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Review

Chiral *N*-heterocyclic Carbene Gold Complexes: Synthesis and Applications in Catalysis

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Abstract: *N*-Heterocyclic carbenes have found many applications in modern metal catalysis, due to the formation of stable metal complexes, and organocatalysis. Among a myriad of *N*-heterocyclic carbene metal complexes, gold complexes have gained a lot of attention due to their unique propensity for the activation of carbon-carbon multiple bonds, allowing many useful transformations of alkynes, allenes, and alkenes, inaccessible by other metal complexes. The present review summarizes synthetic efforts towards the preparation of chiral *N*-heterocyclic gold(I) complexes exhibiting C_2 and C_1 symmetry, as well as their applications in enantioselective catalysis. Finally, the emerging area of rare gold(III) complexes and their preliminary usage in asymmetric catalysis is also presented.

Keywords: chiral *N*-heterocyclic crabene; gold complexes; asymmetric catalysis

1. Introduction

Homogenous, enantioselective gold catalysis has witnessed growing attention of the synthetic community due to the element's unique propensity to act as a soft, carbophilic Lewis acid. This specific mode of activation of multiple bonds enables a plethora of unusual transformations [1–11]. Considering the enantioselective transformations catalyzed by gold compounds [12–21], the main difficulty arises from the structural features of the respective complexes. Gold(I) complexes exhibit a linear geometry with unrestricted rotation around L-Au as well as Au-substrate bonds (Figure 1) [22–25]. In addition, the proposed mechanism of nucleophile approach is believed to proceed via outer-sphere pathways [17]. Due to these geometrical and conformational constraints, the transfer of chiral information from the ligand to the substrate in gold-catalyzed reactions becomes difficult and makes enantioselective gold(I) transformations a challenging field. Although some advances have been achieved using phosphine ligands, their tedious synthesis and, in some cases, intrinsic ease of oxidation excludes practical applications on a large scale. In contrast, the rigid structure of NHCs (*N*-heterocyclic carbenes) provides an excellent opportunity to form stable gold complexes with a well-defined chiral environment, as was proven in the case of other metals, such as palladium [26–29], ruthenium [30–33] or copper [34–42]. Moreover, adequately planned structure of NHC ligands allows for tuning of their electronic and steric properties, which is not easily achievable in the case of phosphines [43,44].

In addition, gold(III) complexes, in contrast to gold(I) compounds, should provide an alternative solution for efficient, enantioselective gold(III) catalysis. Due to their square-planar geometry [45–47] (Figure 1), the creation of a chiral pocket for enantioselective processes seems more viable. The key challenge to overcome is the intrinsic instability of gold(III) complexes arising from the high redox potential and smooth reduction of Au(III) leading to Au(0) or Au(I) compounds [45,48–50].

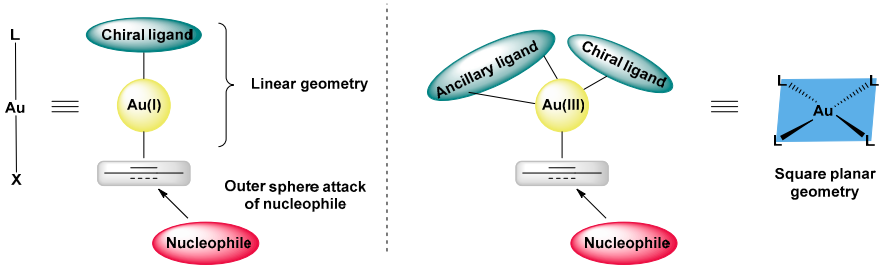


Figure 1. The geometry of gold(I) and gold(III) complexes, reproduced with the permission from Royal Chemical Society from [17] (Figure 1).

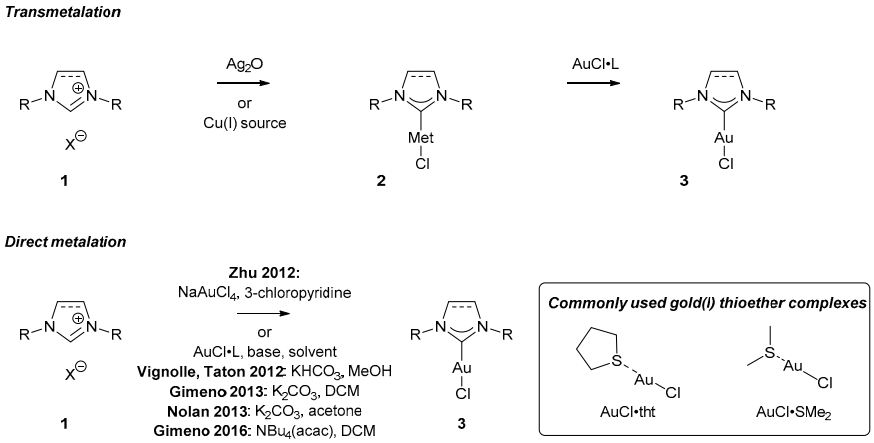
Considering all the above aspects, *N*-heterocyclic carbene gold complexes offer an excellent opportunity for the development of efficient enantioselective processes. Although many excellent reviews devoted to the synthesis of phosphines (and related ligands) and *N*-heterocyclic carbene complexes have been published, no separate review covering the synthesis of chiral *N*-heterocyclic carbene gold(I) and gold(III) complexes has appeared to date. Due to the privileged role of chiral *N*-heterocyclic carbene ligands in stabilizing transition metal complexes, in contrast to phosphines, it is able to create a chiral environment around the metal center, *N*-heterocyclic carbenes enable the development of enantioselective processes. For these reasons, the excellent properties of NHCs as ligands have become the underpinning of the development of modern enantioselective gold catalysis since the beginning of the 21st century. The aim of this comprehensive review is to present the synthetic strategies leading to chiral *N*-heterocyclic carbene gold complexes with special emphasis on the pathways leading to *N*-heterocyclic carbene precursors. The ever-growing synthetic applications of gold complexes in enantioselective processes are also discussed comparatively in a separate section, providing an outlook on the unique catalytic activity in the activation of multiple carbon-carbon bonds for the attack of carbon- or heteroatom-centered nucleophile. The scope of the article covers literature data up to July 2019.

2. Mono-*N*-Heterocyclic Gold(I) Complexes

The synthetic route leading to gold(I) complexes with emphasis on the detailed discussion of the preparation of *N*-heterocyclic carbene precursors is presented in Sections 2.1–2.4. Regarding the final formation of gold(I) complexes, two strategies have been developed thus far (Scheme 1). The older synthetic route involved the formation of a silver complex by the action of silver oxide on *N*-heterocyclic carbene precursor **1** and subsequent transmetalation with gold(I) chloride/thioether complex [51]. Dimethyl sulfide gold(I) chloride is commonly applied. However, higher yields are observed for tetrahydrothiophene (tht) gold(I) chloride in some cases (*vide infra*). Among other metal complexes able to participate in the transmetalation step, achiral *N*-heterocyclic carbene copper(I) chloride complexes have been applied successfully [52]. Although transmetalation of silver complexes has comprised over 70% of published work until 2009 [53], examples of unsuccessful application of this method have also been reported [54].

Because of the low atom economy of transmetalation (one equivalent of silver is consumed) and possible contamination of gold(I) complexes by others metals from precursors (silver or copper), especially undesirable in catalysis, further studies were directed towards more-straightforward methods. Direct reactions of *N*-heterocyclic chloride salts **1** with $NaAuCl_4$ in 3-chloropyridine [55] or *N*-heterocyclic hydrogen carbonate salt [56] with $AuCl{\bullet}SMe_2$ have been reported. Unfortunately, these methods exhibit severe limitations. The real breakthrough in the area was achieved independently at the same time by Gimeno [57] and Nolan [58]. The formation of gold(I) complexes **3** was easily accomplished by the reaction of $AuCl{\bullet}SMe_2$ with chloride salts of *N*-heterocyclic carbene precursors **1** in the presence of K_2CO_3 in DCM or acetone. Recently, the application of $NBu_4(acac)$ as a base has been reported for the efficient preparation of sterically unhindered complexes [59]. In addition, stronger bases are occasionally used, such as KHMDS [potassium bis(trimethylsilyl)amide] [60] or the

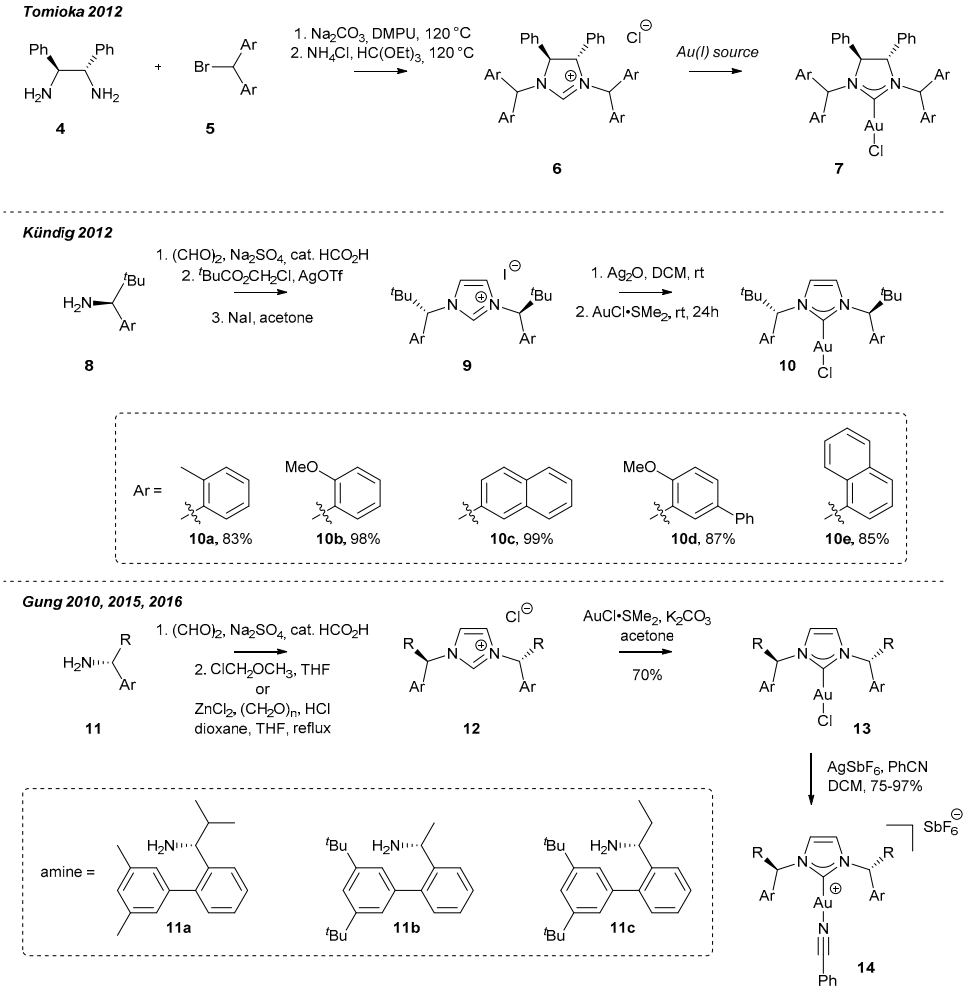
mixture of NaH/KO*t*Bu [61] (NaH is used as the stoichiometric base, whereas KO*t*Bu acts as a phase transfer catalyst) in ethereal solvents. The combination of AuCl•SMe_2/acetone constitutes arguably one of the most popular methods, widely used nowadays also for the synthesis of enantiomerically pure complexes.



Scheme 1. Common strategies for the synthesis of *N*-heterocyclic carbene gold(I) complexes.

2.1. Cyclic C_2-Symmetric Gold(I) Complexes

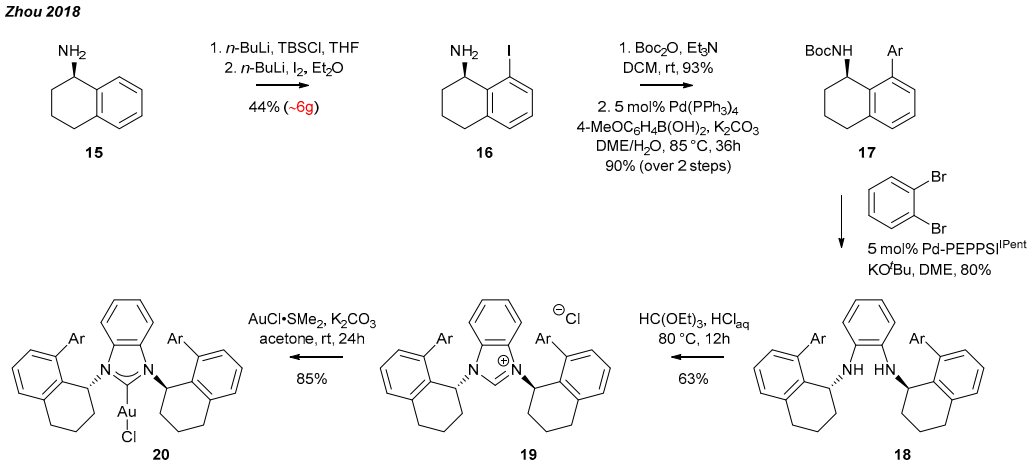
The first example of a chiral NHC-gold(I) complex and its application in asymmetric catalysis was published by Tomioka in 2010 (Scheme 2) [62]. The authors prepared a series of C_2-symmetric *N*-heterocyclic carbene precursors **6** via straightforward alkylation of 1,2-diphenyl diamine (**4**) with benzhydryl bromide and subsequent closure of the imidazolinium ring under standard conditions, i.e., with NH_4Cl and an orthoester as the solvent. Unfortunately, a detailed procedure for the synthesis of the gold(I) complexes is not provided (a detailed procedure of NHC precursor synthesis is reported in a separate article [42]). Shortly thereafter, in 2012, Kündig applied a similar protocol, using a broad range of chiral benzylic amines **8** bearing mainly a *t*-butyl group attached to the benzylic positions. In contrast to Tomioka's ligands, Kündig's synthesis seems to be more complicated for two reasons. First, benzylic amines **8** used in this protocol are not commercially available and had to be prepared by separation of the racemic mixtures. Second, the final cyclization was performed under conditions developed by Glorius [63], which needed a stoichiometric amount of the expensive AgOTf. However, the synthesis of carbene precursor **9** is quite simple and easily scalable [64]. Next, imidazoline **9** precursors were transformed into the respective gold(I) complexes **10** (Scheme 2) via transmetalation of the respective silver complexes with excellent yields, also in the case of imidazolinium derivatives (not shown in Scheme 2).



Scheme 2. The synthesis of C_2-symmetric gold(I) complexes from chiral amines.

