Ligand design in Au-carbene systems for catalytic hydroamination

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The last two decades have been termed by some as a "catalytic gold rush", owing to the many recent advances made in gold-catalyzed transformations.[1] Gold centers command such interest as a catalytic tool in large part due to relativistic effects: strong covalent interactions, high Lewis acidity, and in particular, strong π-acidity.[2] This last feature has opened the door for gold as a premier catalyst for transformations of alkynes and other unsaturated, unactivated carbon backbones. However, gold is incredibly reluctant to engage in redox activity (E°(III/I) = 1.41 V). Despite possessing the same valence electronic structure as the classic Pd(II/0) system, examples of gold-catalyzed oxidative additions are rare.[3] Thus, ligand design has emerged as the primary method of tuning and enhancing the reactivity at gold centers, and carbenes such as *N*-heterocyclic carbenes (NHCs) are of particular interest due to their strong σ-donation to gold and robust derivatization procedures.[4] One field for which this Au/carbene combination has become a potent catalyst is the hydroamination of unsaturated carbons, whereby an amine moiety is installed across a double/triple bond, creating either the amine or enamine product, respectively (Figure 1).[4]

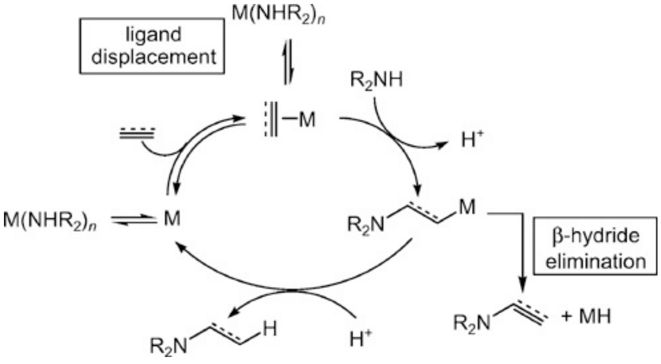

Figure 1. General catalytic cycle for hydroamination of C–C double/triple bonds.

One significant limitation of Au/carbene systems is difficulty in performing asymmetric catalysis: the linear nature favored by Au-carbene complexes means that bound substrates are placed opposite the ligand and thus far from any designed chirality. In 2021, Fensterbank reported the synthesis of a series of Au(I) catalysts supported by a vinylogous cyclic amino aryl carbene (CAArC), dubbed an Indolizy-carbene due to the fused ring (Figure 2a).[5] The sp^3 carbon served as the chiral center, at which bulky groups such as *tert*-butyl and substituted arenes are attached.

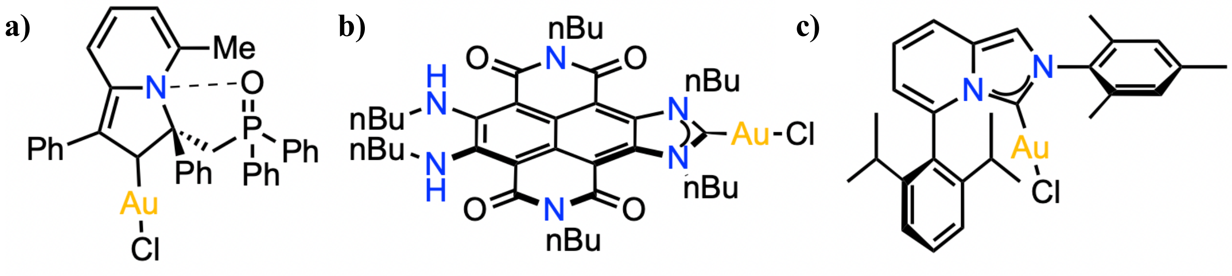

Figure 2. Au-carbene complexes discussed in this abstract a) Indolizy–Au–Cl b) Au–NHC complex bearing the NDI backbone c) [(ImPyDippMes)AuCl]

DFT calculations indicated that the HOMO lies at a much higher energy compared to alkyl analogues, while the LUMO lies at a lower energy, which the authors take as evidence for increased σ-donor and π-acceptor character for the Indolizy ligand. These conclusions were supported by Huynh Electronic Parameter (HEP) analysis, ^{77}Se NMR, and diagnostic cyclization reactions with an allene diene substrate. The authors then demonstrated that these complexes were competent for asymmetric internal hydroamination of a model allene substrate. After heating at 50 °C for 24 hours with 3 mol% catalyst loading and a silver activator, the cycloaminated product was obtained with both good yields (>70%) and enantioselectivity (e.s. 16:84).

