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Fused polycyclic NHC ligands in Gold Catalysis: Recent advances

Paul Teixeira,^[a] Stéphanie Bastin, ^{*[a]} and Vincent César^{*[a]}

Abstract: Thanks to their appealing properties, N-heterocyclic carbene (NHC) ligands gained considerable significance as highly powerful ancillary ligands in gold catalysis. While NHC-gold catalysis is still dominated by the classical imidazole-derived NHC ligands, annelated NHC systems, which feature fused aromatic rings to the carbenic heterocycle, have drawn wider attention over the last few years thanks to their unique structural and electronic properties.

Keywords: Carbenes • Gold • Catalysis • Asymmetric Catalysis • Nitrogen Heterocycles

Fused polyaromatic NHCs are indeed versatile platforms that offer unique stereoelectronic tuning possibilities to exhibit superior activity and/or selectivity in NHC-gold catalysis. But their polycyclic scaffolds also provide further scope for functionalization and the introduction of chirality, stimuli-responsiveness, or cooperativity within the NHC-gold systems. In this review, the recent advances in this area are discussed and a particular attention is drawn on the unique role of the annelation.

1. Introduction

Over the last two decades, molecular gold complexes have been established as the most attractive catalysts for the electrophilic activation of unsaturated carbon-carbon bonds such as alkynes, allenes or alkenes towards the attack of nucleophiles.^{[1],[2],[3]} The most commonly employed ancillary ligands in gold catalysis are phosphines and N-heterocyclic carbene (NHC) ligands,^[4] which display complementary reactivities and activities.^[5] The latter are particularly appealing in gold catalysis thanks to the strong Au-C_{NHC} bonds and electronic donation of the NHC ligands leading to improved stability of the catalysts.^[6] Moreover, the NHC structures can be easily tuned^[7] to optimize the stereoelectronic properties and *in fine* the stability and catalytic activity of the active species.^[8] In particular, the last decade has witnessed the advent of fused polycyclic NHC ligands^[9] in gold catalysis with a huge surge in the last five years. The annelation of the carbenic ring with one or more aromatic rings either at its back or lateral edge (Figure 1) indeed provides electronic delocalization over an extended scaffold and/or constrained geometry, both having impact on the corresponding gold catalysts. These subjects will be discussed in this mini-review, on the basis of selected examples that highlight the unique role of the annelation.

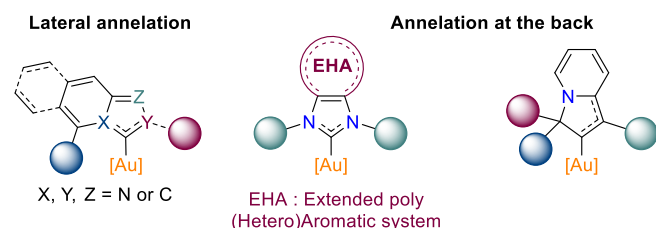


Figure 1. General depiction of the fused polycyclic N-heterocyclic carbene gold complexes discussed in this review.

2. Electronic tuning of NHC catalysts through annelation

2.1. Polycyclic aromatic NHCs based on an imidazolyl carbenic ring

In 2010 and in a seminal study, Fürstner and co-workers showed that the outcome of gold(I)-catalyzed cycloisomerization reactions could be changed by rational adjustment of the π -accepting properties of the NHC ligands, without altering their σ -donor qualities.^[10]

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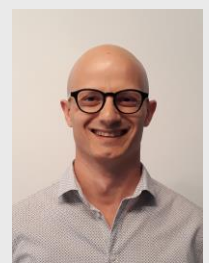
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ijch.201xxxxx>. ((Please delete if not appropriate))

investigating asymmetric catalysis by using chiral N-heterocyclic carbene gold(III) complexes.

Stéphanie Bastin was born in Valenciennes, France. She obtained her Ph.D. in chemistry in 2000 under the supervision of Prof. Jacques Brocard at the University of Sciences and Technologies of Lille I and worked on the synthesis of ferrocene chiral aminoalcohols for catalytic applications. She then obtained a temporary teaching and research position in the same group for one year. In 2001, she joined the group of Prof. Martin Wills at the University of Warwick (UK) where she developed chiral supported catalysts and studied their catalytic activity in asymmetric reduction of ketones by hydrogen transfer. In 2003, she obtained a postdoctoral position in Dr Jean-Pierre Majoral's team at the "Laboratoire de Chimie de Coordination" in Toulouse. In 2004, she joined the CNRS as a permanent researcher in the same laboratory. Her current research focuses on the development of new functionalized (chiral) N-heterocyclic carbenes for catalytic applications.



Vincent César was born in 1977 in Nancy, France, and studied chemistry at the Ecole Normale Supérieure de Lyon. After obtaining his Ph.D. in 2004 under the supervision of Prof. L. H. Gade and Dr. S. Bellemin-Laponnaz at the Louis Pasteur University in Strasbourg, he joined Prof. A. Fürstner at the Max Planck Institute für Kohlenforschung in Mülheim (Germany) as an Alexander-von-Humboldt fellow. In 2006, he was appointed CNRS researcher at the "Laboratoire de Chimie de Coordination du CNRS" in Toulouse where he became CNRS senior researcher in 2000. His research activities mainly concern the chemistry of N-Heterocyclic Carbenes (NHCs) for applications in organometallic chemistry, organic synthesis, and homogeneous catalysis.



This was realized on the fused, bicyclic imidazo[1,5-*a*]pyridin-3-ylidene (ImPy) platform first disclosed independently by Glorius and Lassaletta in 2005.^[11] The ImPy ligand displays relatively similar σ -donicity but enhanced π -acidity compared to the monocyclic imidazol-2-ylidenes due to the annelation.^[12] The addition of a second aromatic layer spanned over the imidazopyridine core of the standard **1a** led to the construction of its cyclophanic counterpart **1b**, whose π^* orbital energy level E_{π^*} significantly decreased relative to the one in **1a**, whereas the E_{σ} values of **1b** and **1a** are almost identical (Figure 2). This electronic bias was shown to have dramatic consequences in the cycloisomerization of the eneallene **2**, in which the intermediate **3** can evolve following two different pathways according to the electron density on the gold(I) center. Indeed, from the common intermediate **3**, pre-catalyst AuCl(**1a**) led to the exclusive formation of the compounds **7a/7b** in a ratio 62/38, through a formal [3+2] pathway, as the electron-rich ligand **1a** allowed stabilization of the cation adjacent to the metal center in **5**. Conversely, the more π -accepting ligand **1b** induced a total selectivity change for the [2+2] pathway and to product **6** in 71% yield, by favoring a carbenium center in beta position relative to the less electron-rich gold center in **4**. Eventually, the use of the triazolo[3,4-*a*]pyridin-2-ylidene (TriPy) ligand **1c**, which is less σ -

donating than **1a** and **1b** and whose π -acidity is in between, afforded a mixture of products with the [2+2]-compound **6** as main product, confirming the starting hypothesis. Noteworthy, it appeared that the correlation between π -accepting properties and switch of selectivity in this reaction was rendered possible only thanks to the peculiar bicyclic structure of the ligands, as the same authors and others observed non-rational trends by varying electronic and steric properties of other ligands.^[10, 13]