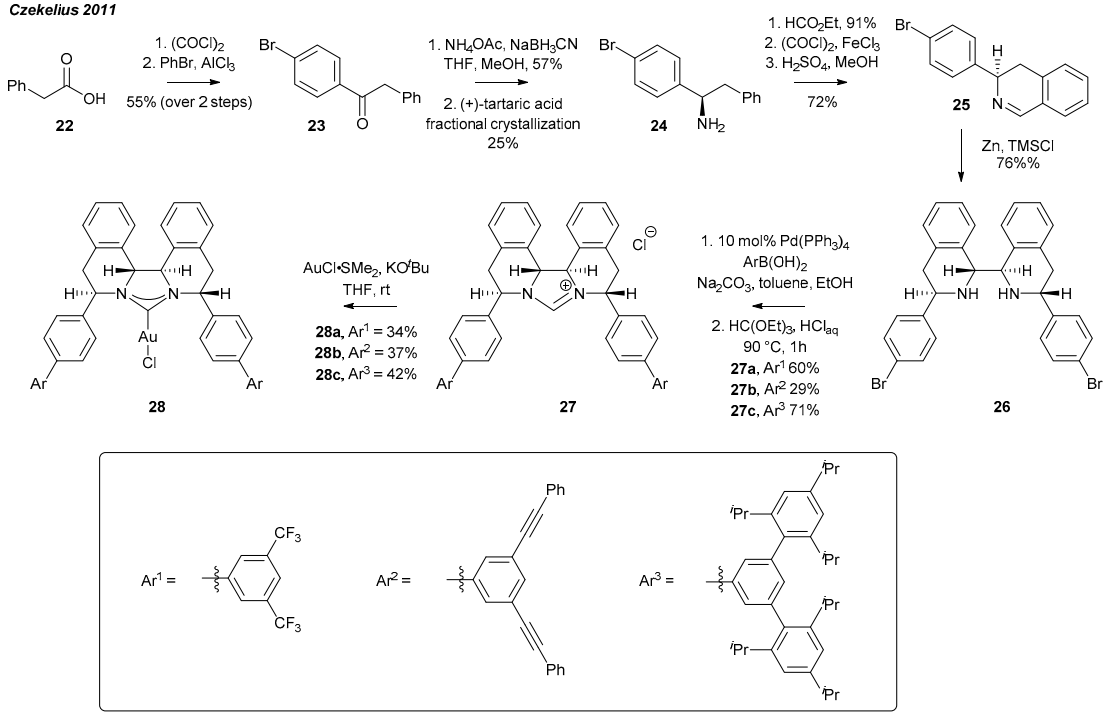
The synthetic route leading to C_2-symmetric complexes **13** decorated with biphenyl subunits was developed by Gung (Scheme 2) [65–67]. In contrast to Kündig's methodology, the authors used less expensive sources of the precarbenic unit, e.g. chloromethyl ethyl ether or paraformaldehyde. In this case, the respective gold(I) complexes **13** were synthesized with moderate yields directly from imidazolium salts **12** via a protocol developed by Nolan [58]. Considering the activity of gold(I) chloride complexes in catalysis, in particular enantioselective processes, they have to be activated prior to use by the abstraction of the halide ion with silver salts bearing weakly coordinating anions, such as tetrafluoroborate or hexafluorophosphate [68]. Indeed, Gung proved that gold(I) complexes **14** could form stable ionic complexes with the metal center additionally protected by a nitrile ligand [66].

A similar approach to chiral sandwich complexes based on chiral *(R)*-1-aminotetralin (**15**) has been developed by Zhou et al. (Scheme 3) [69]. The chiral amine building blocks **17** were synthesized from chiral 1-aminotetralin **15** by *ortho*-metalation-iodination and Suzuki coupling to give amine **17** which was used in subsequent Buchwald-Hartwig amination. The respective chiral diamine **18** was cyclized with triethyl orthoformate under acidic conditions. Benzimidazolium salt **19** was further utilized in Nolan's protocol to give gold(I) complexes **20** with 85% yield. It should be mentioned that Zhou's ligand represents one of the most sterically hindered *N*-heterocyclic carbene ligands, with $\%V_{bur}$ around 51% measured for complex **20** [70,71]. The conformation of compound **20** also revealed that *para*-methoxyphenyl substituents are located in a parallel arrangement relative to the benzimidazolium skeleton.



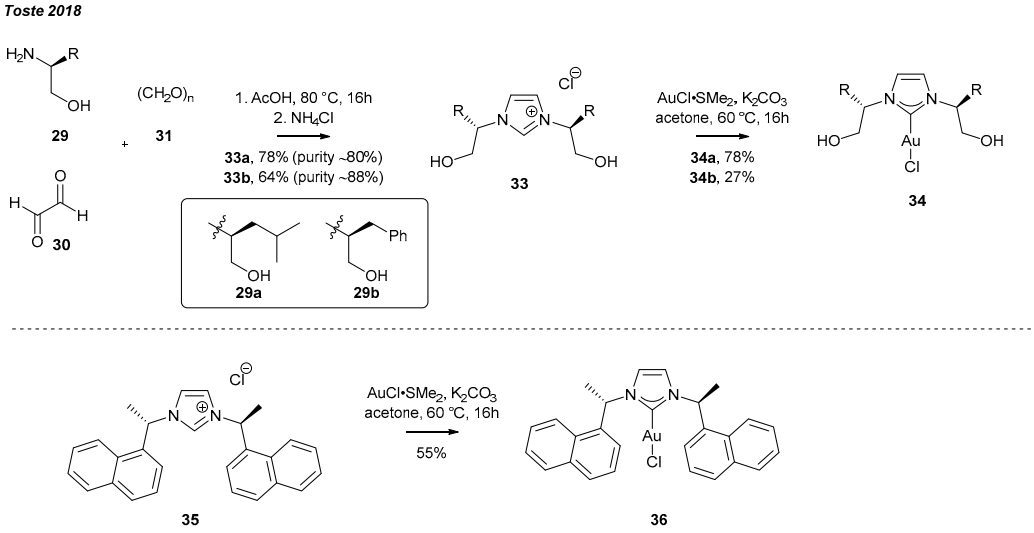
Scheme 3. The synthesis of a gold(I) complex from (*R*)-1-aminotetralin.

An elegant approach to C_2-symmetric gold(I) complexes was described by Czekelius et al. [72] (Scheme 4), inspired by previous Herrmann's work [73]. The synthetic approach involves chiral amines **24**, readily available from the corresponding phenylacetic acid **22** via the Friedel-Crafts reaction of bromobenzene and fractional crystallization of the corresponding tartaric acid amine salt upon reductive amination. The resulting amine **24** was further formylated and subjected to Bischler-Napieralski cyclization to give 3-aryl-substituted dihydroisoquinoline **25**. Subsequent reductive coupling afforded the basic diamine skeleton **26** into a single diastereomer, which appeared a perfect platform for structural ligand diversification via Suzuki coupling. The functionalized diamines **26** were then cyclized into imidazolium salts **27** with triethyl orthoformate to give the products with yields in the range of 49–94% (for selected examples, see Scheme 4). The formation of gold(I) complexes **28** was accomplished under rather unusual conditions, by the reaction of gold(I) chloride with a carbene generated by the action of KO*t*Bu.



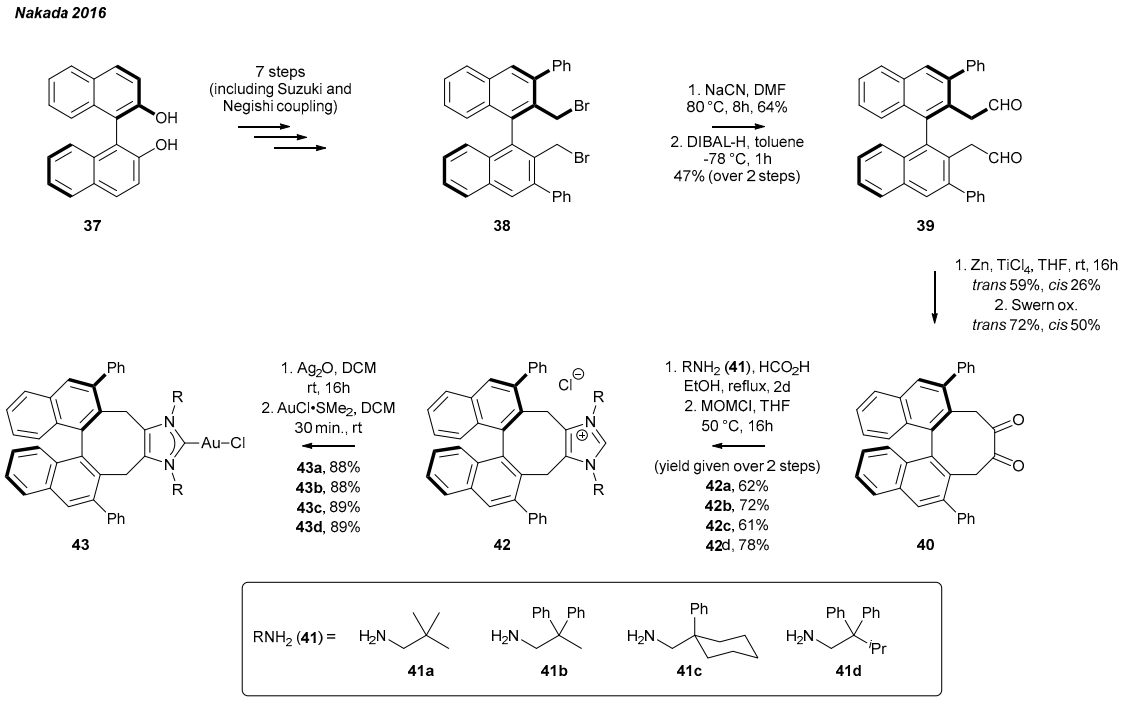
Scheme 4. The synthesis of C_2-symmetric gold(I) complexes accessible via a reductive coupling.

The application of other chiral building blocks has recently been reported by the Toste group (Scheme 5) [74]. Besides chiral amines, amino alcohols **29** were also utilized in the synthesis of C_2-symmetric gold(I) complexes **34**. The respective NHC precursors **33** were obtained via a one-pot protocol [39,75] and were subsequently transformed into gold complexes by the reaction with AuCl•SMe_2 in acetone, mediated by K_2CO_3. However, the yield was strictly dependent on the substituents. A similar protocol was used for the synthesis of gold(I) complex **36** from a chiral naphthylamine.



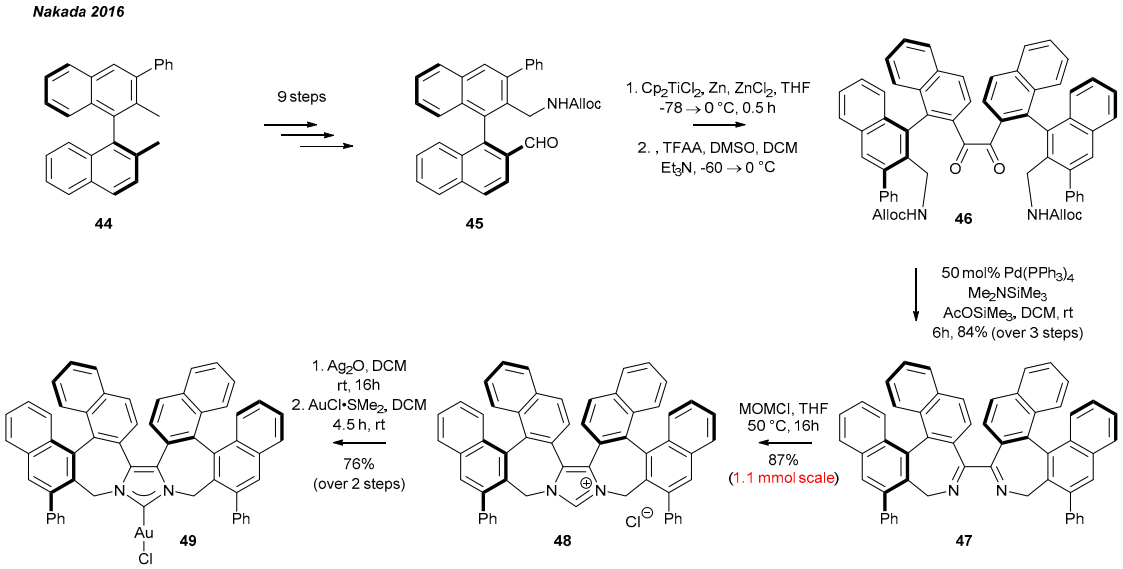
Scheme 5. The synthesis of C_2-symmetric gold(I) complexes bearing chiral amino alcohol subunits.

Further development in this area has focused on the synthesis of NHC complexes bearing an axially chiral subunit (Scheme 6). The first examples of this class of gold complexes were reported by Nakada in 2016 [76]. Starting from commercially available (*R*)-BINOL (**37**), dibromide **38** was prepared in a seven-step linear sequence, including Suzuki and Negishi coupling [77]. Then, dibromide **38** was transformed into bisaldehyde **39** and subjected to titanium-mediated pinacol coupling. After Swern oxidation, the key diketone **40** was obtained in good yield. At this stage, structure diversification was attained applying a series of sterically hindered amines **41**. The final cyclization, forming the imidazolium skeleton, was performed with MOMCl as the precarbenic unit. The respective NHC precursors **42** were transformed into gold(I) complexes **43** via transmetalation of silver complexes. It should be emphasized that the yield of gold(I) complexes **43** remains excellent, taking into account the structural complexity of the NHC ligand.



Scheme 6. The synthesis of NHCAuCl complexes based on a binaphthyl skeleton fused with an eight-membered ring.

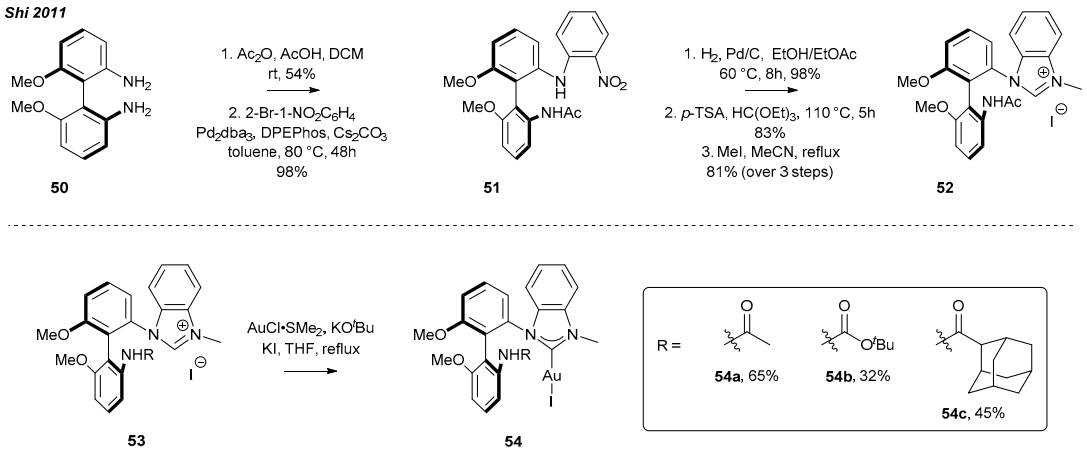
An interesting extension of this approach was published by Nakada's group in 2016, providing access to NHCAuCl complex **49** with an extended aromatic skeleton (Scheme 7) [78]. The developed strategy was based on the construction of acyclic diketone **46** from chiral biphenyl aldehyde **45** by a series of simple transformations (nine steps), including a pinacol coupling. Subsequently, the removal of the nitrogen protecting group caused a spontaneous cyclization to form seven-membered bisimine **47**. Then, **47** was used to prepare imidazolium salt **48** and gold(I) complex **49** under standard conditions. It should be mentioned that Nakada's approach to gold(I) complexes **49** is far from practical due to the long linear sequence needed to build the skeleton of the NHC precursor. However, it offers a unique approach for the transfer of chiral information from a remote chiral skeleton through achiral substituents covalently bonded to nitrogen atoms.



Scheme 7. The synthesis of NHCAuCl complexes based on a binaphthyl skeleton.

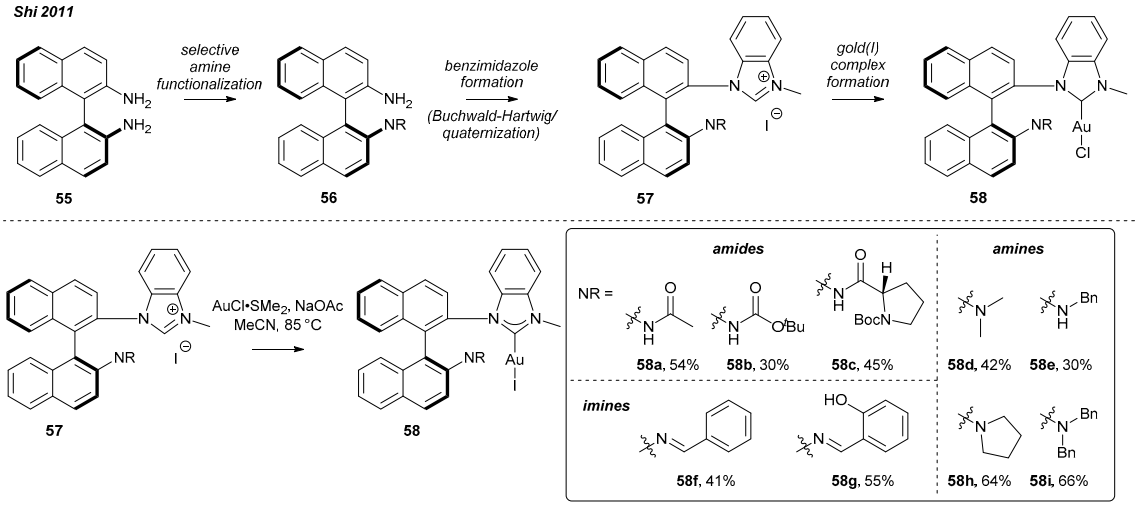
2.2. Cyclic Non-C_2-Symmetric Gold(I) Complexes

C_1-Symmetric gold(I) complexes **54** with an axially chiral backbone were reported for the first time by Shi et al. in 2011 (Scheme 8) [79]. Starting from axially chiral (*S*)-6,6-dimethoxy-2,2′-biphenyl diamine (**50**), monoacetylation and Buchwald-Hartwig amination resulted in nitroamine **51**. The nitro group was reduced and the corresponding amine was subjected to cyclization with triethyl orthoformate. Quaternization of the benzimidazole derivative with MeI resulted in salt **52** with excellent yield. A similar approach was used to synthesize NHC precursors bearing different amide functionalities. Finally, gold(I) complexes **54** were achieved by the treatment of benzimidazolium salts **53** with gold(I) chloride in the presence of strong bases, such as KO*t*Bu.