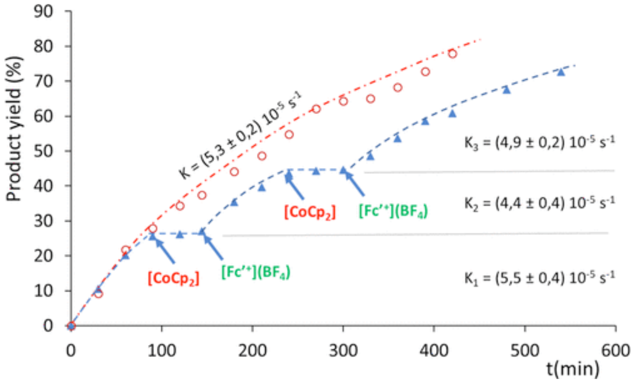

Figure 3. Plot comparing catalytic hydroamination by the NDI-NHC-Au catalyst uninterrupted (red) and with subsequent additions of $CoCp_2$ and $[Fc'^{+}][BF_4]$ (blue)[6]

In 2022, Peris and coworkers reported the synthesis of an Au(I) bearing an NHC fused with a naphthalene diimide (NDI) moiety that has been previously demonstrated to be effective as a redox-switch (Figure 2b).[6] The corresponding NDI-NHC-Au complex was characterized by cyclic voltammetry and differential pulse voltammetry: the complex has two redox features, one reversible wave at -1.22 V and a second quasi-reversible wave at -1.55 V. In the presence of a NaBArF salt, the first wave was unaffected but the second became irreversible, which the authors ascribed to the Na^{+} ions scavenging chlorides lost during the second reduction event. Spectroelectrochemical studies by UV-Vis confirmed the quasi-stability of the doubly reduced complex. The complex was demonstrated to catalyze the hydroamination of terminal phenylacetylene with various arylamines in good yields. Finally, the authors showed that addition of cobaltocene effectively quenched reactivity, indicating that increased electron-density at the metal center in the singly reduced species inhibited the reaction. Due to the stability of the reduced complex, addition of acetylferrocenium to the reaction mixture restored catalytic activity. The authors asserted that the system demonstrates redox switchability and highlighted the potential of using ligands with in situ electronic tunability for mechanistic studies.

In 2024, Szostak and coworkers designed a reductive hydroamination of alkynes (RHAA) catalytic system by nitroarenes via cascade relay.[7] The ligand that demonstrated the best catalytic activity was an imidazopyridine-like NHC bearing a Dipp moiety on one wing-tip and a Mes moiety on the other, dubbed ImPyDippMes (Figure 2c). Optimization of this reaction resulted in addition of $[Ag(MeCN)_2]$BArF as a chloride abstractor and $PhSiH_3$ as a hydride source in toluene at 40 °C for 16 h, leading to yields of up to 98% for certain substrates. The catalytic system was demonstrated to be suited for RHAA with a wide array of substrates, both for the nitroarene and the alkynyl substrates, as well as a number of late-stage functionalizations of pharmaceutically relevant molecules.

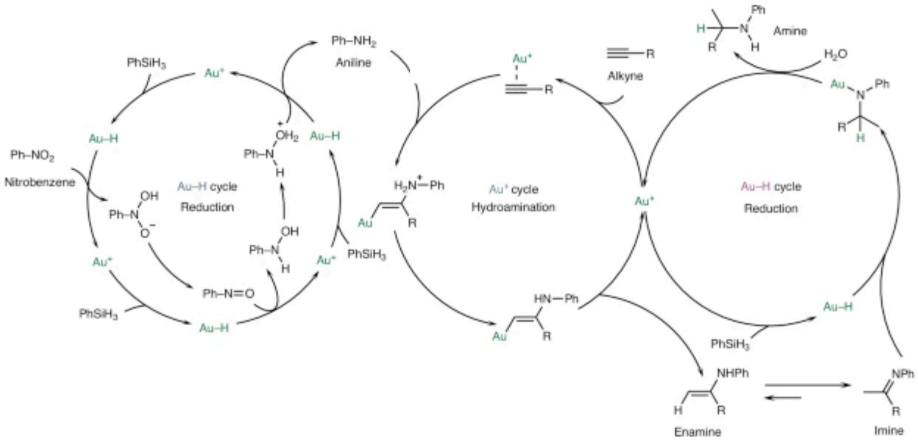

Figure 4. Proposed catalytic cycle involving Au–H (left), Au^+ (center), and (μ_2–H)Au_2 species (right)[7]

To investigate potential hydridic intermediates, two Au-H species were synthesized, isolated, and crystallographically characterized, one featuring a monomeric L–Au–H bond and the other featuring a bridged μ_2–H dimeric structure. The monomeric complex was found to only be catalytically competent for the reduction of nitroarenes to anilines. The dimeric species was shown to be somewhat competent for the amination and imine reduction steps but could not catalyze the nitroarene reduction. The authors thus asserted relay catalysis for RHAA involving three cycles: the monomeric hydride species catalyzes reduction of nitroarenes to the corresponding aniline (Figure 4b, left), the cationic gold species catalyzes hydroamination (Figure 4b, center), and the dimeric hydride species catalyzes reduction of the imine to the final amine (Figure 4c, right).

In conclusion, gold-catalyzed hydroamination of unsaturated carbon bonds remains a transformation of great interest by the chemistry community. Due to the strong π-acidity of gold in addition to its reticence to engage in redox activity, significant focus has been put into the design and application of ligands to influence reactivity. Decoration of NHCs and exploring other cyclic carbenes have opened avenues towards new and improved applications.

References

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