protic NHC complexes as products. This is noteworthy as especially disubstituted complexes are interesting with regard to their potential application as catalysts.

To address this issue, we recently developed a procedure which is based on the utilization of β-substituted ethylamines as starting materials. As mentioned, the initial step is an intermolecular nucleophilic addition,[13] and the subsequent ring

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201500353.

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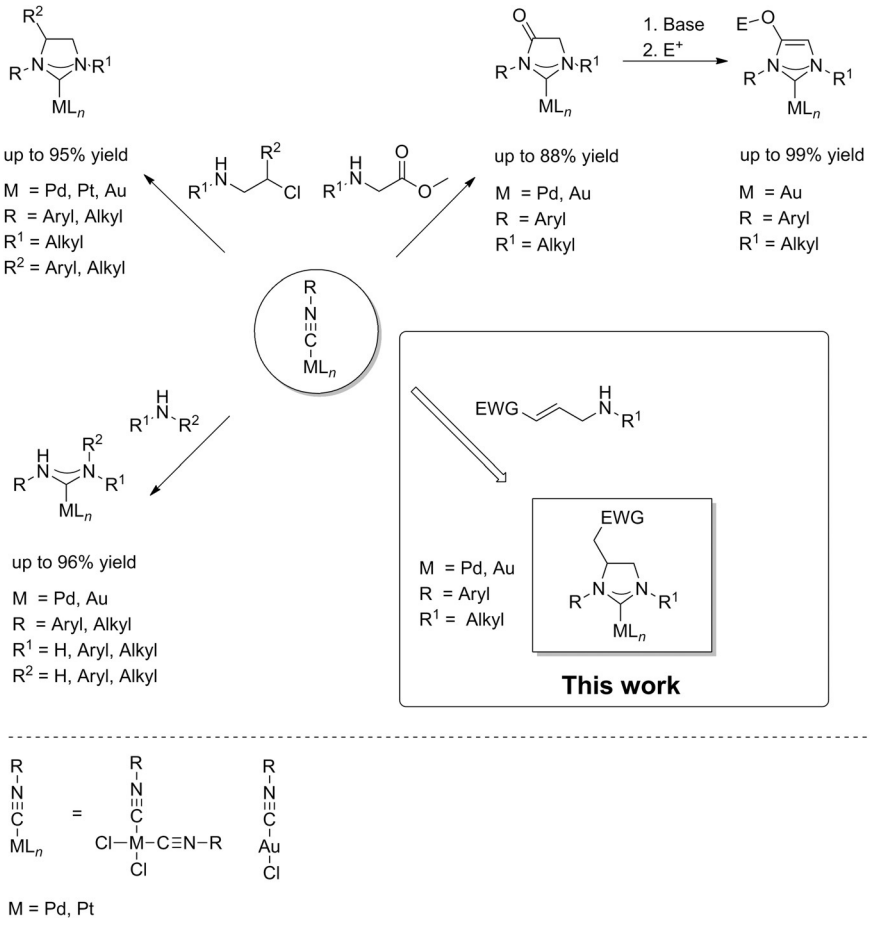
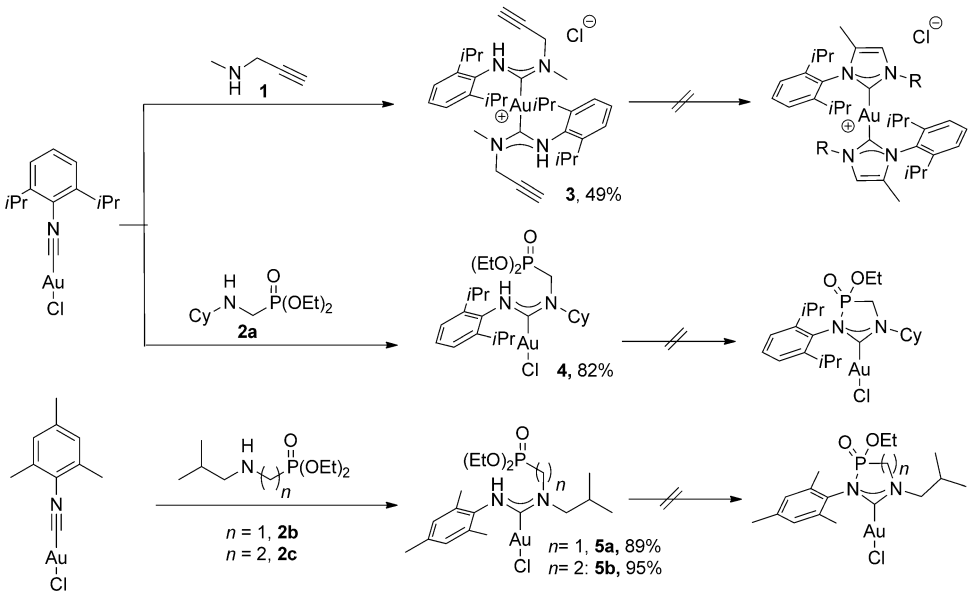
closure proceeds by an intramolecular nucleophilic substitution (Scheme 2).[14] This method allows the construction of disubstituted NHCs in a highly variable way and the modular synthesis of different metal carbene complexes from coordinated isonitriles. In addition, abnormal carbenes were feasible by following a related cycloaddition strategy.[15]



Scheme 2. Summary of our methods for the synthesis of NHC/NHOC metal complexes. NHOC=*N*-heterocyclic-oxo-carbene.