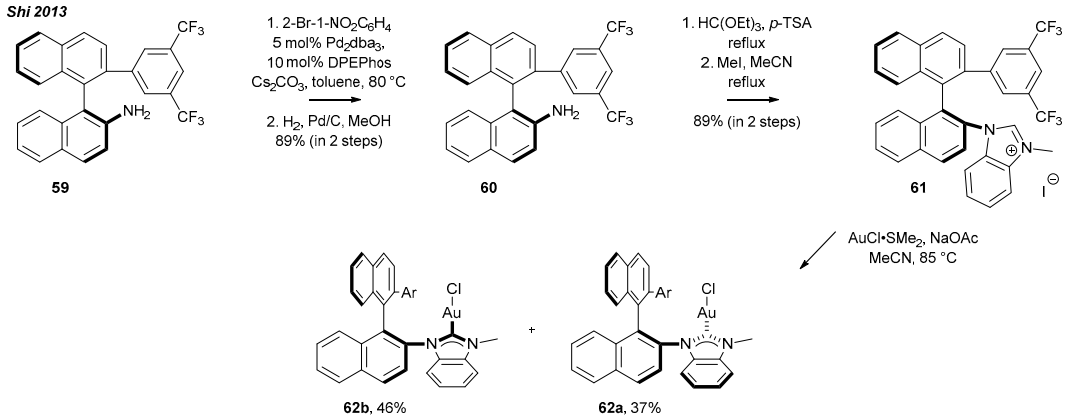
Scheme 8. The synthesis of *N*-heterocyclic carbene precursors bearing a biphenyl subunit.

Bearing in mind the direct availability of compounds for the synthesis of the NHC precursor, Shi et al. developed a similar synthetic route from (*S*)-BINAM (**55**) (Scheme 9) [80,81]. As previously described, the synthetic sequence included the Buchwald-Hartwig monoarylation of (*S*)-BINAM (**55**), benzimidazole formation, and subsequent quaternization with different electrophiles (not shown in Scheme 9). It should be mentioned that an enormous series of C_1-symmetric complexes **58** were obtained with moderate yields, applying the previously developed procedure, irrespective of the functional groups present. Tertiary or secondary amines, amides (including proline) or imines were tolerated under conditions needed for the formation of gold(I) complexes **58** (Scheme 9). In contrast to biphenyl-derived complex **54** (Scheme 8), the preparation of binaphthyl complexes **58** required a weaker base, namely NaOAc instead of KO*t*Bu.



Scheme 9. The synthesis of *N*-heterocyclic carbene precursors bearing a binaphthyl subunit.

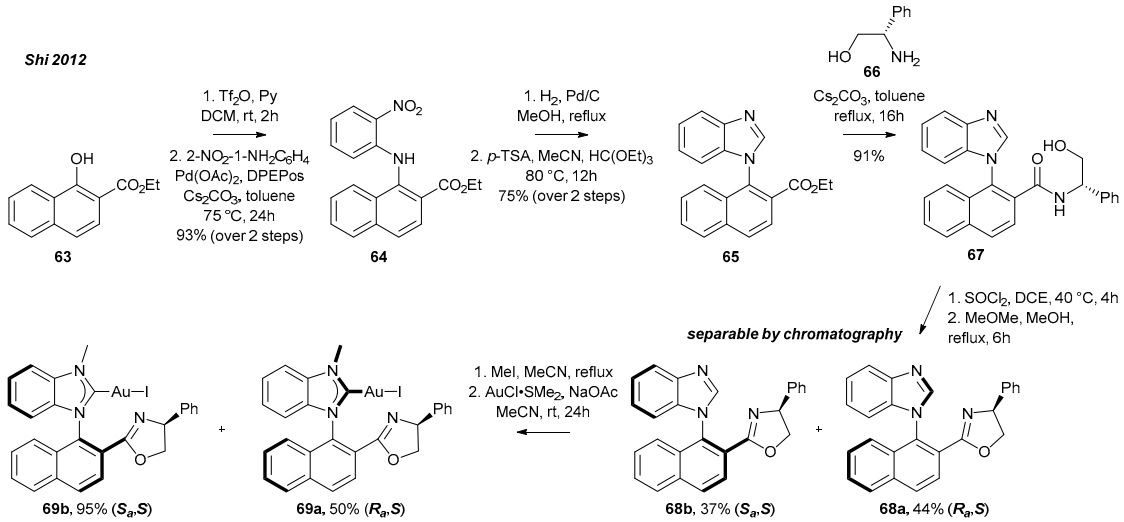
Further studies of the Shi group have provided an elegant route to axially chiral complexes **62**, starting from axially chiral amine **59** decorated with an electron-deficient aryl substituent (Scheme 10) [82]. Similar to previous reports by Shi et al. [79–81], C-N coupling and benzimidazole quaternization were used to prepare the chiral NHC precursor with an excellent 79% yield after four steps. The respective NHC precursor **61** was transformed into gold(I) complex **62**. However, a mixture of diastereomeric complexes **62a** and **62b** was formed and, fortunately, it could be separated by the conventional flash chromatography. Further crystallographic structural studies confirmed the weak gold interaction with the π-electrons of the aromatic ring, responsible for the formation of diastereomeric rotamers. The distance of the gold atom to the aromatic ring of the naphthyl moiety, estimated by X-ray analysis, equals 3.3Å.



Scheme 10. The synthesis of gold(I) complex bearing a biphenyl moiety attached to a benzimidazolium skeleton.

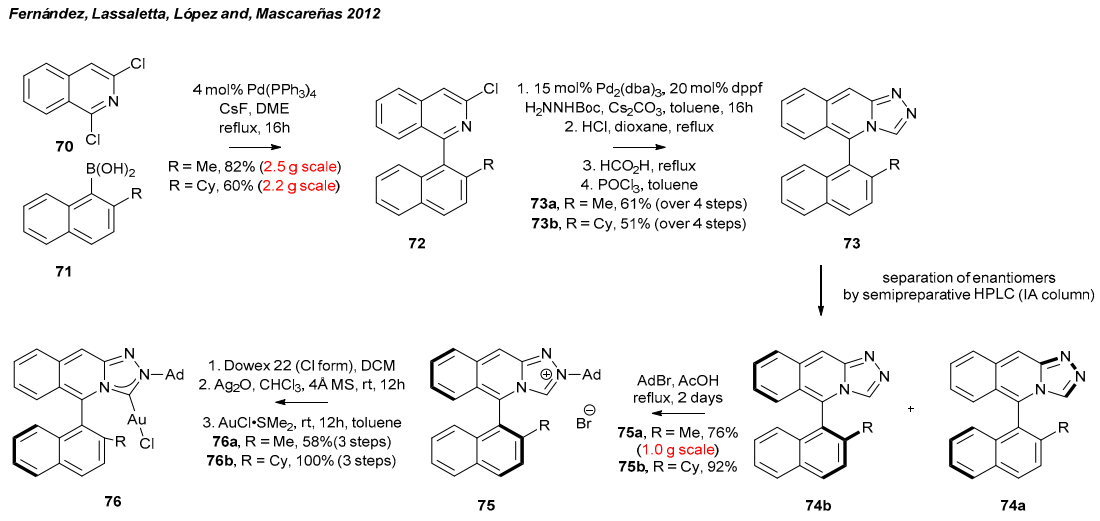
A family of axially chiral NHC precursors **68** accessible via resolution of atropoisomeric diastereomers has recently been developed by the Shi group (Scheme 11) [83]. The synthetic pathway commenced with C-N coupling triflate with 2-nitroaniline to afford a secondary amine **64**. After simple functional group manipulations, ester **65** bearing a benzimidazole subunit was treated with chiral amino alcohol **66** to give amide **67** which was cyclized upon treatment with thionyl chloride. The mixture of atropoisomeric diastereomers **68a** and **68b** was easily separated by chromatography on silica gel, providing access to stereochemically pure oxazolines **68a** and **68b**. Further quaternization resulted

in benzimidazolium salts, which were converted into gold(I) complexes **69a** and **69b**. Interestingly, higher yields were attained for the formation of (S_a,*S*) isomer **69b** than for (R_a,*S*) **69a**.



Scheme 11. The synthesis of axially chiral gold(I) complexes **69a** and **69b** by the chromatographic separation of a benzimidazole precursor.

A much more straightforward approach to the axially chiral gold complexes **76** was developed by Fernández et al. [84]. The proposed short synthetic sequence is based on the initial construction of racemic binaphthyl scaffold **73** and subsequent resolution of enantiomers by preparative chiral HPLC. The merging of the two fragments of binaphthyl derivative **72** was accomplished by the Suzuki coupling of 1,3-dichloroisoquinoline (**70**) with boronic acid **71**. Then, 2-chloroisoquinoline moiety in **72** was used to build the triazole core via coupling with protected hydrazine, deprotection, formylation, and final cyclization. The racemic mixture of triazoles **73** was used to resolve enantiomers on a semi-preparative Chiralpak IA column. The respective triazoles **74a** and **74b** were alkylated with adamantyl bromide to afford triazolium salts **75** which were used to prepare gold(I) complexes **76** via transmetalation (Scheme 12). Although the proposed sequence involves the resolution of atropoisomers by expensive chiral HPLC, it provides access to the unique family of chiral gold(I) complexes **76**, efficient in many enantioselective transformations (*vide infra*). It should be noted that the chromatographic resolution gave access to gram amounts of enantiomer **74b**.



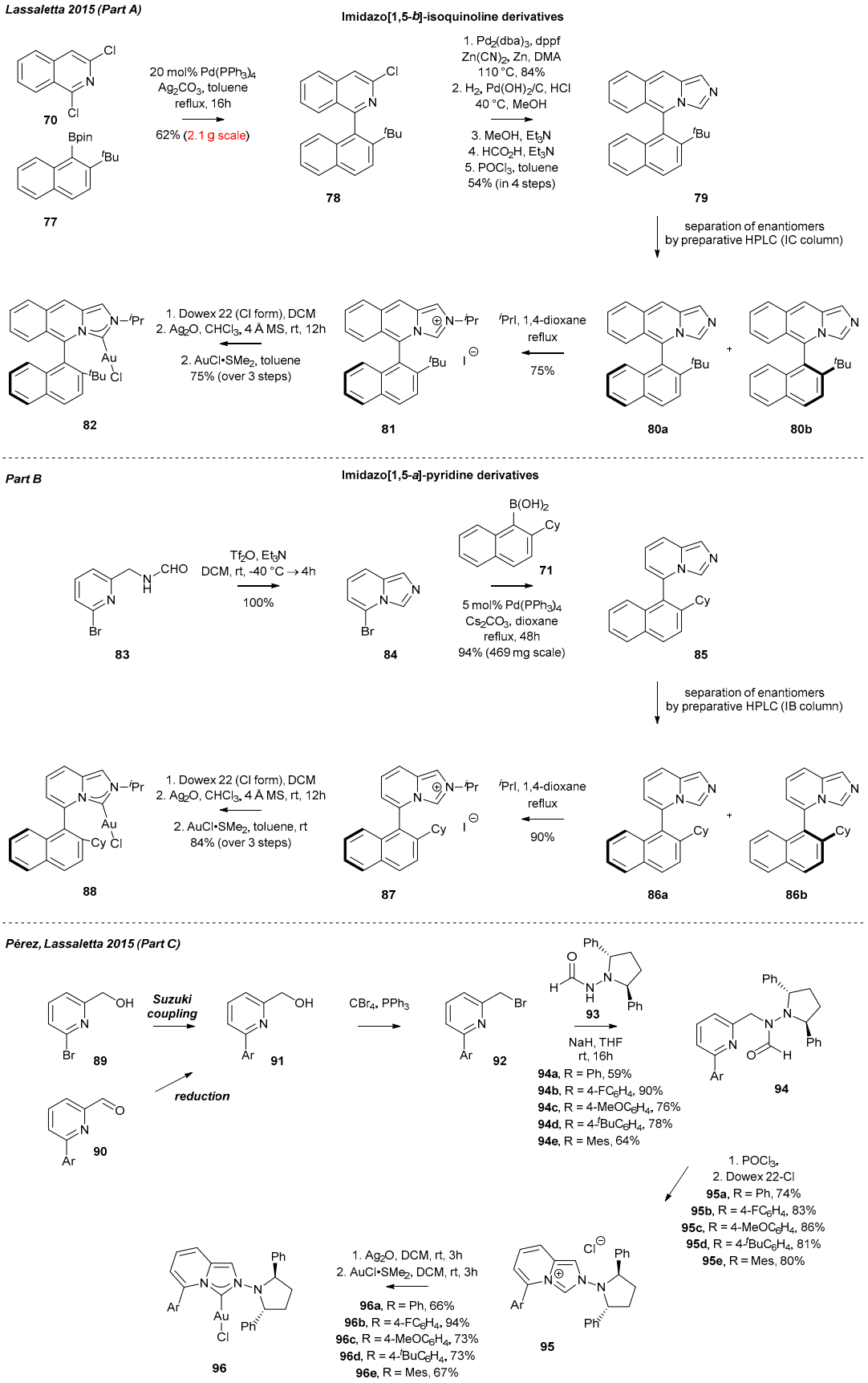
Scheme 12. The synthesis of axially chiral triazolium gold(I) complexes via resolution of a racemate.

Further studies by Diéz et al. [85] have led to an interesting extension of previous studies, providing access to axially chiral complexes **82** with an imidazole subunit fused to a rigid, chiral binaphthyl framework. First, the authors proposed a short synthetic pathway to imidazo[1,5-*b*]quinoline derivatives **79**. Commercially available 1,3-dichloroisoquinoline (**70**) was coupled with functionalized boronic acid **77** via Suzuki coupling to form the key racemic binaphthyl skeleton **78**. The chloropyridine moiety was then transformed into cyanide by a palladium-catalyzed protocol. Subsequent reduction, formylation, and cyclization resulted in imidazo[1,5-*b*] quinoline **79** with high yield. The racemic **79** was separated into enantiomers on a semi-preparative chiral IC column and converted to imidazolium salt **81** by the treatment with an alkyl halide at a higher temperature. The obtained iodide salt **81** was subjected to ion exchange using Dowex-22 chloride form and the respective chloride salt was used to obtain the gold(I) complex **82** via a transmetalation route (Scheme 13, Part A). A similar approach, based on palladium-catalyzed coupling, HPLC resolution of enantiomers, and subsequent Ag/Au transmetalation, has been used to prepare analogues of complex **82** by the same research group [86].

It should be mentioned that the proposed approach also offers access to imidazo[1,5-*a*]pyridine derivatives **88** by a shorter synthetic pathway (Scheme 13, Part B). The key racemic biphenyl derivative **85** was readily accessible in only two steps. Formamide **83** was first cyclized under conditions developed by Shi [87] (Tf_2O/Et_3N), and the fused imidazole derivative **84** was subjected to Suzuki coupling.