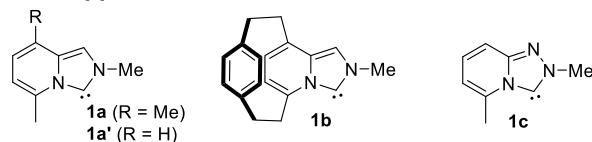
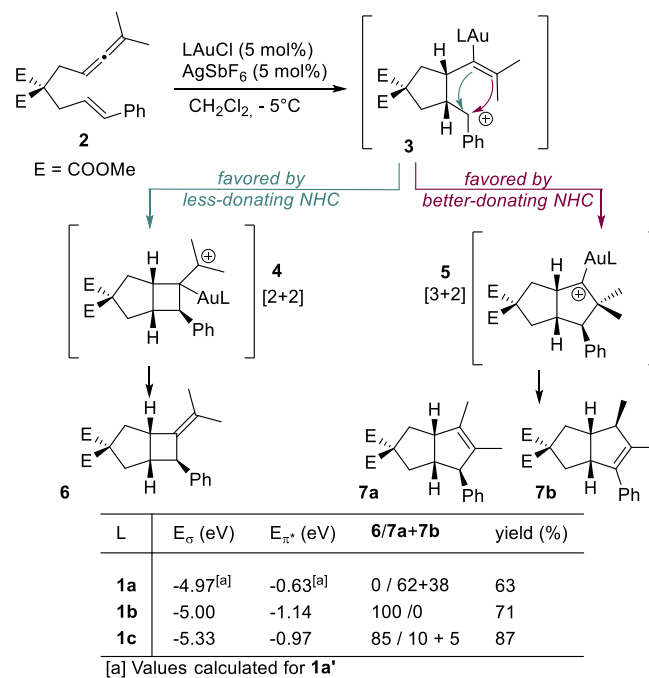


Figure 2. Control over the cycloaddition of eneallene **2** through electronic tuning of N-heterobicyclic carbene ligands **1a-c**.

For a decade, Poyatos, Peris and co-workers have been developing the chemistry of NHC ligands with fused polycyclic aromatic hydrocarbons as well as the effect of supramolecular, non-covalent interactions in homogeneous catalysis.^[14] In this framework they reported a series of gold(I) complexes with extended polyaromatic systems such as the monometallic complex **8** and bimetallic complex **9** (Figure 3).^{[15],[16]} The complexes were tested as catalysts in the hydroamination of phenylacetylene with different aromatic amines, where complex **8** showed moderate activity and complex **9** better efficiency. Interestingly, the addition of a catalytic amount (10 mol%) of polycyclic aromatic hydrocarbons (PAHs), namely pyrene for **8** and coronene for **9**, produced an improvement of 10-30% in the performance of the catalysts. This is due to supramolecular, non-covalent interactions such as π -stacking between the external PAHs and the extended NHC-backbone, leading to new host-guest complexes, such as (**8**•pyrene) or (**9**•coronene). While the beneficial effect of the addition of coronene to **9** could be explained in terms of allosteric

effects,^[17] the addition of pyrene to catalyst **8** was shown to result in the modification of the reaction order in catalyst. Through π - π stacking interactions, complex **8** self-dimerizes forming the dimer (**8**)₂ inactive in catalysis, leading to a reaction order of 0.5 in catalyst. The interaction of complex **8** with pyrene being stronger than with another complex **8**, the dimer (**8**)₂ is partially broken by forming the adduct (**8**•pyrene) active in catalysis and restoring a reaction order between 0.5 and 1.

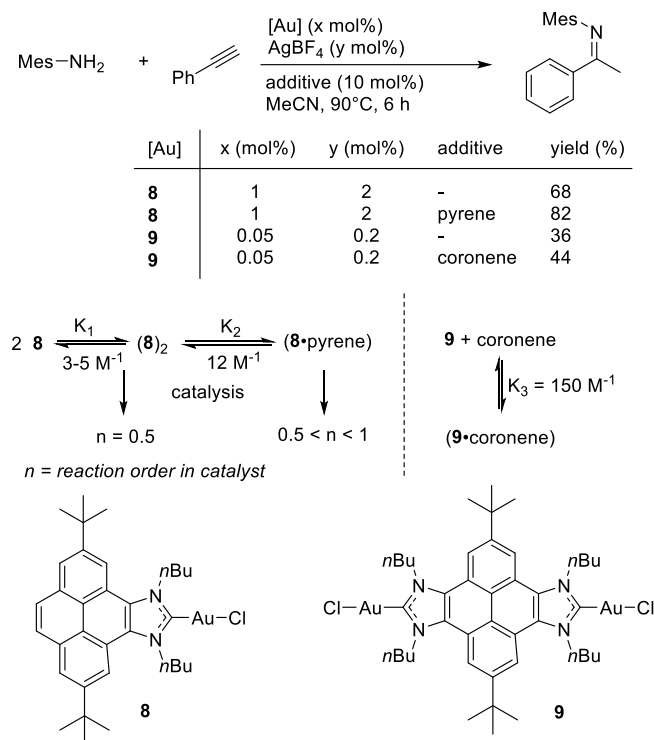


Figure 3. Au(I)-catalyzed hydroamination of phenylacetylene using fused polycyclic aromatic NHCs and influence of the supramolecular interactions on the catalytic activity.

More recently, the same authors reported the redox-switchable gold(I) pre-catalyst [AuCl(**10**)] supported by the naphthalene-di-imide (NDI) functionalized NHC ligand **10** (Figure 4).^[18] Two reduction events associated with the reduction of the NDI moiety were observed by electrochemical studies and induced a sequential increase of the electronic donicity of the ligand in the order $\mathbf{10} < \mathbf{10}^- < \mathbf{10}^{2-}$. As the first reduction process is reversible, the redox behavior of catalyst [AuCl(**10**)] was evaluated in the model hydroamination of phenylacetylene. While the neutral catalyst [AuCl(**10**)] showed a moderate-to-high activity, the catalyst could be “switched off” by addition of [CoCp₂] and, more importantly, it could be “switched on” by addition of the oxidant [FeCp₂](BF₄). This redox switch was correlated with the modulation of the electronic properties of the ligand.

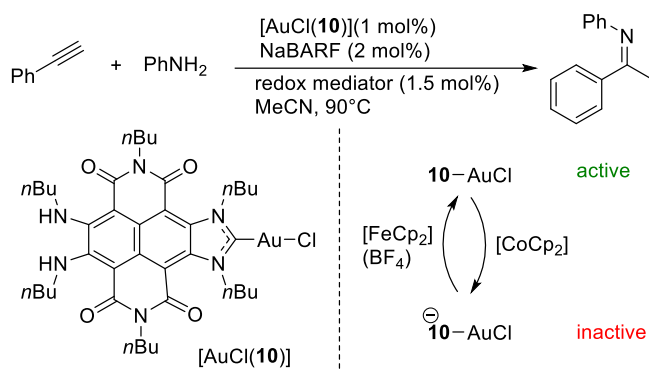


Figure 4. Use of redox-switchable catalyst [AuCl(**10**)] in hydroamination reaction of phenylacetylene.

Tu and co-workers recently described two efficient and general protocols for the gold(I)-catalyzed alkyl- and arylsulfonation of arylboronic acids to synthesize various functionalized arylalkyl and diarylsulfones. These latter compounds represent important pharmacophores routinely encountered in drugs and biologically active compounds (Figure 5).^[19]

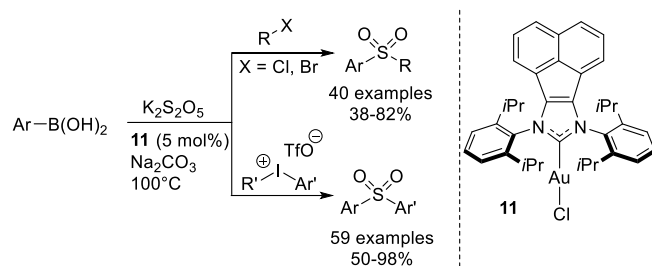


Figure 5. Alkyl- and arylsulfonation of boronic acids catalyzed by the acenaphthoimidazolyliene gold(I) complex **11**.