Scheme 3. Syntheses of new non-cyclic metal carbene complexes (isolated yields).

All these reactions are selective and proceed under mild conditions without the necessity of dry or degassed solvents. In the case of the gold carbene complexes it is even possible to start from (tetrahydrothiophene)AuCl ((tht)AuCl) or (dimethyl sulfide)AuCl as precursors and to form the isonitrilegold(I) chloro complexes in situ in a one-pot three component procedure. In this manuscript, we describe our efforts on the extension of this short and simple one-pot route and the scope and limitations of other potential electrophiles in the precursors.

Results and Discussion

As mentioned, the methodology for the carbene synthesis is based on the combination of an electrophile and a nucleophile in the same molecule. Inspired by this simple concept, we considered several other potential carbene precursors. Scheme 3 summarizes our attempts to synthesize new cyclic *N*,*N*-carbene complexes. In addition to the use of carbon–halogen bonds[14a] and esters[14b] we considered to use other electrophiles like alkynes and phosphonic acid esters. The corresponding precursors **2a–c** were synthesized according to standard procedures (see the Supporting Information for synthetic details).

Interestingly, we did not observe the formation of cyclic carbenes in any of these experiments. To our surprise, in the case of propargylic amine **1** as precursor, we observed the formation of bis-NAC-gold(I) complex **3** (Figure 1). Even heating or the addition of acid did not initiate ring closure to the NHC

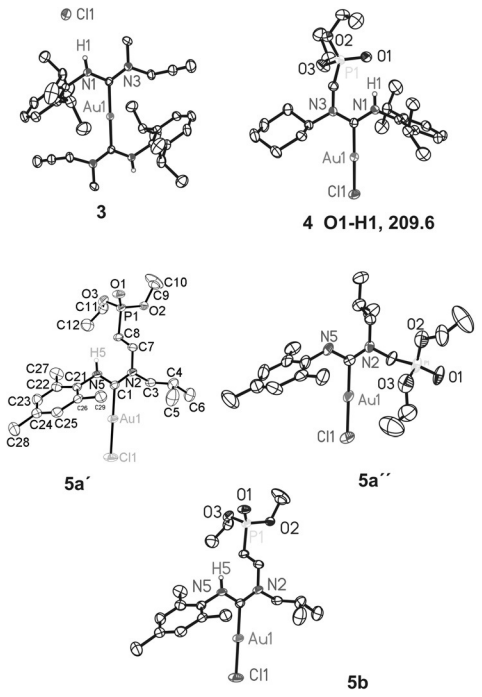


Figure 1. Structures of compounds **3**, **4**, **5a**, and **5b** in the solid state and selected structural parameters. Thermal ellipsoids are shown at 50% probability. Selected bond distances (pm) and angles (°): **3**: Au–C2, 204.3(2); C2–N1, 133.9(3); C2–N3, 132.8(3); N1-C2-N3, 117.5(2); H1–Cl, 260. **4**: Au–C2, 199.9(3); C2–N1, 133.8(4); C2–N3, 134.0(4); N1-C2-N3, 117.3(3); O1–H1, 210. **5a′**: Au–C1, 200.2(2); C1–N2, 134.0(3); C1–N5, 133.4(2); N2-C1-N5, 118.33(18). **5a′′**: Au–C1, 199(2); C1–N2, 132(3); C1–N5, 136(3); N2-C1-N5, 118(2). **5b**: Au–C1, 199.1(5); C1–N2, 134.3(6); C1–N5, 134.3(6); N2-C1-N5, 117.5(4).

complex.[16] The reactions of gold isonitrile complexes with substituted phosphonic esters proceeded in high yield to the *n*on-cyclic *a*mino *c*arbene (NAC) complexes, no matter if two or one methylene groups were in the tether. These compounds show interesting properties. The solid-state structure of **4** shows a hydrogen bond between the oxygen atom of the phosphonic acid group and the carbene moiety, forming a seven-membered ring (besides the calculated distance of 210 ppm between the oxygen and the hydrogen atom from the X-ray data, the chemical shift of 10.3 ppm in the ^{1}H NMR indicates the hydrogen bond). Although this rotamer seems to be favored, two different rotamers were obtained for all complexes (visible by NMR). In the case of NAC complex **5a** the two rotamers were even obtained as different modifications (**5a′**, **5a′′**) in the solid-state structures (Figure 1). It should be mentioned that the incorporation of the phosphorous atom in the backbone of the ligand opens up new possibilities for in situ NMR studies.