A similar strategy for sterically demanding chiral gold(I) complexes **96** based on imidazo[1,5-*a*]pyridine has been proposed by Pérez and Lassaletta (Scheme 13, Part C) [88]. The synthetic approach involved the preparation of formamide **94** by the alkylation of chiral *N*-formyl hydrazine **93**. The corresponding bromides **92** are readily accessible by the reduction of aldehyde **90** or, alternatively, by the Suzuki coupling of bromopyridine **89**. The corresponding amides **94** were then cyclized and subjected to anion exchange with Dowex-22 Cl, resulting in imidazo[1,5-*a*]pyridin-3-ylidene salts **95**. It should be mentioned that the cyclization step can also be achieved with a sterically crowded 2,4,6-triisopropylphenyl substituent connected to the pyridine skeleton (not shown in Scheme 13). However, it was necessary to use a combination of Tf_2O and Et_3N [88]. This synthetic method provides access to the most sterically crowded salts. The % Vbur, characterizing the steric hindrance [70], was calculated using the SambVca web applications [71,89] and ranges from 41.5% to 59.9%. The preparation of the gold(I) complexes **96** was carried out in the usual way by transmetallation.

The structural studies of imidazo[1,5-*a*]pyridine-3-ylidene metal complexes **96** revealed that complexes of **96** type exhibit a remarkable degree of flexibility resulting from the rotation of the pyrrolidine unit around the N-N bond, as well as Walden inversion at the exocyclic nitrogen atom (Figure 2). The authors also suggested that the Walden inversion involved the possible syn- or antiperiplanar spatial arrangement of the nitrogen lone pair with respect to metal-carbene carbon bond. As a consequence, the authors suggested that the Walden inversion is mainly responsible for different values of $\%V_{bur}$. For examples, $\%V_{bur}$ of the silver complex **96c** varies from 47.3% to 54.7%.



Scheme 13. The synthesis of gold(I) complex based on imidazo[*1,5-b*]-isoquinoline and imidazo[*1,5-a*]-pyridine skeleton, reproduced with the permission from Georg Thieme Verlag KG from [44] (Scheme 26).

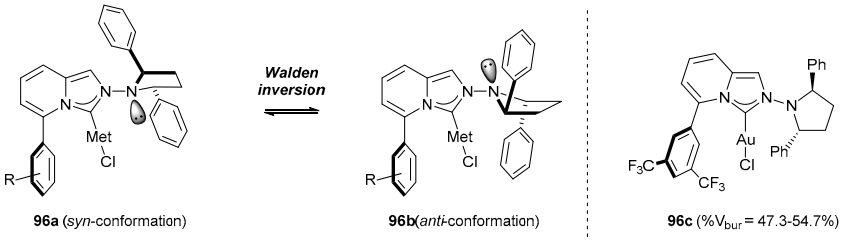
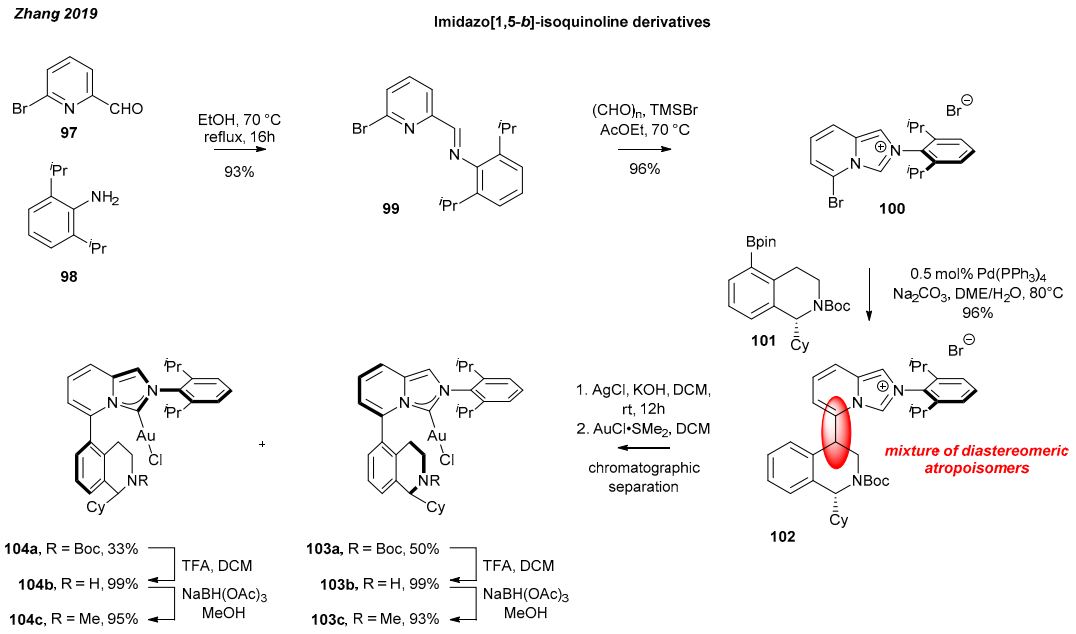


Figure 2. Walden inversion of metal complexes bearing chiral 2,5-diphenylpyrrolidin-1-yl subunit.

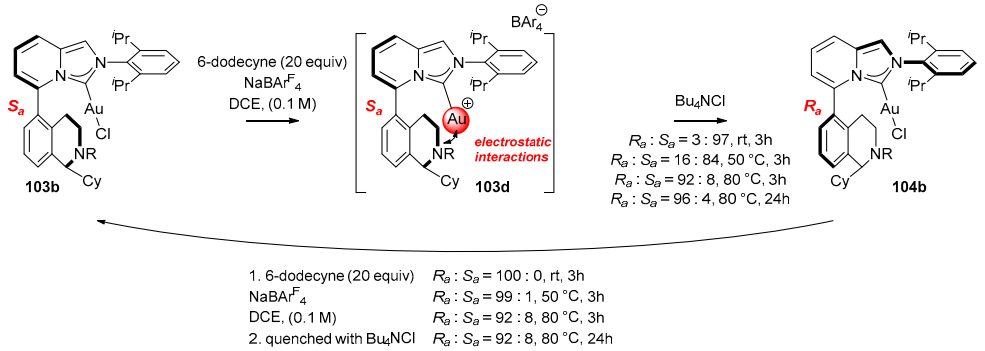
A similar synthetic sequence leading to imidazo[1,5-*a*]pyridine **85** (Scheme 13, Part B) and triazolium derivatives **73** (Scheme 12), reported in 2012 [84] and 2015 [85] and by Fernández et al., has been proposed recently by Zhang et al. (Scheme 14) [90]. The silent feature of this strategy was based on the resolution of diastereomeric atropoisomers **103** and **104** on commonly used silica gel, in contrast to rather expensive racemic mixture separation by HPLC on a chiral column (see Schemes 12 and 13). First, the authors developed a straightforward approach to the gram-scale synthesis of imidazo[1,5-*a*]-pyridine skeleton **100** by the condensation of aldehyde **97** with aniline **98**, subsequent cyclization of imine **99** with a paraformaldehyde/TMSBr mixture, and final Suzuki coupling with chiral boron derivative **101** possessing an amine function. The corresponding mixture **102** was transformed into silver complexes in an unusual way, applying AgCl as the source of silver in the presence of KOH. Subsequently, the silver compounds were subjected to transmetalation to afford a mixture of diastereomeric atropoisomers **103a** and **104a**, easily separated by conventional silica gel chromatography. Finally, the amine functional group was deprotected by treatment with TFA and subjected to reductive methylation. It should be mentioned that the two last steps proved excellent stability of gold(I) complexes **103** and **104** under acidic and reductive conditions.



Scheme 14. The synthesis of a gold(I) complex based on imidazo[1,5-*a*]pyridine skeleton by the chromatographic resolution of diastereomeric atropoisomers.

Additional investigations were devoted to the fluxional nature of the biaryl ligand of complexes **103b** and **104b**. The authors anticipated that the cationic gold complex **103d**, formed in situ by the treatment of **103b** with the source of a weakly coordinating ion could undergo epimerization. Indeed, the authors proved this idea experimentally and almost complete conversion of S_a isomer **103b** into R_a isomer **104b** was detected by ^{1}H NMR after 3 h at 80 °C (See Scheme 15). In contrast, when R_a isomer

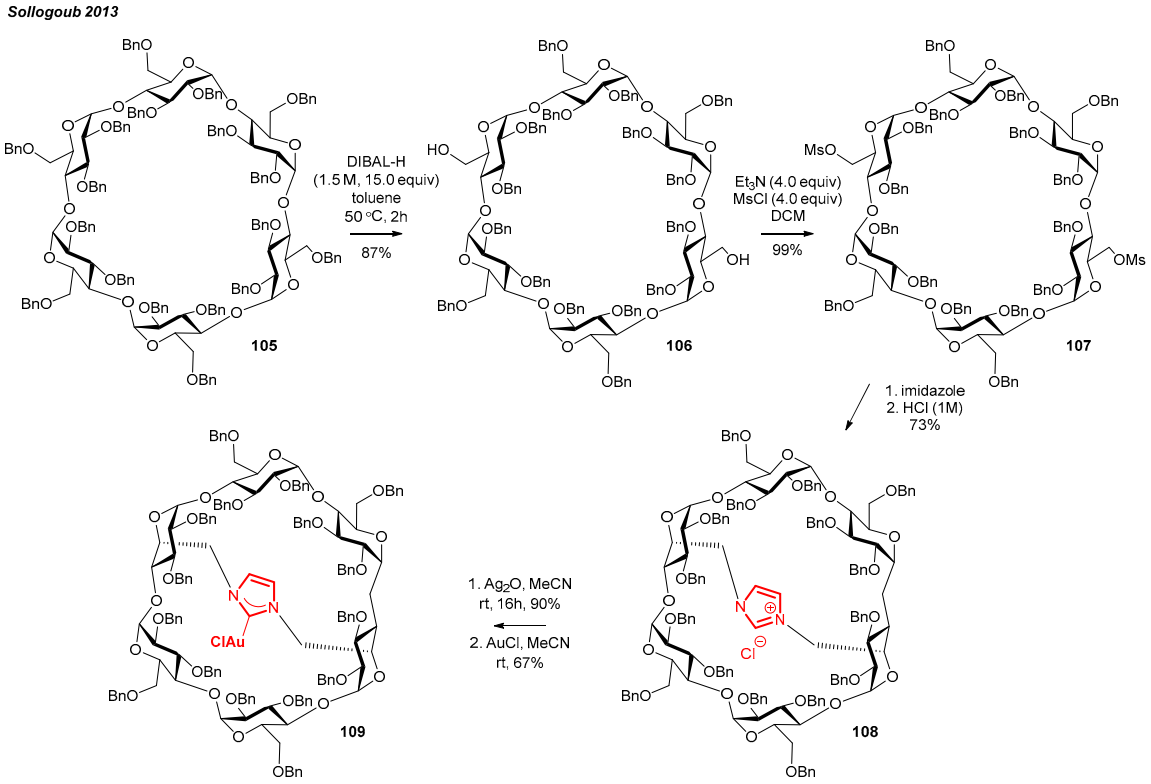
104b was heated to 80 °C for 24 h, only 8% of isomer **103b** formed, confirming better thermodynamic stabilization of the R_a isomer. The authors also suggested that electrostatic interaction of positively charged gold with the unhindered nitrogen atom is the main factor responsible for the difference in stability.



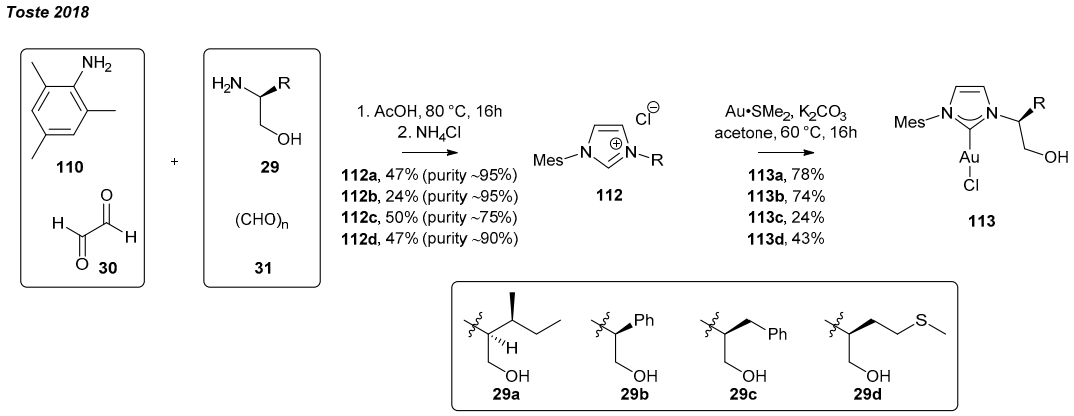
Scheme 15. Fluxional nature of the biaryl axis in complexes **103b** and **104b**.

Sinai and Sollogoub described structurally complex salts by introducing the imidazole subunit into α-cyclodextrins (Scheme 16) [91]. The crucial stage of this synthetic route was the selective deprotection of two benzyloxy groups in the macrocycle **105**. The preferred method definitely depends on the appropriate reducing agent, its concentration, and the use of its excess in the reaction mixture. After several trials, DIBAL-H and triisobutylaluminum (DIBAL) were selected as the best option for a wide group of carbohydrates. The authors confirmed that 15 equiv of DIBAL-H at 1.5 M concentration was appropriate for the selective deprotection of benzylated cyclodextrin **105**. Subsequent mesylation of diol **106** and sequential reaction with imidazole or benzimidazole gave highly functionalized precursors of *N*-heterocyclic carbene **108** (Scheme 16), easily converted to gold(I) complex **109** via a transmetallation route.

A straightforward approach to imidazolium salts **112** and gold(I) complexes **113** has recently been developed by Toste (Scheme 17) [74]. Implementing Baslé and Mauduit's protocol [39,75], the authors have prepared a series of C_1-symmetric NHC precursors via an elegant one-pot protocol, directly from chiral β-amino alcohols **29**, mesityl amine (**110**), glyoxal (**30**), and paraformaldehyde (**31**). The developed protocol includes two experimentally common steps. In the first step, two mixtures of reagents should be prepared in separate reaction vessels: formaldehyde with glyoxal in AcOH and mesityl amine with the amino alcohol, also in AcOH. In the next step, the resulting reaction mixtures should be combined after 5 min of stirring at 80 °C to give imidazolium salts (Scheme 17). The respective precursors were further converted to gold(I) complexes by Nolan's procedure [58] to give products moderate to good yield.



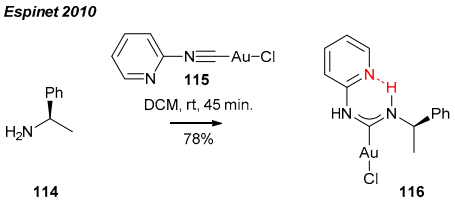
Scheme 16. The synthesis of cyclodextrin-derived NHC gold(I) complexes, reproduced with the permission from Georg Thieme Verlag KG from [44] (Scheme 38).



Scheme 17. The synthesis of gold(I) complexes bearing a chiral amino alcohol moiety.

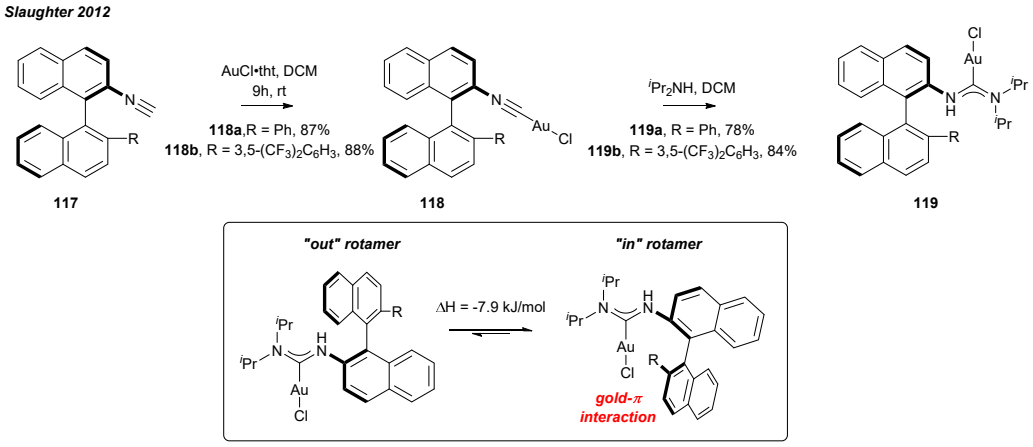
2.3. *Acyclic Gold(I) Complexes*

The first example of chiral acyclic gold(I) complex **116** was reported by Espinet in 2010 (Scheme 18) [43]. The authors proved that chiral amine **114** undergoes smooth addition to achiral gold(I) isonitrile complex **115** to form the acyclic carbene complex **116** which is additionally stabilized by an intramolecular hydrogen bond.