The procedure relied on the use of potassium metabisulfite (K₂S₂O₅) as SO₂ surrogate and the acenaphthoimidazolyliene gold(I) complex **11** was shown to provide better results than the standard, non-substituted IPrAuCl and IMeAuCl. The better activity of **11** was assigned to the stronger σ -donor and weaker π -acceptor properties of the acenaphthoimidazolyliene ligand relative to the classical imidazolyliene ligands,^[20] even if protection of the NHC backbone by substitution against undesired attack by the reagents could not be totally ruled out. The proposed mechanism consists in the formation of insertion of SO₂ into the Au-Ar bond of a (NHC)Au-Ar species to generate (NHC)Au-SO₂Ar intermediate which can liberate the crucial sulfonate anion ArSO₂⁻, which is further trapped by the electrophilic reagent [RX or Ar⁺ from (R'-I-Ar)⁺].

2.2. Less heteroatom stabilized polycyclic NHC ligands in gold catalysis

Compared to the widely used and powerful Cyclic Alkyl-Amino-Carbenes (CAACs),^[21] the chemistry of Cyclic Aryl-Amino-Carbenes (CAArCs) and indazolin-3-ylidene is still in its infancy and only the few gold(I) complexes **12-15** have been reported up to now (Figure 6a). While the CAArC gold(I) complex **12** was reported

by Bertrand's group in 2015,^[22] the indazolin-3-ylidene gold(I) complexes **13-15** were reported by several groups.^[23] In those compounds, the direct interaction of the carbene lone pair with the neighboring π -system of the aromatic ring renders the NHC highly π -accepting by lowering the energy level of its LUMO, but it does not affect to a great extent the σ -donation relative to the CAAC (Figure 6b). Although the free NHCs are not stable, the NHC complexes **12-15** could be isolated in generally good yields from the isoindolium and indazolinium precursors respectively. Complex **12** was able to catalyze the three-component preparation of 1,2-dihydroquinoline from 3-methoxyaniline and phenylacetylene, demonstrating the competency of CAAC ligands in transition-metal catalysis (Figure 6c).^[22] Complex **14** was tested as catalyst in the hydration of various alkynes but showed relatively modest activity compared to classical IPrAuCl catalyst.^[23b, 24] By substituting the aryl group with a lateral bulky aryl group, Szostak generated the complex **15**, which promotes the hydroamination and hydrohydrazination of alkynes, outcompeting the standard (IPr)AuCl and (IMes)AuCl.^[23c] This last result should be seen as another example of the effectiveness of the strategy consisting in employing L-shape NHC ligands as valuable ligands in gold(I) catalysis (vide infra).

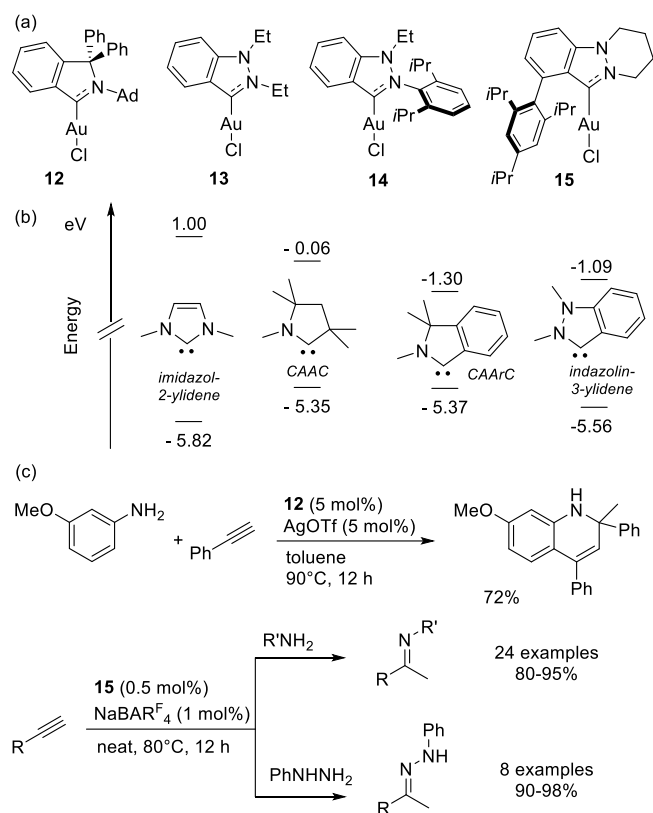


Figure 6. (a) Reported Au(I) complexes with CAACr and indazolin-3-ylidene ligands. (b) Calculated energy for the HOMO and LUMO of imidazol-2-ylidene, CAAC, CAACr, and indazolin-3-ylidene for comparison (B3LYP/def2-TZVPP level of theory). Values taken from ref^[21] (c) Three component synthesis of 1,2-dihydroquinoline catalyzed by **12**. Hydroamination and hydrohydrazination of acetylenes with **15**.

A related family of less-heteroatom stabilized polycyclic NHC gold(I) complexes is represented by the Indolizy gold(I) complexes **18**, where Indolizy is the acronym for indazolin-2-ylidene ligand (Figure 7). While the direct isolation of these ligands has not been realized so far, the gold(I) complexes **18** were obtained through a gold(I)-promoted cyclization of the corresponding allenepyridine **17**, obtained by SN₂' reaction on the propargyl acetates **16/16'**.^[25] The synthetic access is quite modular as various functionalized or non-functionalized substituents R₂ can be incorporated onto the stereogenic quaternary carbon atom vicinal to the carbene center. When R₂ ≠ Ph, the complexes **18** are chiral and were obtained under racemic form, the two enantiomeric complexes (*R*)- and (*S*)-**18** being separated through preparative HPLC using a chiral stationary phase. DFT calculations and experimental evaluation of the donor properties confirmed the strong σ -donor and π -accepting properties of the Indolizy ligand.

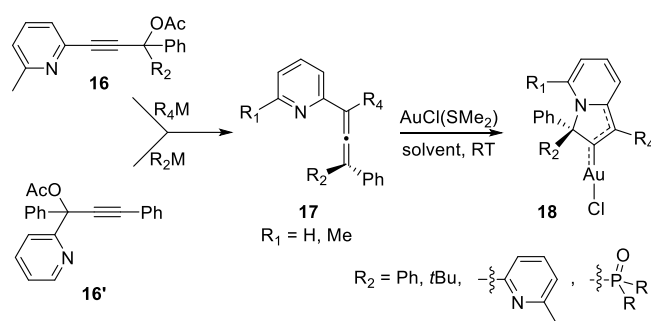


Figure 7. Gold(I)-promoted cyclization of allenepyridines **17** leading to Indolizy gold(I) complexes **18**.