As a next step, we considered unsaturated esters as electrophiles. These were supposed to close the NHC ring via a Michael reaction which would enable the simple incorporation of an electron-withdrawing group in the backbone of the NHC ligand. This is of high importance as for classical NHC approaches the installation of an additional functional group such as an ester moiety in the backbone of the ligand is complicated due to the acidic proton in α-position of the ester. We faced this problem and found a straightforward solution, which is based on principles from our earlier work.[14] In order to generate suitable precursors, we used commercially available methyl 4-bromobut-2-enoate. The reaction with a primary amine in the presence of Cs_2CO_3 as a base exclusively gave a substitution at the γ-position, and no products of a Michael addition or amide formation were observed (Scheme 4).

Next we treated (tht)AuCl with compound **6c** in presence of various isonitriles (Scheme 5). All of the reactions proceeded cleanly and the corresponding *e*ster-*m*odified NHC (emNHC) complexes were obtained after a reaction time of 3 days in CH_2Cl_2 at room temperature.

Monitoring the progress of the reaction by ^{1}H NMR spectroscopy indicated a full conversion in each case. The moderate yields for some of the reactions result from the workup procedure, which was not optimal for a reaction scale of only 100 μmol. To prove this hypothesis, we also performed the synthesis of **7a** on a 2 mmol scale, resulting in a much better yield of 89% (vs. 60%) of the analytically pure product. Figure 2 shows the structure of **7a** in the solid state.[17] All bond lengths and other structural parameters are in the typical range for these compounds.

Noteworthy, an expansion of this methodology towards conjugated phophonic esters as Michael acceptors was also possi-

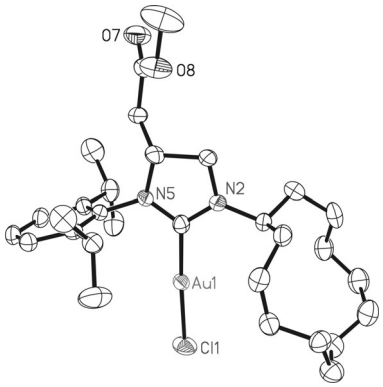
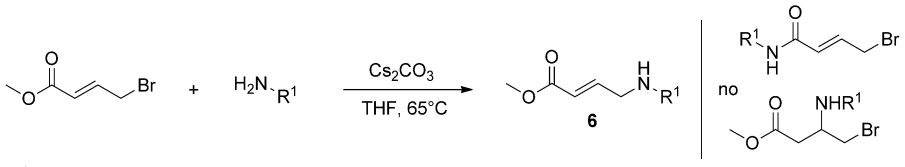
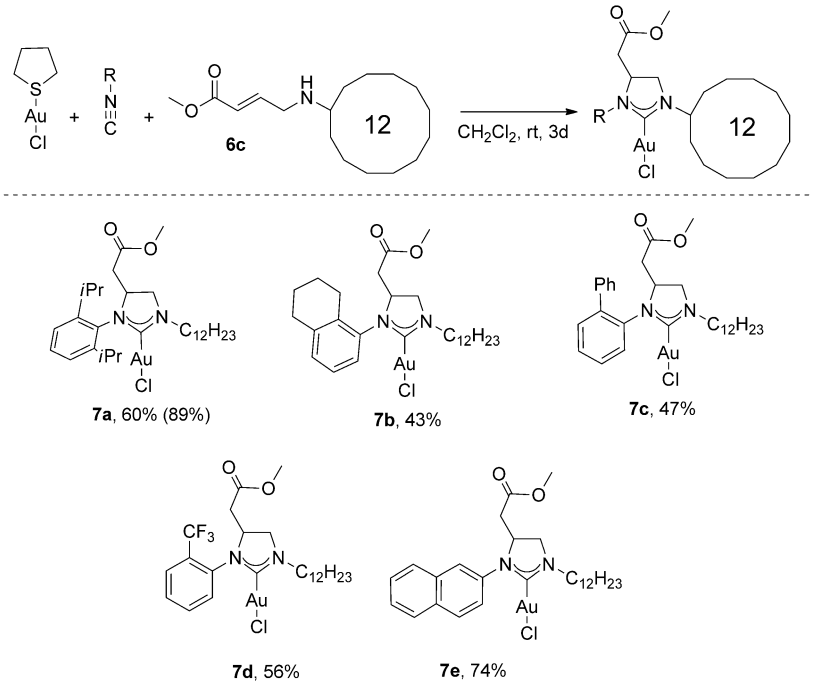


Figure 2. Structure of compound **7a** in the solid state. Thermal ellipsoids are shown at 50% probability. There was one molecule of CH_2Cl_2 in the elementary cell, which was omitted for clarity. Bonding distances (pm) and angles (°): Au–C1, 197.5(4); Au–Cl, 227.7(11); C1–N2, 133.6(4); C1–N5, 134.0(4); N2-C1-N5, 108.7(3).