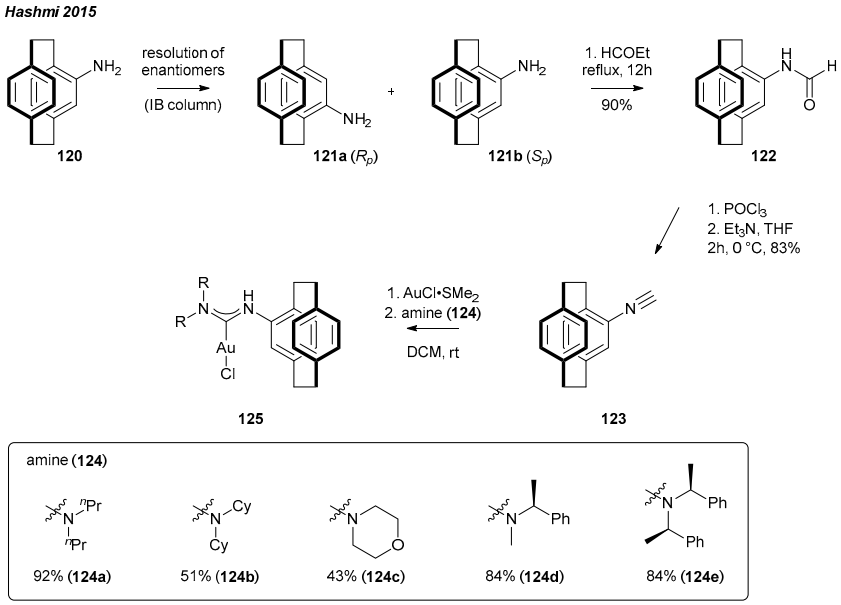
Scheme 18. The synthesis of chiral acyclic gold(I) complex from achiral isonitrile gold(I) complex.

Chiral, mononuclear, C_1-symmetric, and acyclic gold(I) complexes have been reported by Slaughter (Scheme 19) [92]. Regarding the synthetic route to gold(I) complexes **119**, the disclosed approach offers straightforward access directly from readily accessible isocyanide **117**, as reported earlier by Espinet [93] and Toste [94,95]. As a result, the formation of diastereomeric "in" and "out" rotamers was observed in the case of acyclic carbene gold(I) complexes bearing a binaphthyl skeleton (Scheme 19) [92]. The authors confirmed the existence of gold-π interactions by X-ray crystallography. These stabilized the "in" rotamer. In addition, DFT (density functional theory) calculations confirmed that the "in" rotamer is more stable than the "out" rotamer (ΔH = −7.9 kJ/mol) and the presence of these weak interactions was critical for the development of efficient enantioselective cyclization (*vide infra*). Similarly, the presence of atropoisomeric diastereomers as a result of weak gold-π interaction was also mentioned by Shi et al. [82].



Scheme 19. The synthesis of acyclic NHC gold(I) complexes with C_1-symmetry.

Further studies of the Hashmi group [96] have revealed that the same methodology could be applied for the synthesis of chiral acyclic gold(I) complexes **125** bearing a chiral [2.2]paracyclophane moiety (Scheme 20). The respective racemic amine **120** was separated by chromatography on a preparative chiral column and transformed into isonitrile **123**. The corresponding isonitrile group was complexed with gold chloride(I) and further reacted with a variety of amines **124**, including achiral and chiral ones. The respective gold complexes **125** were obtained with good to excellent yields.

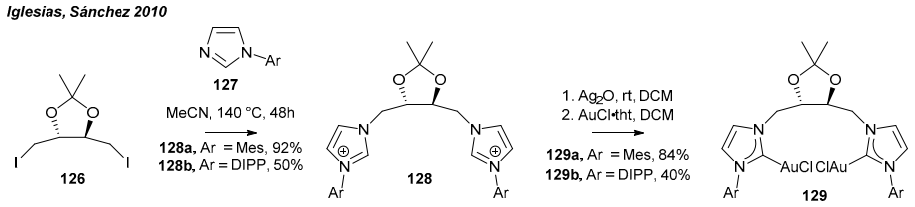


Scheme 20. The synthesis of chiral acyclic [2.2]paracyclophane-derived gold(I) complexes.

2.4. Bis-NHC Gold(I) Complexes

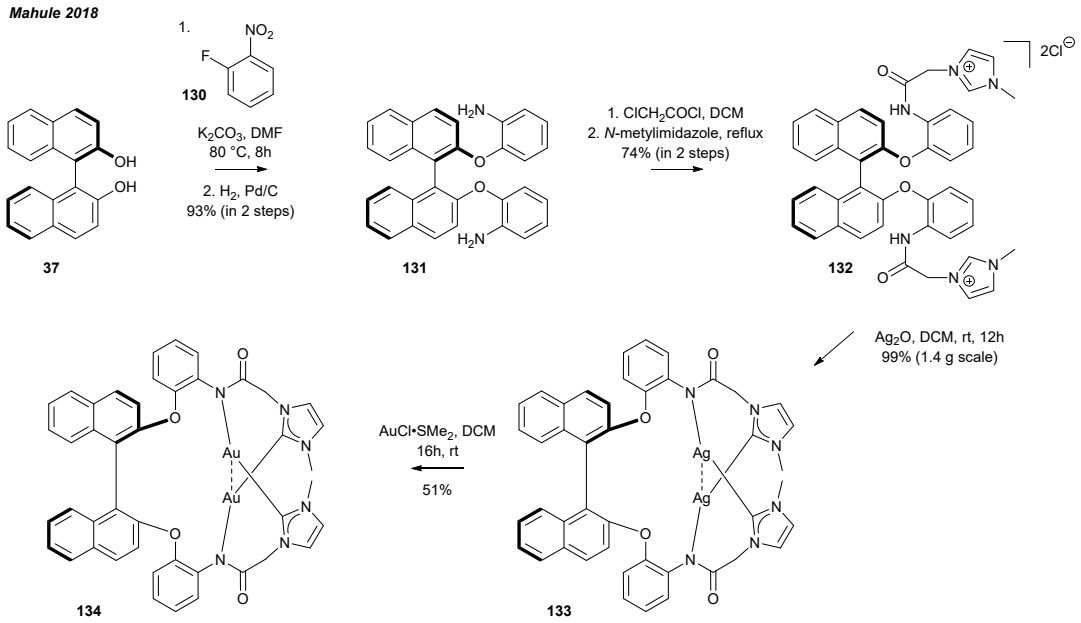
2.4.1. Cyclic Bis-NHC Gold(I) Complexes

The first examples of *bis*-NHC gold(I) complexes were published by Iglesias and Sánchez in 2010 (Scheme 21) [97]. The authors developed a straightforward synthesis of the biscarbene precursor **128** from tartaric acid. The readily available diiodide **126** was used as the alkylating agent used to form bisimidazolium salt **128** from the respective *N*-substituted imidazole **127**. The subsequent formation of gold(I) complexes **129** was accomplished via transmetalation of silver complexes. Higher yields were achieved in the case of mesityl derivative **129a**. Shortly thereafter, the same research group has demonstrated the possibility of heterogenization of a chiral NHC-Au-Cl complex on porous silica support [98].



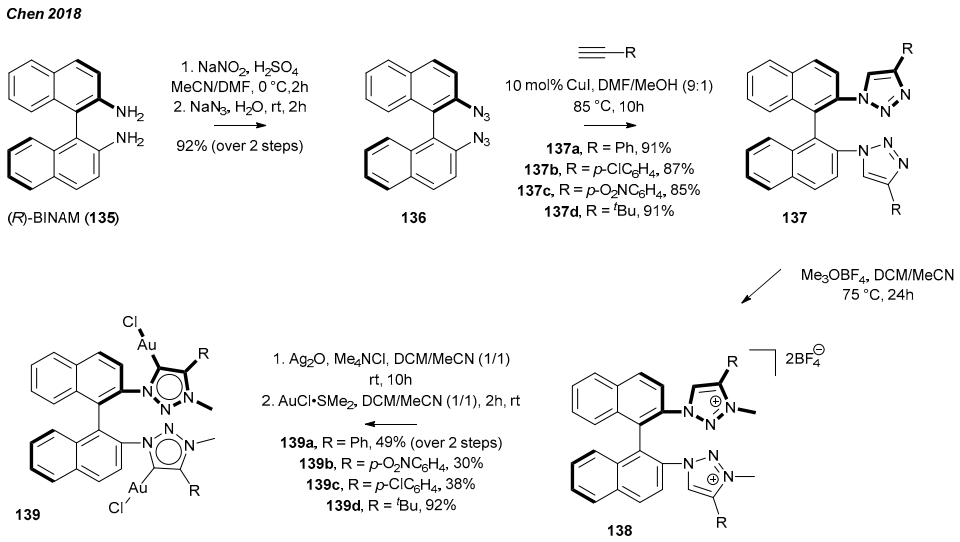
Scheme 21. The synthesis of *bis*-NHCAuCl complexes containing a tartaric acid-derived moiety.

Further investigations in this area provided a straightforward synthetic route to bimetallic complexes from (*R*)-BINOL (**37**, Scheme 22) [99]. The synthesis commenced with fluorine substitution in 2-fluoronitrobenzene (**130**) by a bisphenoxide ion. Subsequent hydrogenation resulted in diamine **131**, which was further acylated. The respective bisamide was used as the alkylating reagent to give bisimidazolium salt **132** with high 69% yield after four steps. The metalation step of the tetradentate ligand provided bimetallic silver (**133**) and gold (**134**) complexes, where each metallic center is coordinated to the amide and carbene functions. It should be mentioned that careful analysis of X-ray crystallographic data confirmed the presence of argentophilic interaction. In contrast, the widely studied aurophilic interaction [100,101] has not been observed in this case.



Scheme 22. The synthesis of a 12-membered macrocyclic gold(I) complex.

A similar approach to C_2-symmetric, axially chiral complexes **139** has been developed by Chen et al. (Scheme 23) [102]. In this case, gold(I) complexes **139** were prepared via a short modular synthetic sequence involving (*R*)-BINAM (135). Initially, **135** was converted into bisazide **136**, which was treated with terminal alkynes under click conditions. The respective *bis*-1,2,3-triazoles **137** were alkylated with Meerwein's salt to provide bistriazolium salts **138**. The synthesis of abnormal gold complexes **139** was accomplished via transmetalation of silver complexes. The argentophilic interactions were confirmed by X-ray analysis, whereas no Au-Au interaction has been detected in this case.

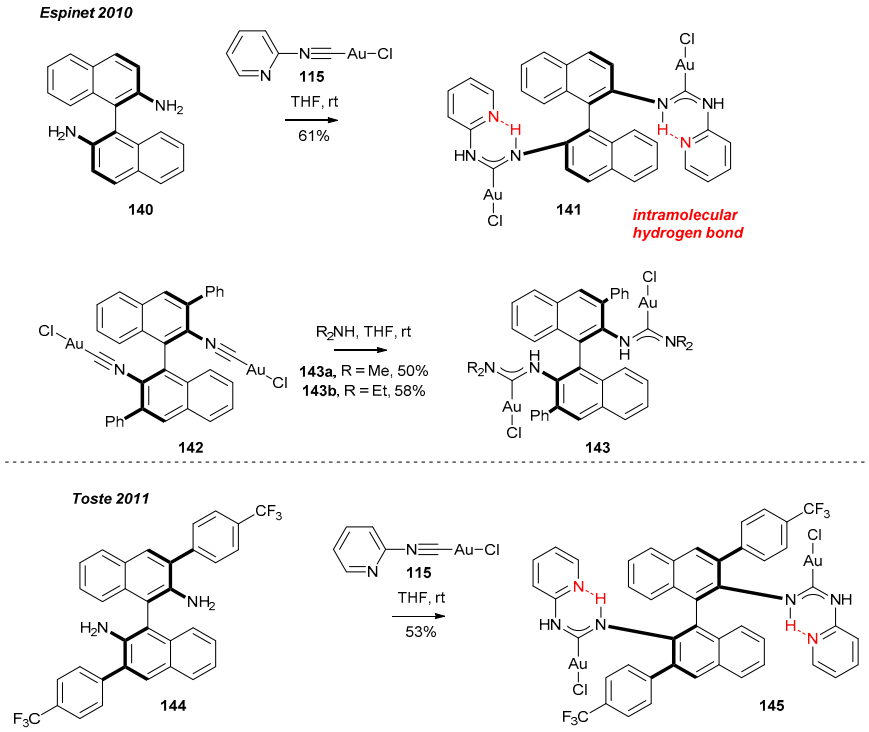


Scheme 23. The synthesis of bistriazolylidene gold(I) complexes derived from (*R*)-BINAM.

2.4.2. Acyclic Bis-NHC Gold(I) Complexes

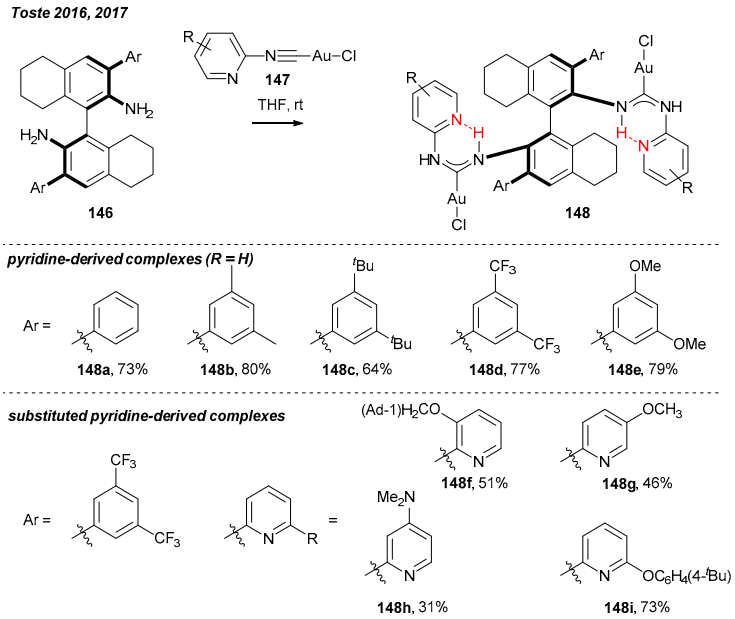
The first example of chiral acyclic *bis*-NHC gold(I) complexes was reported almost a decade ago by Espinet et al. (Scheme 24) [93]. This pioneering work in the area of chiral gold(I) complexes **141** and **143** revealed that the respective complexes could be easily generated by the reaction of amine

with gold(I) isocyanides **115** and **142**. The authors applied this methodology for the synthesis of binuclear **141** bearing a hydrogen bonded heterocyclic carbene (HBHC), starting from chiral amine and 2-pirydyl isocyanide gold(I) chloride (**115**). In addition, the preparation of gold(I) complexes **143** was also accomplished by the reaction of axially chiral bisisocyanide **142** precursors with structurally simple secondary amines to give direct access to nitrogenous acyclic carbene gold(I) complexes. Shortly thereafter, Toste et al. demonstrated that acyclic aryl 3,3′-substituted gold(I) complexes **145** are easily available employing the same synthetic path [103]. Unfortunately, the yield of their formation was given in only one example (Scheme 24).



Scheme 24. The synthesis of acyclic gold(I) complexes based on the BINAM scaffold.

A few years later, Toste et al. disclosed a huge library of acyclic diamine carbene gold(I) complexes **148** based on a partially hydrogenated backbone (Scheme 25) [94,95]. The partial saturation of the naphthyl substituent was critical for the facile purification of the respective metal complexes, as well as for the higher enantioinduction in catalytic processes (*vide infra*). As depicted in Scheme 25, many chiral diamines **146** participated in the reaction with gold isocyanide **147** to provide products with high yields.



Scheme 25. The synthesis of acyclic NHC gold(I) complexes with C_2-symmetry, containing a partially hydrogenated backbone.