While Munoz and co-workers showed the potency of complexes **18** as catalysts in alkoxyacylation of 1,6-enyne,^[25b] Fensterbank's group very recently reported the use of the chiral, enantiopure Indolizy gold(I) complexes in the asymmetric methoxycyclization of 1,6-enyne **19**, and the intramolecular hydroalkoxylation of **21** and hydroamination of **23** (Figure 8).^[25a] They showed that the phosphine oxide arm is crucial for enantioselectivity, and the best catalysts were **18a** and **18b**. While the enantiomeric excesses (ee's) obtained in the methoxycyclization were rather moderate, the two catalysts led to very good ee in the intramolecular cycloisomerization of γ -functionalized allene derivatives **21** and **23**. In the last two reactions, the tosylate anion brought by AgOTf was shown to play also a crucial role for the outcome of the reaction. DFT calculations suggested different catalytic pathways in which the phosphine oxide and the tosylate counteranion act as hydrogen bonding sites and proton shuttles to stabilize and direct the transition states.

Running title

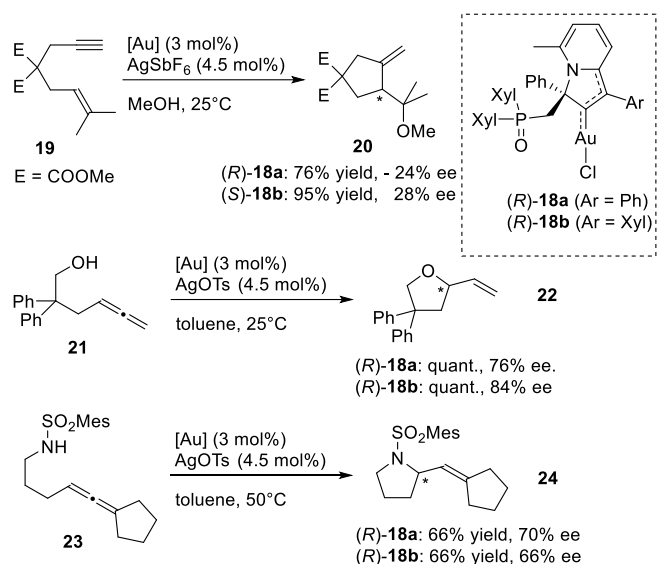


Figure 8. Asymmetric methoxycyclization, intramolecular hydroalkylation and hydroamination catalyzed by gold(I) catalysts **18a-b**. Xyl = 3,5-xylyl.

3. L-shape bicyclic pyridine-fused NHCs as privileged ligand platform in gold catalysis

Besides the electronic effect described in part 2.1, the formal lateral annelation of the classical five-membered NHCs based on imidazole and triazole rings with a pyridine moiety has also a strong effect on the three-dimensional arrangement of the resulting bicyclic NHCs. Indeed, the functionalization of the C5 position (*i.e.* in *ortho* position of the pyridinic nitrogen atom) of the specific, rigid structure of the bicyclic imidazo[1,5-*a*]pyridin-3-ylidene (ImPy) and [1,2,4]-triazolo[4,3-*a*]pyridin-3-ylidene (TriPy) platforms leads to L-shape NHC ligands, in which the C5-substituent is positioned in front of the gold center and forms a kind of “lateral wall” (Figure 9). This special geometry would thus favor: *i*) a strong steric congestion/protection of the coordination sphere; *ii*) possible weak stabilizing interactions between gold center and the lateral substituent; *iii*) the design of bifunctional catalysts using a functional lateral group; and *iv*) the generation of efficient chiral NHC-Au catalysts by providing the chiral information near the active site. These aspects will be discussed and the following parts.

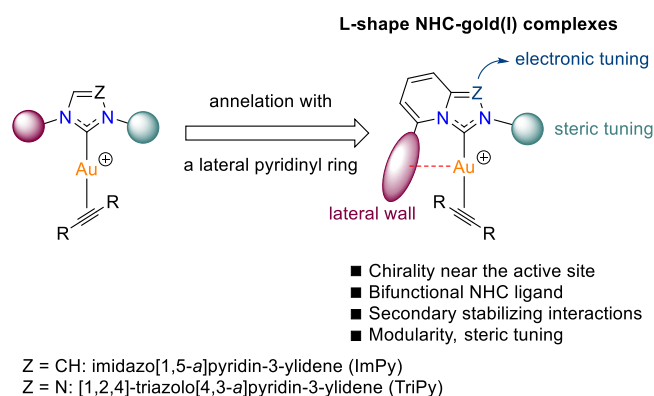


Figure 9. Specific features of laterally-substituted L-shape N-heterobicyclic carbenes in gold(I) chemistry and names of the two NHC platforms.

3.1. ImPy-gold(I) catalysts with weak intramolecular interactions

In 2019, our group in collaboration with Michelet’s group reported the anionic complex **25** and its neutral derivatives **26a-b**, from a common ImPy-based NHC, C5-functionalized by a flanking, anionic barbituric heterocycle (Figure 10).^[26] The anionic nature of the latter heterocycle allowed its post-complexation functionalization by reaction of complex **25** with electrophiles such as methyl triflate for **26a** or triflic anhydride for **26b**, and a rapid and efficient stereoelectronic tuning of the NHC ligand. All complexes **25** and **26a-b** showed high activities as catalysts in the intermolecular hydroamination of phenylacetylene, with the *O*-methylated catalyst **26a** giving the best result with a TON of 7600 among the best systems reported up to date (Figure 10, eq. 1).^[27] Noteworthy, complex **26a** also catalyzed the addition of benzoic acids to 1-dodecyne at a 1 mol% catalyst loading, while the classical IPrAuNTf₂ was previously reported inactive under these conditions (Figure 10, eq. 2). Eventually, complex **26a** was shown to outperform the anionic **25** and neutral **26b** as well as more classical IMesAuCl, IPrAuCl and (PPh₃)AuCl in the domino cyclization/nucleophilic addition of 1,6-enynes with various nucleophiles (Figure 10, eq. 3). The remarkable efficiency of catalyst **26a** was mostly explained by the high steric protection brought by the *O*-methylated barbituric ImPy ligand, but also by an additional, non-covalent, electronic stabilizing interaction between the lateral barbituric heterocycle and the cationic active gold(I) center.

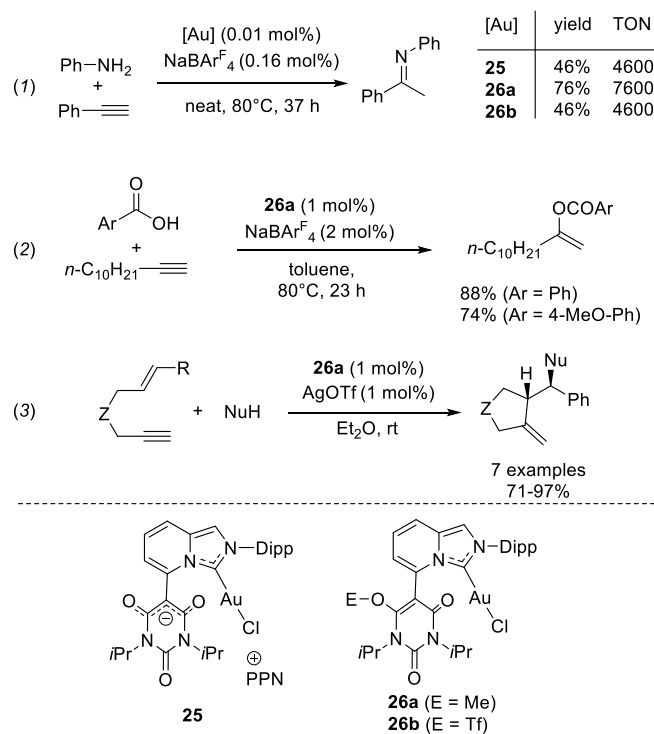


Figure 10. Intermolecular hydroamination and hydrocarboxylation of alkynes and domino hydroamination and hydrocarboxylation of alkynes and domino

cyclization/nucleophilic addition of 1,6-enynes catalyzed by catalysts **25** and **26a-b**. Dipp = 2,6-diisopropylphenyl.