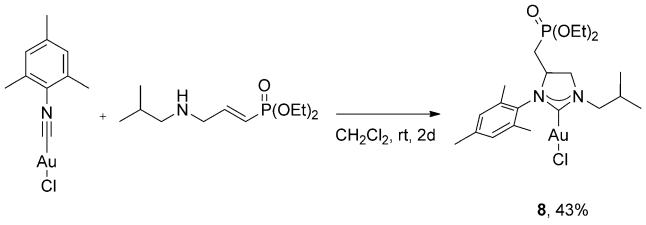


R^1 = **6a** *tert*-Butyl (48%), **6b** cyclohexyl (54%), **6c** cyclododecyl (58%)

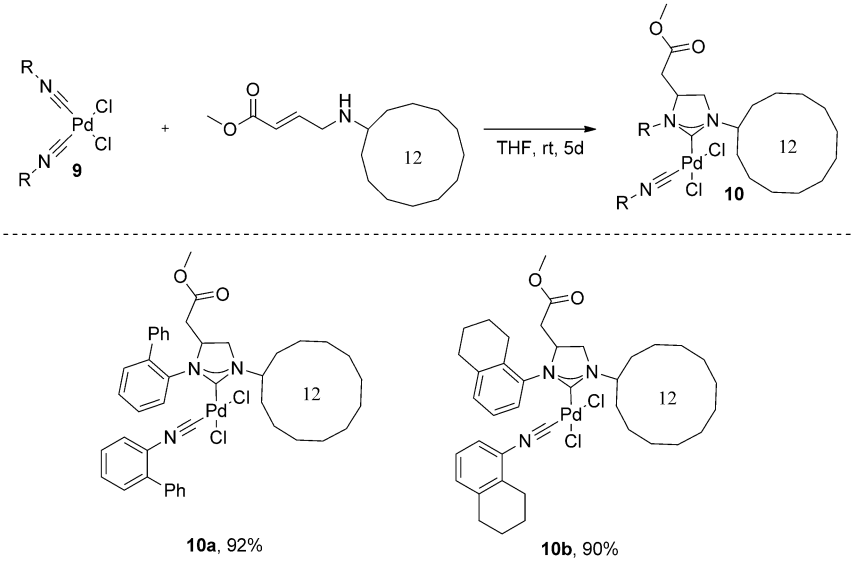
Scheme 4. Synthesis of the amine precursors **6**.



Scheme 5. First examples of the emNHC-Au^{I} complexes. Scale, 100 μmol. The yield in parentheses is that obtained by a 2 mmol scale.



Scheme 6. Synthesis of phosphonic ester-modified NHC complex **8**.



Scheme 7. Synthetic scheme and examples of the synthesis of emNHC-Pd^{II}-complexes.

ble which was demonstrated via the synthesis of phosphonic ester substituted NHC complex **8** (Scheme 6).

Next we considered palladium as central metal for the conjugate addition approach. As depicted in Scheme 7, the analogous reaction with bis-isonitrile precurors **9** was highly efficient, and the target NHC complexes **10a** and **10b** could be isolated in excellent yields, but the reaction times were quite long.

Conclusions

We could demonstrate a new and efficient way for the synthesis of ester- and phosphonic ester-modified NHC complexes based on the isonitrile route. These types of NHC complexes offer an additional functionality for further modifications. Due to the acidic ester protons these types of complexes are not easily accessible via classical routes, which underlines the advantages of the isonitriles approach. In addition, the modular synthetic access allows the fast synthesis of catalyst libraries, which is a positive aspect concerning the potential use in catalyst screenings. Furthermore, the scope and limitations for other electrophiles were evaluated which led to the synthesis of new types of non-cyclic carbenes with additional functional groups; a potential use of these functional groups for anchoring the complexes on solid support can be envisioned.

Acknowledgements

We thank Umicore AG & Co. KG for the generous donation of noble metal salts; C.L. is grateful for financial support by the Studienstiftung des deutschen Volkes e.V.

Keywords: amines · gold · isonitriles · Michael acceptors · phosphonates

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Manuscript received: April 5, 2015
Revised: May 15, 2015
Accepted Article published: May 28, 2015
Final Article published: July 3, 2015