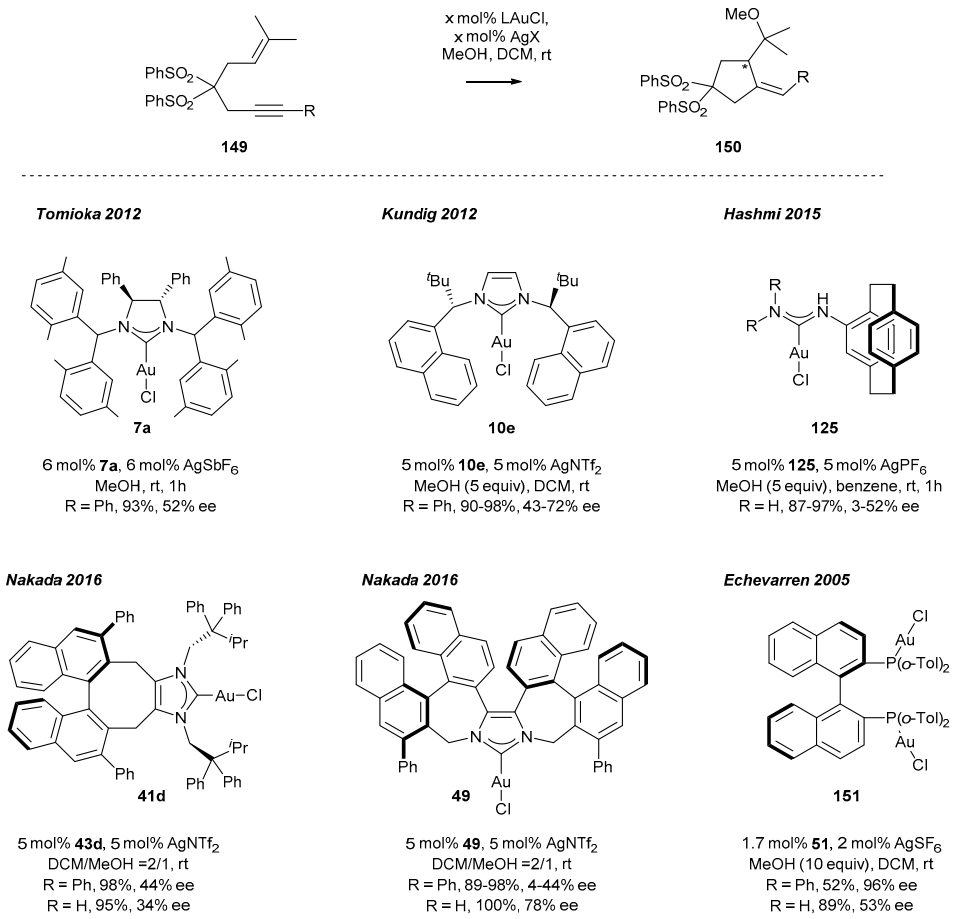
2.5. Applications of Chiral N-Heterocyclic CarbeneG(I) Complexes in Asymmetric Catalysis

2.5.1. Intramolecular Reactions

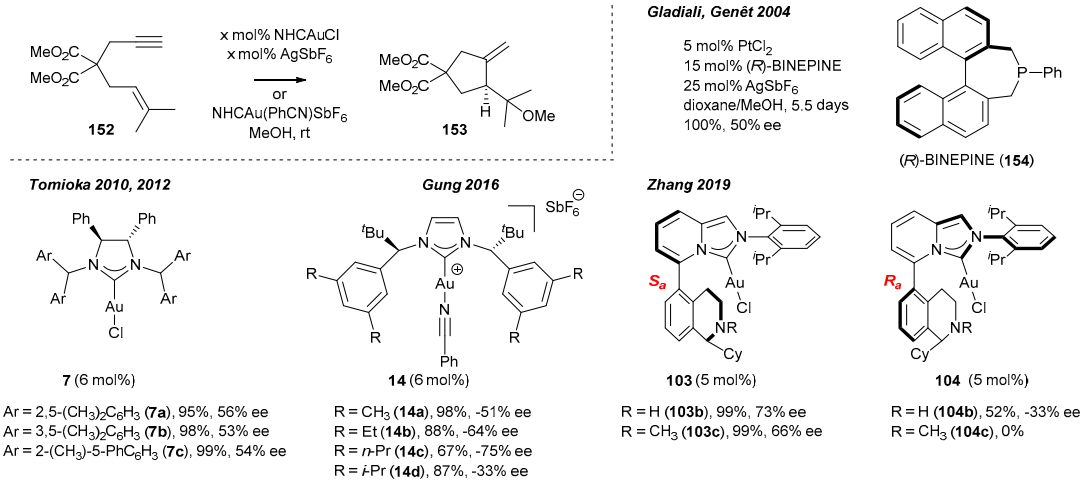
Alkylidene Cyclopentane Derivatives

Cyclopentane derivatives **150** bearing a bissulfone moiety are readily accessible by the cyclization of 1,6-enyne **149**, which was studied by Tomioka [62], Kündig [104], Hahsmi [5], and Nakada (Scheme 26) [76,78]. In all cases, a rather large amount of the gold(I) complex, namely 5–6 mol%, was necessary to achieve a good yield. In contrast, enantioselectivity was low to moderate, irrespective of the ligand used for the 1,6-enyne bearing a monosubstituted triple bond. The highest ee was observed with complex **49**, developed by Nakada [78], where the remote chiral skeleton efficiently transfers chirality to the gold center. The application of 1,6-enyne with a disubstituted alkyne proved difficult, and enantioselectivity reached 72%. It should be noted that complexes **7a**, **10e**, **43d**, and **49** used in these studies had to be activated prior to use by the sequestration of the chloride anion by a silver salt, and the cyclization/methoxylation sequence was performed at rt. Comparable results were obtained with bisphosphine complex **151** in term of yield and enantioselectivity [105]. It should be mentioned that direct comparison of NHCAuCl and phoshpine-AuCl catalyzed reactions will be presented to compare directly the efficiency of the catalytic systems in the selected enantioselective transformations.

Structurally similar cyclopentane derivatives **153** bearing a malonate moiety were also investigated by Tomioka [62,106], Gung [66], and recently, Zhang [90] (Scheme 27). Tomioka's catalysts **7** resulted in cyclopentane derivative **153** with moderate enantioselectivity, whereas Gung's ionic catalyst **14** appeared to be slightly better in terms of stereoselectivity. The authors also observed that the elongation of the alkyl chain attached to the aryl ring from a Me group to an *n*-Pr group led to an increase in the enantioselectivity (Scheme 27, structures **14a**–**d**). However, complex **14d** bearing an *i*-Pr group gave the product with a low 33% yield. Much better results were achieved by Zhang [90]. In this case, diastereomer **103b** allowed to obtain cyclopentane derivative **153** with 73% ee, whereas its *N*-methyl counterpart **103c** appeared to be less efficient. The corresponding Au/phosphine complexes have not been used in this transformation. Application of $PtCl_2$/(*R*)-BINEPINE (**154**) has been only reported [107] leading to cyclopentane derivative **153** with comparable enantioselectivity and yield.



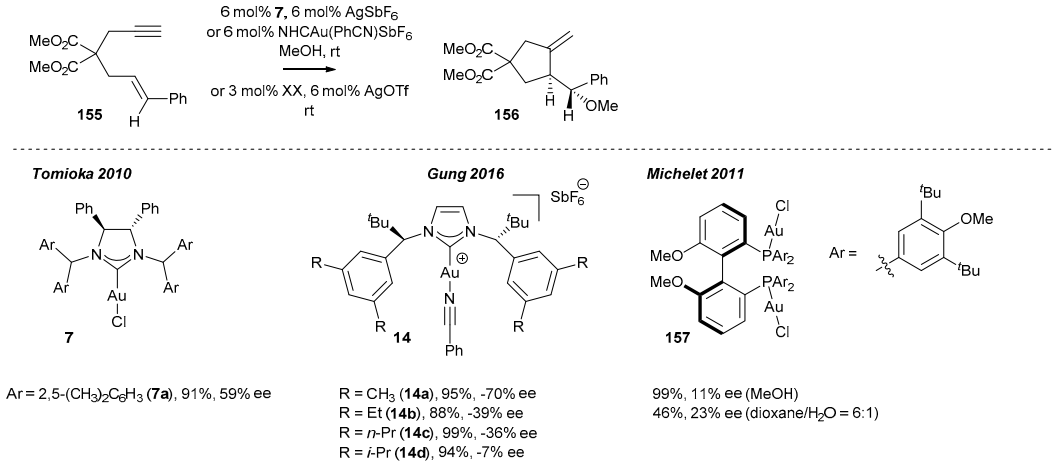
Scheme 26. 1,6-Ene-yne cyclization leading to cyclopentane derivatives bearing sulfone functional groups.



Scheme 27. 1,6-Ene-yne cyclization leading to cyclopentane derivatives bearing a malonate moiety.

Further investigation of the alkoxycyclization was devoted to enynes **155** bearing a monosubstituted double bond (Scheme 28). A similar level of stereoselectivity was reported by Tomioka [62]. In contrast to the cyclization of enyne **152**, Gung observed a close dependence of enantioselectivity on the substituent present [66]. The highest 70% enantiomeric excess was achieved

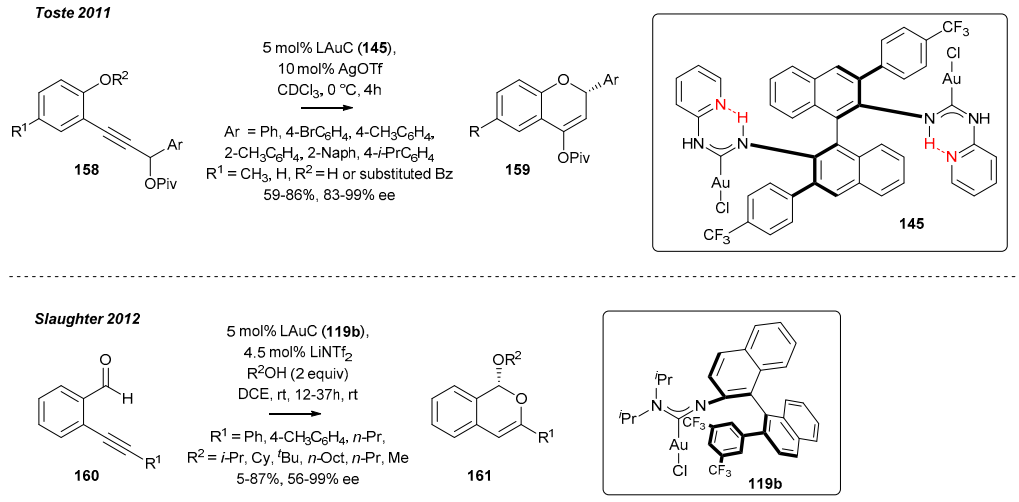
with complex **14a** bearing a methyl attached to the aromatic ring in the *meta* position. Bimetallic gold complex **157** was less efficient in the methoxycyclization [108].



Scheme 28. Cyclization of 1,6-enyne bearing a monosubstituted double bond.

Chromane and Isochromane Derivatives

In 2011, Toste et al. developed an efficient route to isochromane derivatives **159** via dynamic kinetic resolution of racemic propargyl pivalate (Scheme 29) [103]. The transformation included a [3,3]-sigmatropic rearrangement and subsequent intramolecular hydrophenoxylation. The key to a successful cyclization was the structure of the ligand used. The best results in terms of enantioselectivity were achieved when acyclic biscarbene bidentate gold(I) complex **145** was applied, bearing a pyridine moiety able to form an intramolecular hydrogen bond. Unfortunately, common chiral bisphosphine ligands (such as Segphos, Biphep, or phosphoroamidite) has led to isochromane derivatives with low enatioselectivity [103].

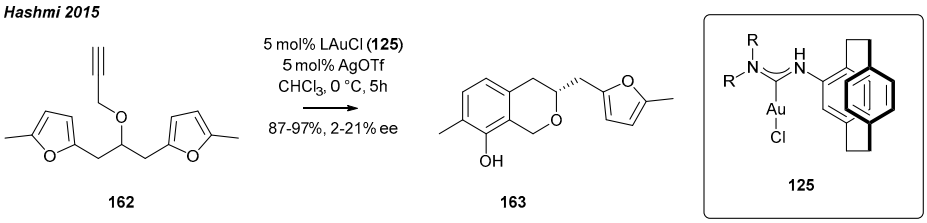


Scheme 29. The synthesis of chromane and isochromane derivatives via cyclization.

A similar approach, based on the activation of alkynes by gold(I) complex **119b** in tandem acetylation/cycloisomerization has been developed by Slaughter et al. [92]. The authors demonstrated for the first time that the monodentate, axially chiral binaphthyl ligand **119b** could induce a high level of enantioselectivity. X-Ray crystallography and DFT calculations revealed that a weak gold-arene interactions of the electron-deficient 3,5-bis(trifluoro)phenyl group with the metal center are essential for the conformational stabilization. Further studies proved that the absence of these weak interactions

in analogous complexes bearing a phenyl ring led to a dramatic decrease in enantioselectivity. It should be mentioned that metal complexes or inorganic salts were applied as catalyst (e.g., silver [109,110], copper [111], or palladium [112]). Gold-phosphine complexes have not been reported for this transformation.

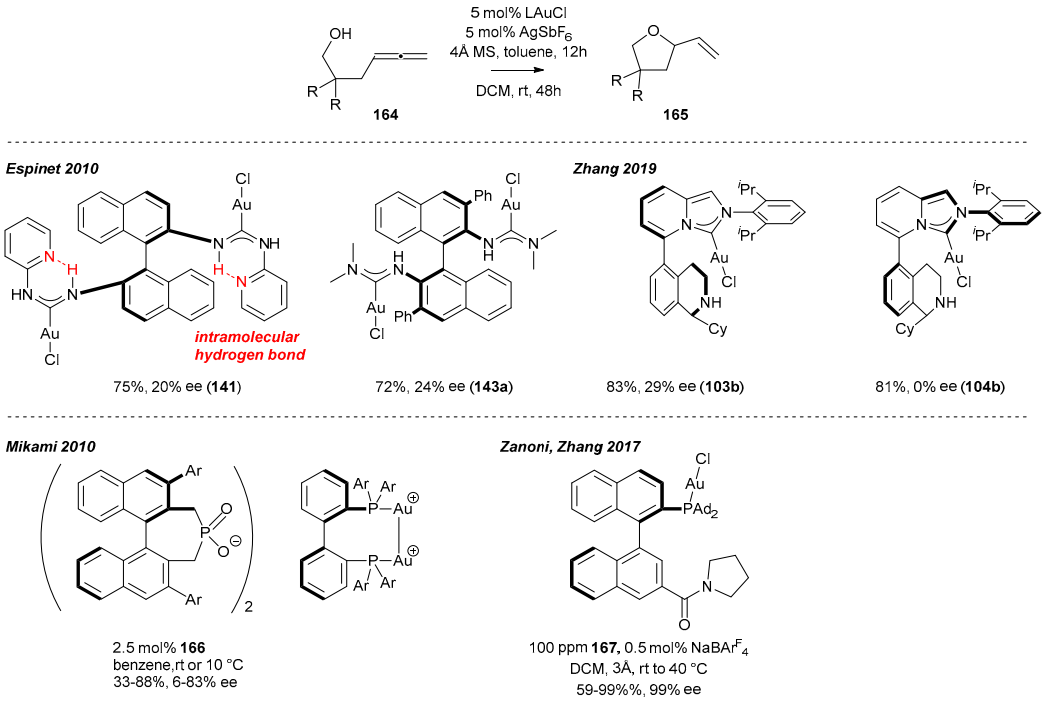
A few years later, Hashmi et al. developed an elegant gold-catalyzed furan-yne cyclization leading to isochromane derivatives **163** (Scheme 30) [96]. Although many chiral and acyclic gold(I) complexes **125** have been tested, the corresponding heterocycles of **163** type were obtained with low enantiomeric excess. It should be noted that gold-phosphine complexes have not been used in this transformation.



Scheme 30. Furan-yne cyclization leading to an isochromane derivative.