Very recently, Monari, Bandini and coworkers reported that controlling the weak secondary interactions between gold center and the ancillary NHC ligand constitutes a viable and rational strategy to boost the activity of the corresponding cationic gold(I) species (Figure 11).^[28] To this purpose, they developed a series of modular ImPy-Au(I) complexes, whose C5-position is functionalized by electronically-differentiated aryl and oligothieryl groups, whose complexes **27a-e** are selected examples.^[29] As a first model, the dearomatization of 1,3-dimethylnaphth-2-ol with N-phenyl-N-tosyl allenamide was selected. Complex **27b** having the electrodeficient 3,5-di(trifluoromethyl)phenyl group as the lateral aryl substituent delivered the best catalytic activity leading to a 95% yield and with an initial reaction rate 2.8 higher than the one recorded for catalyst **27c** bearing an electron-rich 3,5-dimethoxyphenyl moiety. This result was counter intuitive since ligands incorporating electron-rich moieties generally stabilize the cationic active gold species. Nevertheless, the authors observed the same trend of activity in the cyclization of 2-alkynylbenzaldehyde (Figure 10) or the cyclopropanation of olefins (not shown), which led to the conclusion that the substitution of the lateral aryl group on C5-position of the ImPy ligand by electron-withdrawing CF₃ groups has a booster effect on the activity of the corresponding gold(I) catalysts. Crystallographic analysis of the pre-catalysts **27a-c** and DFT calculations associated with topological analysis of the obtained electron density using atoms in molecules (AIM) and non-covalent interactions (NIC) models indicated the presence of secondary Ar...Au contacts. Eventually the Natural Bond Orbital (NBO) partial charges calculated at the electrophilic end of the allenamide framework in the postulated intermediate **28** were in agreement with a fine-tuning of the electrophilic properties of the cationic Au(I) species by the electronic nature of the C5-pendant aryl group.

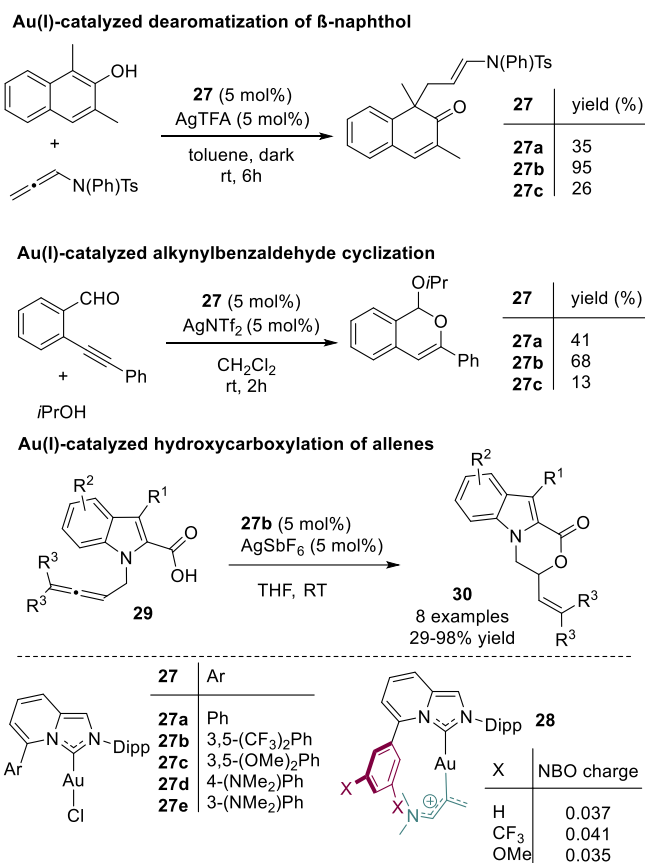


Figure 11. Impact of the secondary intramolecular Au...Arene interactions in Au(I)-catalyzed activation of alkynes and allenes using complexes **27a-c**.

Encouraged by these results and in collaboration with Ollevier, the authors applied this series of complexes in intramolecular Au(I)-catalyzed hydrocarboxylation of allenes **29** for the synthesis of the tricyclic oxazinoindolones **30**, a widespread scaffold in natural, biologically-active and pharmaceutical compounds (Figure 11).^[30] Taking into account that secondary hydrogen interactions between the carboxylic acid and a basic amino group, they extended the family to complexes **27d** and **27e** having respectively a 4-dimethylaminophenyl and a 3-dimethylaminophenyl group as lateral substituent. However, the electron-rich aryl groups in **27c-e** induced a shielding of the electrophilic properties of the gold center and led to a decrease in catalytic activity, while the presence of electro-deficient group in **27b**, inducing a destabilization of the intermediate catalytic species, allowed for an acceleration of the ring closure step. The optimized catalytic system based on **27b** is tolerant to the presence of electro-donor and electro-attractor substituents on the indole ring and to the use of trisubstituted allene substrates. Comparative catalytic tests performed in the presence of gold(I) complexes based on phosphorus ligands or classical NHC ligands such as IPr confirmed the superiority of ImPy platform in this catalysis.

3.2 Bifunctional ImPy ligands in π -acid catalysis

In 2021, Higashida, Sawamura and co-workers leveraged the ImPy platform to develop acid-base cooperative silver catalysts for the cyclization of alkyne-

tethered carboxylic acids **31**.^[31] The strategy relied on the grafting of a basic imidazole group at the C5 position in close proximity to the metal center, the basic site activating the carboxylic acid while the alkyne function undergoes a π -electrophilic activation (Figure 12). Under optimized conditions, a wide substrate scope was achieved with generally very good to excellent yields. NMR experiments and DFT calculations showed that the cationic dimer $[32](PF_6)_2$ dissociates in the reaction medium to give the monomeric species 32^+ with an interaction between the imidazole basic site and the carboxylic acid.

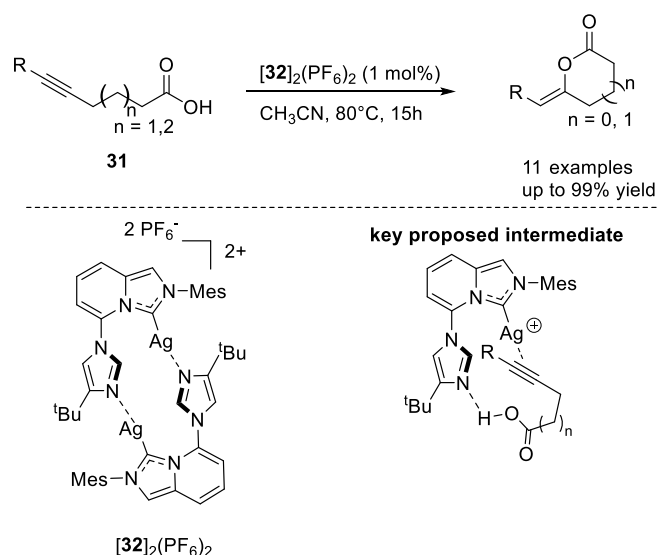
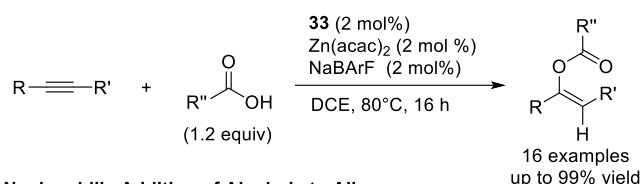


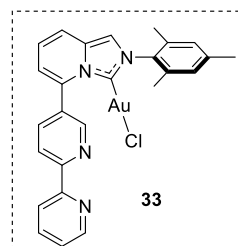
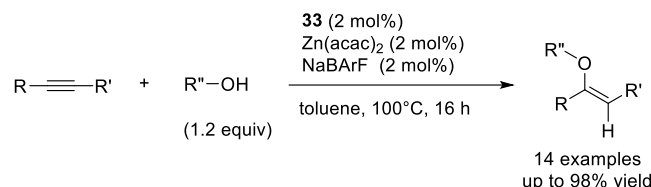
Figure 12. Ag-catalyzed cyclization of alkyne-tethered carboxylic acids **31**.