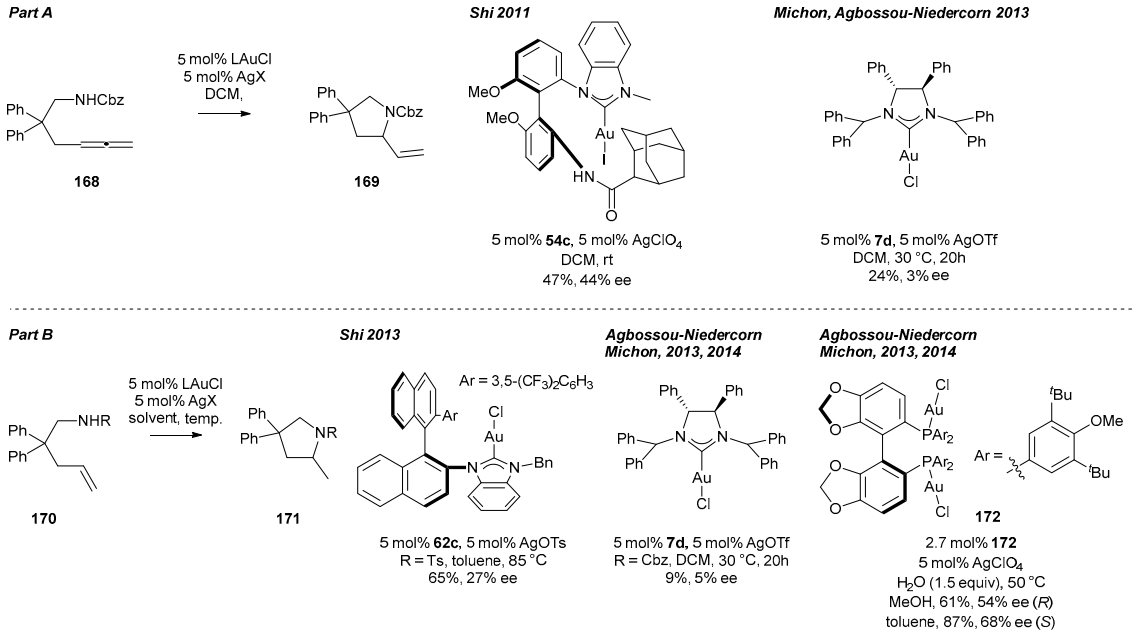
Furan, Pyrrolidine, and Indanone Derivatives

New chiral gold(I) complexes are usually tested in the enantioselective cyclization reactions leading to five-membered heterocycles which have become a benchmark of their catalytic activity. Among cyclizations, much attention has been paid to the hydroalkoxylation of allenic alcohol **164** leading to vinylfuran derivatives **165** in the case of phosphine gold(I) complexes. In the case of *N*-heterocyclic carbene ligands, only two examples have been reported thus far, by Espinet [93] and Zhang [90]. Although the yield of the corresponding heterocycles **165** remained high, the enantioselectivity was low, no higher than 30% ee. The respective gold(I)-phosphine complexes were also used in the above-mentioned cyclization (Scheme 31) [113,114]. It should be underlined that axially chiral sterically hindered phosphines bearing amide function appeared to be excellent ligand for gold leading to the vinyl tetrahydrofurane derivatives **165** with high enantioselectivity [114].



Scheme 31. The synthesis of a vinylfuran derivative via alkoxycyclization.

Much more synthetic effort has been expended for the synthesis of nitrogen analogues, namely pyrrolidine. It should be emphasized that successful hydroamination of multiple bonds (alkene or allene) is strictly dependent on the protecting group on the nitrogen atom. The first example of hydroamination of allene catalyzed by complex **54c** has been reported by Shi (Scheme 32, Part A) [79]. However, moderate enantioselectivity was achieved. Further studies of Michon and Agbossou-Niedercorn [115] have proven that a C_2-symmetric complex was able to catalyze the hydroamination of allene **168**. Unfortunately, the cyclization proceeded with very low enantioselectivity. It should be mentioned that chiral gold-phosphine complexes have not been reported to date. Few years ago, Widenhoefer et al. have developed an efficient dehydrative amination of allylic alcohols leading to the enantiomerically enriched vinyl pyrrolidine [116]. Similarly, silver complexes were also applied in this transformation leading to the heterocycle **169** with enantioselectivity around 50% [117].

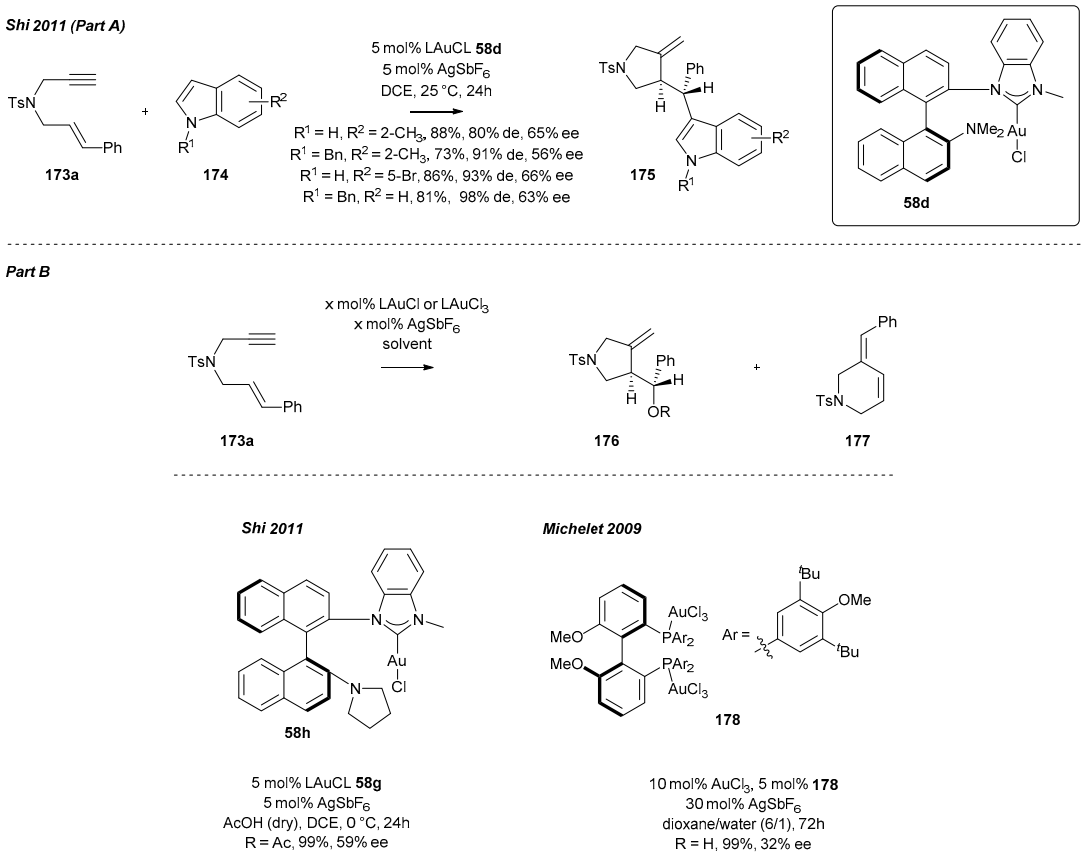


Scheme 32. Hydroamination of allene and alkene leading to 2-substituted pyrrolidines.

Intramolecular hydroamination of alkenes has also met with limited success. Only two articles devoted to this subject have appeared, reported independently by Shi [82] and Agbossou-Niedercorn [115,118] (Scheme 32). Unfortunately, higher temperature was needed to reach moderate yield, which was responsible for low enantioselectivity. Many more synthetic efforts have been made in this area with gold(I)-phosphine complexes. Michon and Agbossou-Niedercorn investigated intramolecular hydroamination of alkenes in details, and better enantioselectivity were obtained in the case of bisphosphine ligand **170** [115,119,120]. The authors also observed a rare dependence of configuration of newly formed stereogenic center on the presence of silver salt [120].

Apart from the simple cyclization of amido allene or alkene leading to pyrrolidines, tandem cyclization coupled with the attack of an external nucleophile was explored by Shi et al., catalyzed by complexes **58d**, bearing a chiral binaphthyl scaffold. First, tandem Friedel-Crafts reaction of indoles **174** with concomitant cyclization of 1,6-enyne has been explored, leading to product **175** with excellent yields and moderate enantioselectivity (Scheme 33, Part A) [81]. It should be noted that a substituted aryl instead of a phenyl ring attached to the double bond and lack of protection of the indole nitrogen atom have been tolerated under the reaction conditions. Similar results in terms of enantioselectivity have been achieved in the acetoxycyclization of amide **173a**, where AcOH was used as the external nucleophile (Scheme 33, Part B) [80]. To suppress the hydrolysis of the ester group in **176**, 20 equivalents of anhydrous AcOH appeared to be optimal. It should be noted that piperidine **177** was detected in

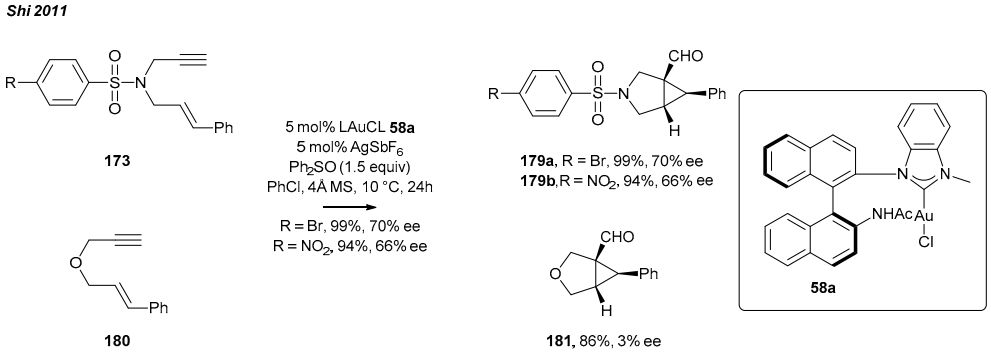
some cases as the side product resulting from a skeletal rearrangement. Enantioselective version of cyclization of enyne **173a**, where indole is involved as nucleophile has not been reported. In contrast, acetoxycyclization of amide **173a** has been performed with gold(III)-bisphosphine complexes leading to the pyrrolidine derivatives in excellent enantioselectivity [121].



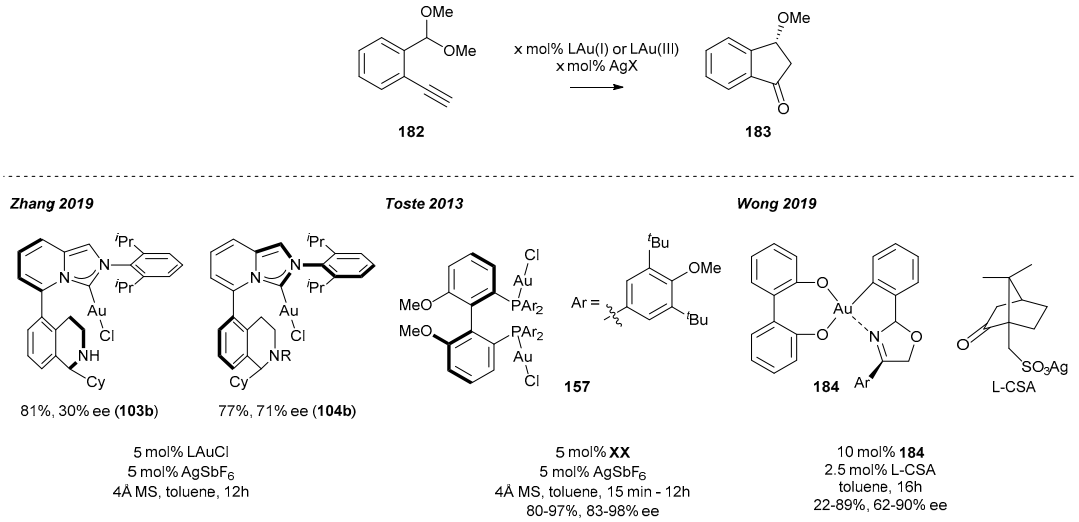
Scheme 33. Asymmetric intramolecular cyclization of 1,6-enynes coupled with the attack of an external nucleophile.

Further studies of Shi's group [80] have revealed that 1,6-enyne could be efficiently cyclized under oxidative conditions to form bicyclic aldehydes **179** with good enantioselectivity and excellent yield and diastereoselectivity (only one diastereomer has been observed, Scheme 34). Diphenyl sulfoxide appeared to be the oxidant of choice, whereas the addition of a small amount of molecular sieves allowed to improve the yield. Unfortunately, the application of the same catalytic system for the synthesis of tetrahydrofuran derivatives **181** led to the product with very low enantiomeric excess. Application of chiral phosphines for this transformation has not been reported thus far.

Further studies of Zhang et al. [90] have revealed that structurally similar NHCAuCl complexes **103b** and **104b** can also catalyze the formation of indanone **183** via carboalkoxylation of alkyne **182**. Although the enantioselectivity level was far from practical (Scheme 35), especially in comparison to the bisphosphine ligand used in the seminal work of Toste [122], the high yield proved excellent catalytic activity. Recently, Wong proved that formation of indanone **183** could catalyzed by the cyclometalated gold(III) complexes **184** [123].



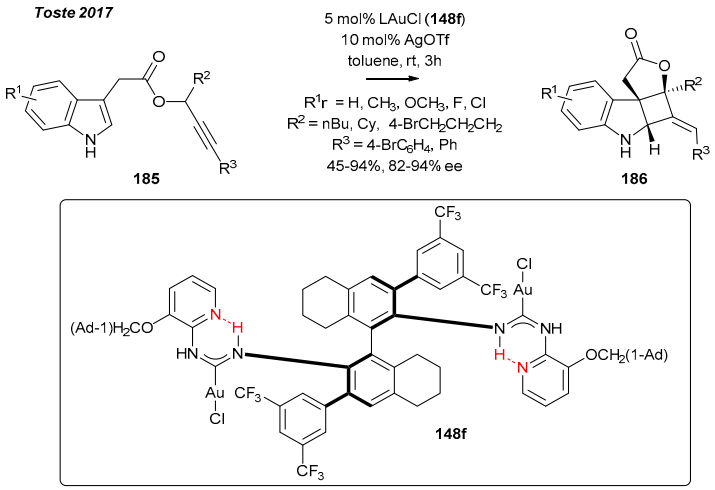
Scheme 34. Asymmetric intramolecular cyclization of 1,6-enynes coupled with simultaneous oxidation.



Scheme 35. The synthesis of indanone via carboalkoxylation.

Complex Fused Cyclobutane Derivatives

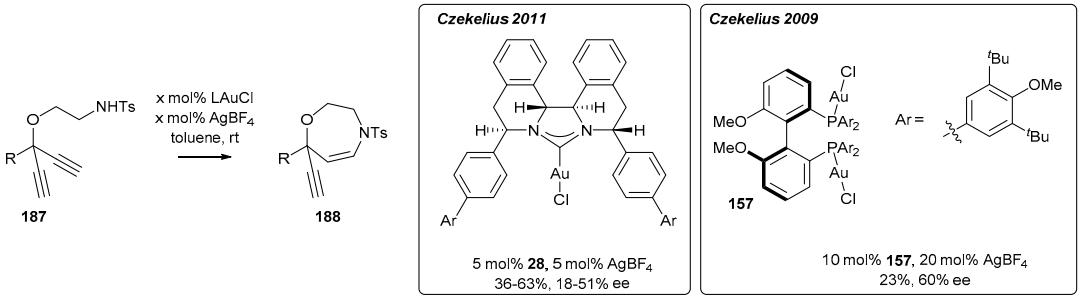
Chiral diaminocarbene ligands have also found an application in the synthesis of a fused-ring system possessing an indole, 5-membered lactone, and cyclobutane rings (Scheme 36) [95]. It should be mentioned that the experimental work was preceded by theoretical calculations. Toste and Sigman proposed a simple mathematical model and then optimized the structure of ligands by the calculation of $\Delta\Delta G‡$ as a function of substituent present in the structure of the complex. Theoretical predictions revealed that the pyridine moiety with alkoxy substituents in the appropriate positions is critical. Indeed, further experimental work confirmed that the highest enantioselectivity was achieved with a pyridine bearing an adamantyloxy function (complex **148f**). The 17 gold(I) complexes have been tested in the presented [3,3]-sigmatropic rearrangement-[2+2] cyclization, showing good agreement of the theoretical calculations with the experimental results. It should be mentioned that only achiral gold(I)-phosphine complexes were used in this transformations [124].



Scheme 36. The synthesis of indole derivatives **186** bearing a fused ring system.