Very recently, the same authors reported the Au(I) complex **33** in which a 2,2'-bipyridine unit is introduced at the C5 position of the ImPy ligand for the design of cooperative Au-Zn heterobimetallic catalysis (Figure 13).^[32] The bimetallic catalytic system generated *in situ* was tested in the reaction of *O*-nucleophiles such as carboxylic acids, phenols and fluorinated alcohols, with non-activated internal alkynes. The corresponding (acetylated) enol products were obtained in very good yields. The catalytic system was tolerant to the presence of electron-withdrawing and electron donating groups on the carboxylic acid and to a large range of functional groups. However, the presence of a pyridyl group inhibited the catalytic reaction, most likely due to the coordination of pyridine to gold and/or zinc. The comparison of the catalytic activity obtained with the bipyridinyl and monopyridinyl moiety highlighted the crucial role of zinc chelation, which tended to prove the involvement of a cooperative bimetallic Au-Zn system. When the bipyridine unit was replaced by a phenyl group and catalysis was carried out in the presence of 2,2'-bipyridine, the catalytic activity dropped drastically, highlighting the importance of the proximity of the Au and Zn sites to allow for cooperativity. The Au-Zn cooperative mechanism was supported both by single crystal crystallographic studies and by DFT calculations.

Nucleophilic Addition of Carboxylic Acids to Alkynes



Nucleophilic Addition of Alcohols to Alkynes



Proposed catalytic intermediate for the addition of benzoic acid onto alkyne

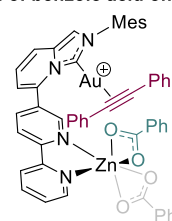


Figure 13. Gold-catalyzed addition of carboxylic acids and alcohols onto non-activated internal alkynes based on heterobimetallic catalysis.

3.3. Asymmetric catalysis with chiral ImPy and TriPy gold(I) catalysts

Despite the outstanding advances realized in homogeneous gold(I) catalysis over the last two decades, the asymmetric version has not experienced the same growth.^[33] The main difficulty resides in the specific, linear coordination geometry of gold(I) center, placing the active site in *trans* position to the ancillary (chiral) ligand, associated with unrestricted rotation around the L-Au and Au-substrate bonds. In addition, the proposed mechanism of the nucleophilic attack onto the coordinated unsaturated CC bond is believed to proceed via an outer-sphere pathway. Three main strategies have been developed up to date: *i*) use of bimetallic gold(I) pre-catalysts supported by atropisomeric diphosphine ligands;^[34] *ii*) Au(I)-based asymmetric counterion-directed catalysis (ACDC);^[35] and *iii*) Development of efficient chiral monodentate ligands mainly based on phosphines and NHC ligands. Although notable examples of efficient systems have been reported up to now,^[36] the design of efficient and selective ligands for given applications is still the subject of intensive research. In this context, the bicyclic ImPy and TriPy NHC platforms have taken a prominent place in the design of chiral NHC ligands for enantioselective gold catalysis,^[8b] as the chiral information could be transferred efficiently to the gold center and to the active site thanks to the L-shape, extended three-dimensional architecture of the ligand platform.

The first breakthrough in this area was realized by Fernández, Lassaletta, López, Mascareñas and co-workers in 2012 with the axially chiral TriPy-gold complexes **34a-b** (Figure 14).^[37]

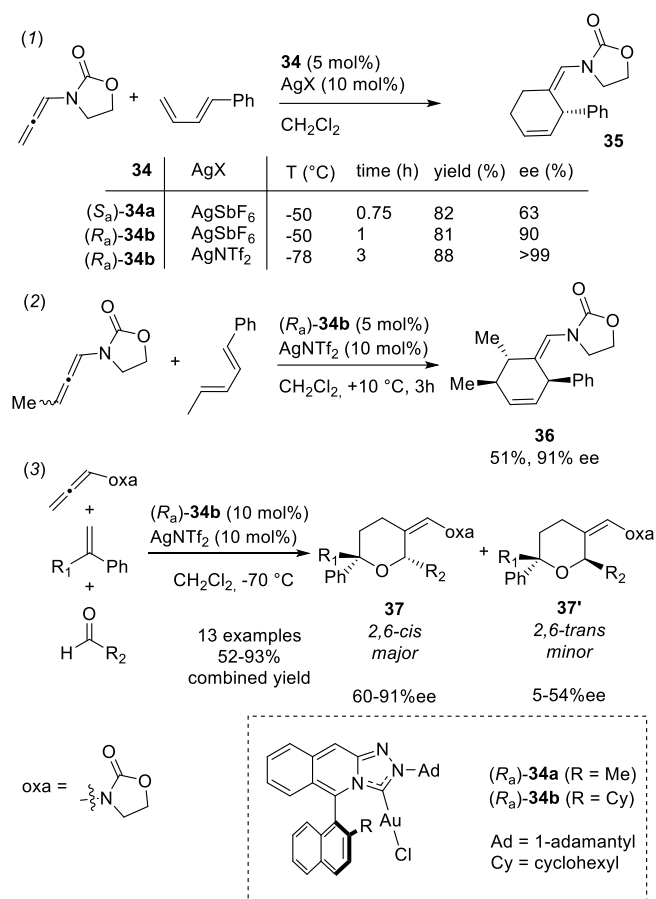


Figure 14. Enantioselective [4+2] cycloaddition of allenamides with dienes and [2+2+2]-cycloaddition of allenamide, alkenes and aldehydes catalyzed by complexes **34**.

Here, the chiral information is brought by the blocked atropoisomerism around the C5-naphthyl bond and is transferred to the gold center by discrimination between the two sides of the naphthyl substituent facing it. The asymmetric induction could be further tuned by modulating the steric demand of the R group (Me or Cy). This new family of ligands was implemented in the enantioselective [4+2] cycloaddition reaction of allenamides and dienes to form the corresponding optically active cyclohexenes and the conditions were optimized on cyclohexene **35** (Figure 14, eq. 1). The bulkier complex **34b** gave better enantioinduction than **34a** and the catalytic system was optimized based on **34b**. The optimal system was compatible with a large range of substrates and its efficiency was highlighted by the reaction of the 1-phenylpent-1,3-diene with the allene-oxazolidinone **36** leading to the synthesis of chiral cyclohexene **37** displaying three new stereogenic carbon centers with complete regio- and diastereo-selectivity and 91% ee (Figure 14, eq. 2). These seminal and promising results of the implementation of TriPy-based ligands in asymmetric gold(I) catalysis highlighted the potential of such N-fused NHC platforms, the rigidity of the latter being the key point to orientate the gold catalytic active species close to the chiral information.

They further took advantage of the efficiency of this system to develop a straightforward and atom-economical enantioselective approach to highly substituted tetrahydropyrans (THP), which are privileged

scaffolds in natural and biologically-active molecules (Figure 14, eq. 3).^[38] The process, consisting in the intermolecular [2+2+2]-cycloaddition between allenamides, alkenes and aldehydes, implied not only the control of the enantioselectivity but also of the regio-, chemo- and diastereo-selectivity. By using catalyst (*R*_a)-**34b**, this three-component coupling reaction afforded the optically active THP as two isomers **37** and **37'** in good to excellent combined yields. Apart from one example, the major isomers **37** were obtained with good to excellent enantiomeric excess up to 91%, while the minor isomers **37'** were obtained with more modest enantioselectivity up to 54% ee. The catalytic system was found tolerant to aromatic, aliphatic and α,β -unsaturated aldehydes. The reaction also performed well with different α -substituted styrene.

Encouraged by the excellent performances of the chiral TriPy-gold(I) complex **34b**, Díez, Fernández, Lassaletta and co-workers developed the axially-chiral ImPy-gold(I) complexes **37** and **38** and evaluated them in the challenging enantioselective gold-catalyzed intermolecular [2+2] cycloaddition of phenylacetylene and methylstyrene (Figure 15).^[39] To meet the steric hindrance requirements of this reaction, the authors introduced bulky groups such as *t*-butyl or cyclohexyl moiety onto the binaphthyl facing the gold center. Of note, the third aromatic cycle was shown not necessary for configurational stability of the ligand in **38** and more importantly of its imidazopyridinium precursor. The corresponding cyclobutene was obtained with relatively low enantiomeric excess (ee) up to 30%. Although modest, these results provide a better understanding of the influence of steric hindrance of the ligand on the enantioselectivity of the reaction.

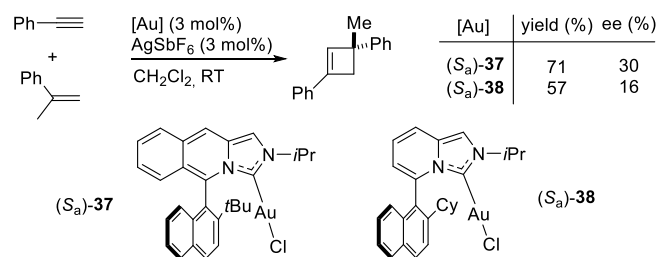


Figure 15. Gold-catalyzed intermolecular [2+2] cycloaddition.

In 2019, Liming Zhang's group reported the synthesis of ImPy-based complexes [(*R*_a,*R*)-**39^R**]₂AuCl and [(*S*_a,*R*)-**39^R**]₂AuCl, displaying a chiral tetrahydroquinoline at the C5-position of the ImPy bicycle, a chiral biaryl axis generated along the coordination process, and a remote amino function susceptible to interact with substrates through secondary interactions (Figure 16).^[40] These ImPy ligands can be seen as the carbenic analogues of the family of chiral bifunctional biarylphosphines, successfully and extensively studied by the same group, and whose general structure is represented by **40**.^[41]

Running title

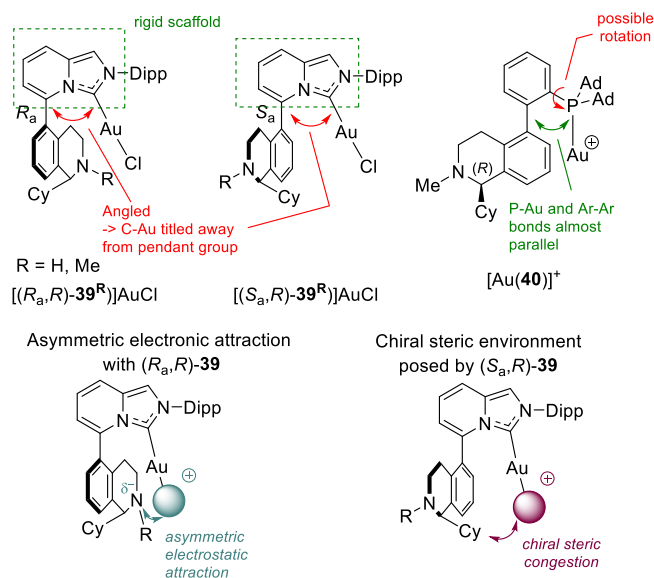


Figure 16. Chiral bifunctional ImPy-gold(I) complexes AuCl(**39**), comparison to bifunctional phosphine **40**, and proposed modes of inducing chirality depending on the chiral axis configuration.

Main differences with the phosphine-based ligands are a stronger donor character of the ImPy ligand, the rigidity of the bicyclic scaffold, and an open angle between the $\text{C}_{\text{NHC}}\text{-Au}$ and the aryl-aryl bonds which might diminish the second-coordination sphere interactions. Noteworthy, the biaryl axis was shown to be fluxional in both $[(R_a,R)\text{-39}^H]\text{AuCl}$ and $[(R_a,R)\text{-39}^H]\text{Au}^+$ complexes with a $(R_a,R)/(S_a,R)$ ratio of 1.00/0.5 and 1.00/0.04 respectively at 80°C at the equilibrium point. It was hypothesized that the preferred (R_a) over the (S_a) configuration and the difference in ratio would arise from electrostatic interaction between the nitrogen atom and the cationic center. Catalysts $[(R_a,R)\text{-39}^R]\text{AuCl}$ and $[(S_a,R)\text{-39}^R]\text{AuCl}$ were then tested in a number of gold(I)-catalyzed model reactions, including the alkoxylation of 1,6-enynes, the cyclopropanation of styrene, and the [2+2] or [4+2] cycloaddition between allenamides and styrene or diene derivatives (Figure 17). Despite the semifluxional nature of the biaryl axis, the two atropisomers were found to induce an effective chirality transfer, with enantiomeric excesses up to 84%. Two modes of transfer of the chirality information were proposed: *i*) either via electrostatic interactions between the partially negatively charged nitrogen atom and the cationic catalytic center with the (R_a,R) atropisomer, or via chiral steric constraint generated by the proximity of the cyclohexyl group and the gold center with the (S_a,R) atropisomer (Figure 15). The two modes are dictated by the axial configuration and often lead to opposite chiral induction, with usually a more effective chiral induction obtained with ligand $(S_a,R)\text{-39}^H$ than with $(R_a,R)\text{-39}^H$.

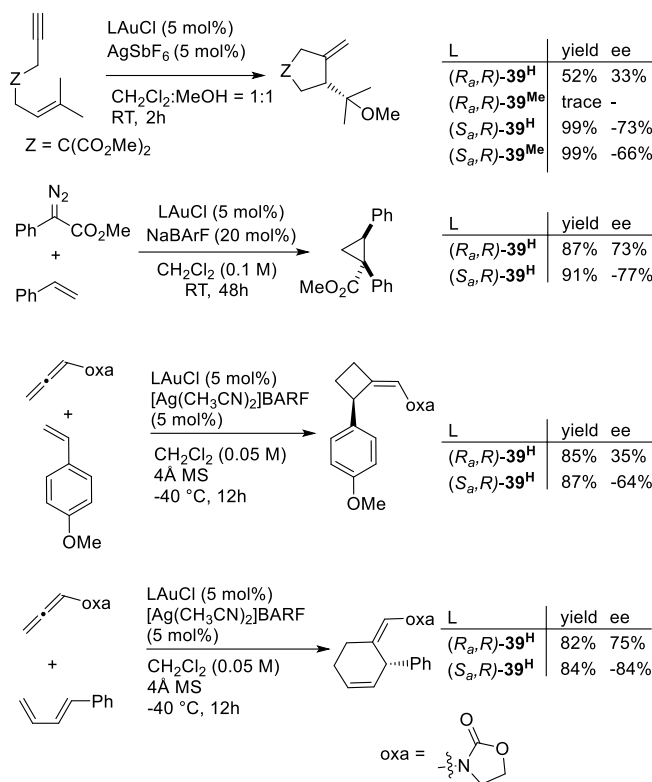


Figure 17. Evaluation of the diastereomeric complexes $[(R_a,R)\text{-39}^R]\text{AuCl}$ and $[(S_a,R)\text{-39}^R]\text{AuCl}$ in a number of gold(I)-catalyzed transformations.

Based on the promising results they obtained in the intramolecular Au(I)-catalyzed hydrocarboxylation of allenenes **29** for the synthesis of the tricyclic oxazindolones **30** (Figure 11), Monari, Ollevier, and Bandini developed an unprecedented enantioselective variant of this transformation on the model substrate **41** (Figure 18).^[30] They took advantage of the geometry of the ImPy platform to introduce chirality in the near-metal environment by introducing an enantiomerically pure secondary alcohol function in the C5 position and developed catalysts **43**. Although the enantiomeric excesses in product **42** remained relatively moderate, this work represented the first enantioselective version of this transformation and showed promising opportunities for future developments by means of the high modularity of the ImPy platform.

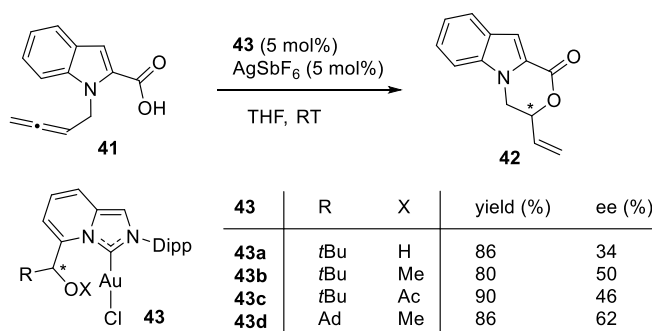


Figure 18. Enantioselective synthesis of the 2,3-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one **42**.

Due to their intrinsic chirality, helicenes and helicene-like units constitute interesting chiral building blocks leading to the development of N- and P-based efficient ligands in asymmetric catalysis.^[42] Considering that creating an extended 3D chiral pocket embedding the distal active site is required for a good chirality induction in gold(I) catalysis, our group in collaboration with Crassous' and Autschbach's groups developed the new L-shape, anionic, helicenic-ImPy ligand class **44**, in which a fluorenyl-derived [5]helicene is grafted on the C5-position of the ImPy bicycle (Figure 19).^[43]

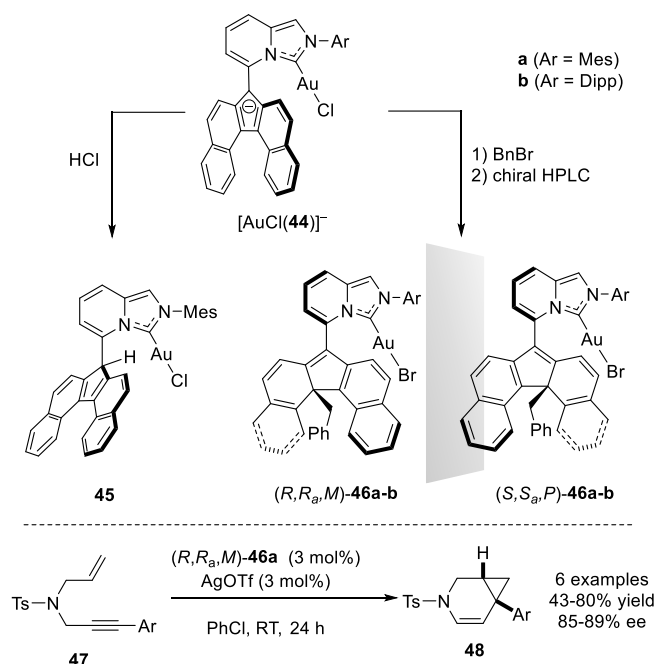


Figure 19. Helicenic-ImPy complexes **45** and **46a-b** and enantioselective cycloisomerization of 1,6-enynes **47**.

In a first move, the protonation of the anionic gold complex $[(\mathbf{44})\text{AuCl}]^-$ led to the achiral neutral complex **45**, in which the fluoreno[5]helicene moiety is not configurationally stable. As the acidic fluorenic proton was shown detrimental to the stability of complex **45** under catalytic conditions, the alkylation of this fluorenyl position was undertaken. Surprisingly, benzylation of complex $[(\mathbf{44})\text{AuCl}]^-$ did not occur at the 'apical' fluorenyl position, mainly due to steric reasons, but at its allylic counterparts in the inner rim of the helicene and led to the racemic mixture of the two enantiomers (R,R_a,M) and $(S,S_a,P)\text{-}\mathbf{46a-b}$ in good yields. Noteworthy, this post-complexation functionalization created three intercorrelated types of chirality, namely a central chirality by generating a stereogenic $\text{C}(\text{sp}^3)$ carbon atom, an axial chirality around the biaryl axis and a helical chirality. More importantly, the ligand functionalization placed the gold(I) center in the asymmetric groove of the helix. After chiral resolution of the two enantiomers by chiral preparative HPLC, their potential of chiral induction was evaluated in the benchmark enantioselective cycloisomerization of N-tethered 1,6-enynes **47** leading to the bicyclic products **48**. The enantioselectivity of the reaction appeared to be dependant of the steric hindrance of the aryl group positioned on the nitrogen atom, the mesityl-based

derivatives **46a** leading to the best results. The optimal system based on $(R,R_a,M)\text{-}\mathbf{46a}$ was then found quite general as it allowed the cycloisomerization of enynes **47** having various stereoelectronic aryl substituents in 43-80% yield and almost constant, good ee between 85 and 89%. This report constituted also the first example of the successful implementation of a configurationally-stable [5]-helicenoid unit in enantioselective catalysis.

4. Summary

In conclusion, fused poly-heterocyclic carbenes have emerged as privileged NHC platforms in gold catalysis over the last few years. Their inherent rigid structure and specific geometry, their synthetic modularity allowing tuning of electronic and steric effects, and the π -delocalization over their extended polyaromatic scaffold render them unique and particularly suited for NHC-gold catalysis. The recent major achievements using the N-fused heterobicyclic imidazo- and triazo-pyridine NHC-gold(I) complexes are especially remarkable and promising for further developments. We indeed believe that this rigid, bicyclic platform offers unique opportunities to develop efficient asymmetric, cooperative, or stimuli-controlled gold catalysts among others by grafting the suitable functionality on the lateral, 'gold-center facing' substituent, thanks to the 'L-shape' geometry of the scaffold. It is also worth noting that the CAaRC and indazolin-3-ylidene ligands display the same geometry as ImPy and TriPy carbenes but with drastically-different electronic properties and synthetic approaches. New and interesting perspectives could be envisaged by combining the 'L-shape' concept with these latest electrophilic carbenic scaffolds.

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