Diynamide Desymmetrization

A unique approach to substituted oxazepines **188** featuring a quaternary stereocenter has been proposed by Czekelius et al. [72]. The authors utilized highly sterically demanding gold(I) complexes **28** based on a bis(tetrahydroisoquinoline) skeleton for the desymmetrization of 1,4-diyne **179** to form a seven-membered heterocyclic ring as a result of the addition of a sulfonamide across the triple bond (Scheme 37). The yields and the enantioselectivities were low to moderate. A slightly better enantioselectivity was obtained with axially chiral bimetallic gold(I)-phosphine complex **157** [125]. However, the cyclization offers direct access to a heterocyclic skeleton important from the point of view of medicinal chemistry. It should be noted that cyclization of 1,4-diynes seemed challenging in reactions catalyzed by standard phosphine gold(I) complexes [125].

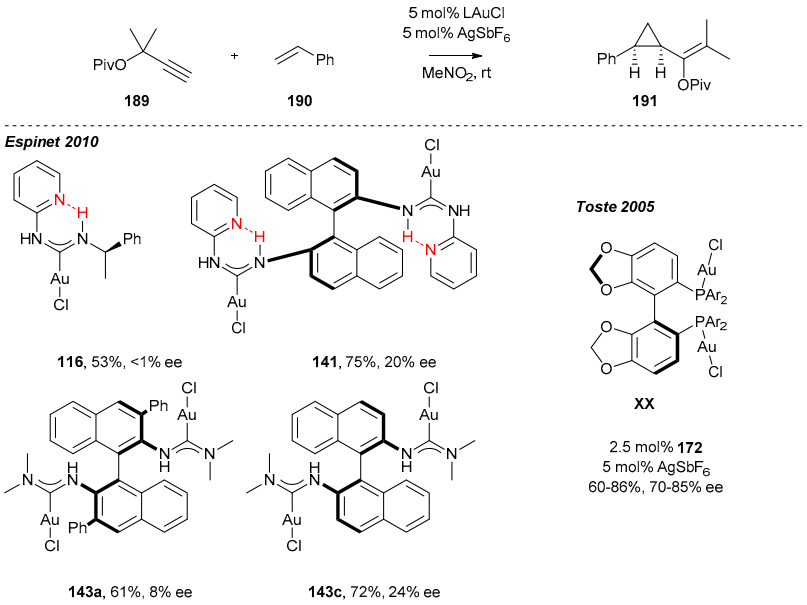


Scheme 37. Asymmetric cyclization of a diynamide.

2.5.2. Intermolecular Reaction

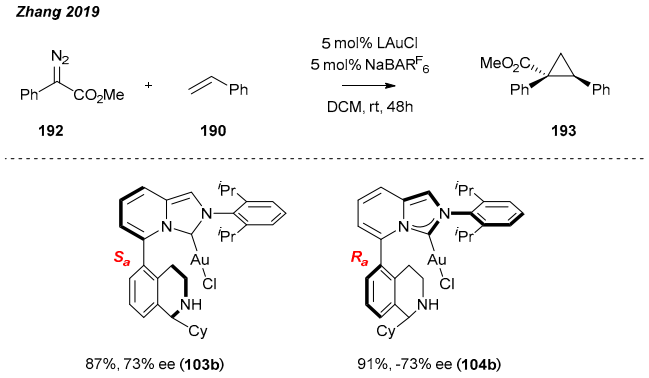
Cyclopropanation

Chronologically, the first example of an intermolecular cyclopropanation reaction catalyzed by a chiral *N*-heterocyclic carbene gold(I) complex was reported by Espinet in 2010 (Scheme 38) [93]. The authors applied monodentate and bidentate complexes to the cyclopropanation reaction between styrene (**190**) and propargylic pivalate **189**. Unfortunately, low enantioselectivity was observed in all cases, irrespective of the mode of substitution of the chiral backbone or the nitrogen atoms. Nevertheless, the pioneering work of Espinet initiated the era of chiral *N*-heterocyclic gold(I) complexes in enantioselective catalysis. Considering the enantioselectivity, much more better results were obtained with gold(I)-bisphosphine complex **172** [126].



Scheme 38. Enantioselective cyclopropanation.

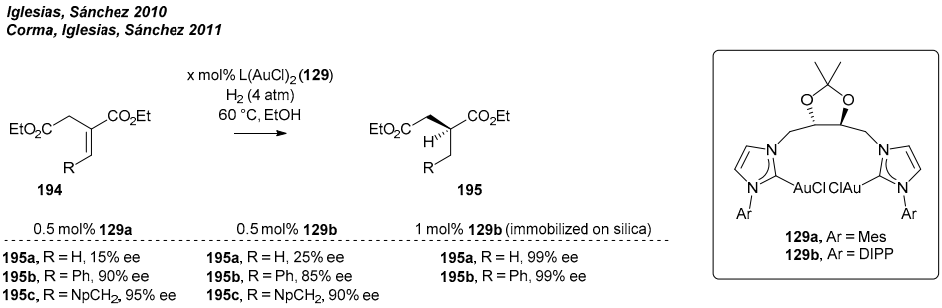
Recently, Zhang et al. [90] have demonstrated the utility of gold(I) complexes in the cyclopropanation of styrene using diazo compounds (Scheme 39). It was found that diastereomeric gold complexes **103b** and **104b** were able to catalyze cyclopropane **193** formation leading to a single diastereomer with moderate enantioselectivity of around 70% and excellent yield. It should be mentioned that gold-catalyzed cyclopropanation between styrene and diazo compounds has not been reported with gold-phosphine complexes.



Scheme 39. Enantioselective cyclopropanation of styrene with diazo compounds.

Hydrogenolysis

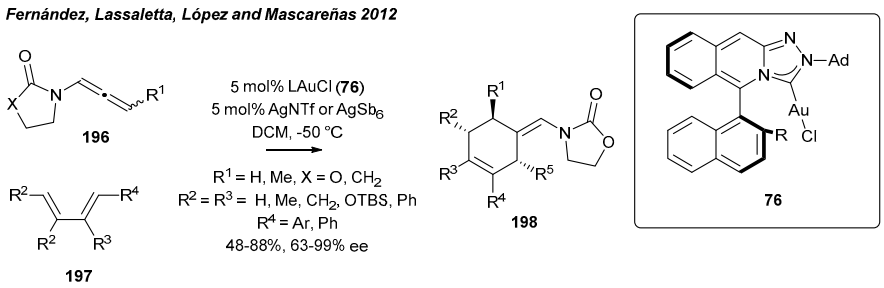
The work of Espinet, Iglesias, and Sánchez [97] has proved the efficiency of *bis*-*N*-heterocyclic carbene complexes **129** in the hydrogenolysis of diethyl alkylidene itaconate **194**. The corresponding gold(I) complexes **129** operated well under mild conditions (4 atm of H_2, 40 °C). However, a bulky substituent, such as phenyl or benzhydryl was needed to achieve a high level of enantioselectivity around 90% ee. It should be mentioned that only 0.5 mol% of the catalysts was applied in the reduction of trisubstituted alkene **194b**-**c**. Although DIPP (2,6-diisopropylaniline) **129b** derivatives appeared to be less active than Mes derivatives **129a**, the level of stereocontrol was comparable (Scheme 40). Further research performed by the same group demonstrated that gold(I) complex **129b** could be immobilized on mesoporous MCM-41 (Mobil Composition of Matter No. 41) and applied in hydrogenolysis to afford the product with excellent 99% enantioselectivity [98].



Scheme 40. Enantioselective hydrogenolysis.

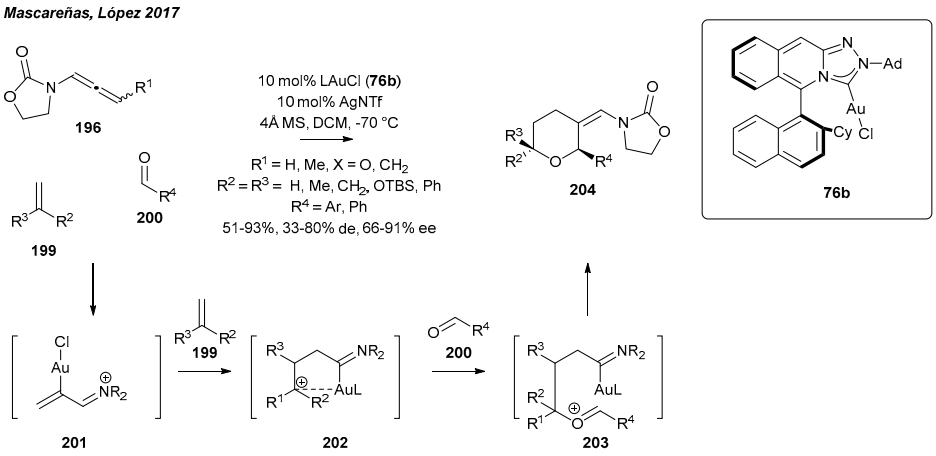
[4+2] and Related Cycloadditions

The largest group of intramolecular reactions explored in the context of enantioselective transformations involves a different type of cycloaddition of allene amides **196**. The first impressive example was published by Fernández et al. in 2012 [84]. The authors developed a series of [4+2] cycloaddition with 1,3-dienes **197** for the first time to form densely substituted cyclohexene derivatives **198** with excellent enantio- and diastereoselectivity (See Scheme 41). The key enantiodifferentiation was achieved by steric shielding of a linear $C_{carbene}$-Au bond by the sterically-hindered binaphthyl backbone (complex **76**). It should be noted that this pioneering work proved that steric effects are sufficient to achieve high stereoselectivity and no additional weak interactions, such as Au-arene (for examples, see Schemes 10 and 19), are needed to reach high enantioselectivity. Recently, Zhang et al. [90] have applied atropoisomeric gold(I) complexes **103** and **104** for the above-mentioned [4+2] cycloaddition. It should be mentioned that Pirovano and Rossi has recently developed enantioselective [4+2] cycloaddition catalyzed by (*R*)-Segphos/AuCl complex between allene vinyl indoles (as diene partner) with similar yields and enantioselectivities [127].



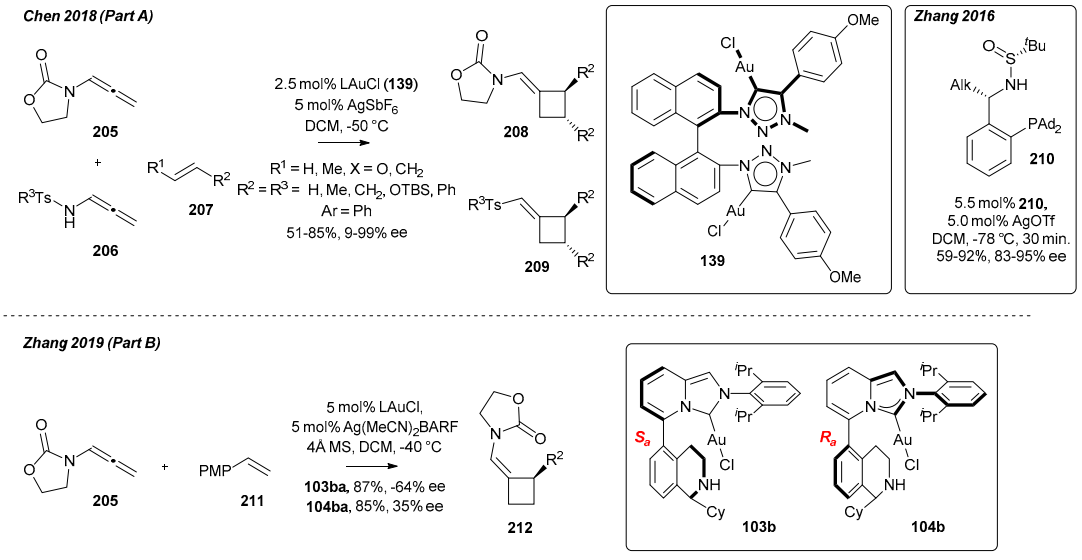
Scheme 41. The synthesis of densely substituted cyclohexene derivatives by [4+2] cycloaddition.

A few years later, Mascareñas and López extended the scope of cycloadditions to the three-component [2+2+2] cycloaddition leading to tetrahydropyran **204** in a highly atom-economical fashion (Scheme 42) [86]. Regarding the proposed mechanistic scenario, the initially activated allene amide **196** forms gold iminium species **201** which reacts further with alkene **199** and subsequently with aldehydes **200** to give the final tetrahydropyran **204**. The Prins cyclization is believed to proceed via a nucleophilic attack of gold enamine (structure **203**, Scheme 42) intermediate on the oxonium moiety. Considering the scope of the method, a broad range of styrene derivatives **199** (or 1,1-disubstituted alkynes) and aldehydes **200**, including aromatic, heteroaromatic, as well as aliphatic and α,β-unsaturated ones were tolerated under the reaction conditions affording tetrahydropyran derivatives **204** with high diastereoselectivity (from 33% to 100%). The observed enantioselectivity was slightly better in the case of aromatic aldehydes (up to 92% ee) in comparison with aliphatic ones (up to 51% ee). It should be underlined that achiral gold(I)-phosphine complexes could catalyze the above-mentioned cycloaddition [128]. However, enantioselective version of this transformation catalyzed by the gold-phosphine complexes has not been reported.



Scheme 42. [2+2+2] cycloaddition of allene amides, alkenes, and aldehydes leading to tetrahydropyrans.

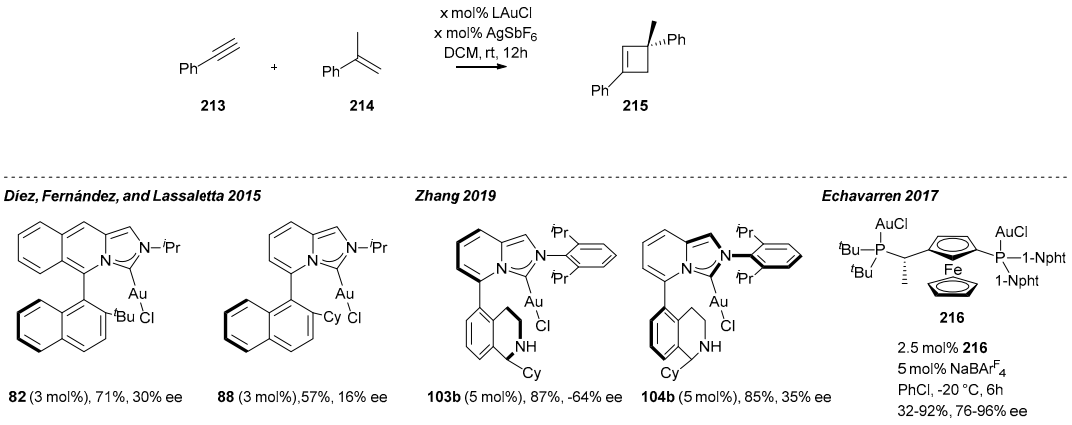
A practical approach to the synthesis of tri- and tetrasubstituted alkylidene cyclobutane derivatives **208** has been recently proposed by Chen et al. [102]. The corresponding cyclobutane **208** derivatives were easily accessible by [2+2] cycloaddition of oxazolidinone **205** and *N*-sulfonyl allene amide **206** with styrene or stilbene derivatives **207**. A different substitution pattern in allene amide **205** or olefin partner **207** has led to enantioselectivity higher than 61% ee. Only the presence of *N*-phenyl and *N*-tosyl groups led to a significant decrease in enantioselectivity to 9%. The observed low stereoselectivity was attributed to poor stereodifferentiation of both the *N*-phenyl and *N*-tosyl substituent covalently bonded to the same nitrogen atom. Similarly, Zhang et al. [90] have applied allenyl amides for the synthesis of disubstituted cyclobutenes with a comparable level of enantioselectivity (Scheme 43, Part B). The same research group has previously developed phosphine-based catalytic system for this transformation [129]. Sterically hindered phosphine **210** bearing chiral sulfoxide structural motif appeared to be excellent ligand leading to the product of type **208** with comparable enantioselectivities.



Scheme 43. The synthesis of di- or trisubstituted alkylidene cyclobutane derivatives as a result of [2+2] cycloaddition.

Regarding the possible formation of a cyclobutene bearing an internal double bond **215**, [2+2] cycloaddition of terminal alkynes **213** and 1,1-disubstituted alkenes **214** has also been developed (See Scheme 44). The first example of this transformation, catalyzed by NHC-gold(I) complexes **82** and **88**,

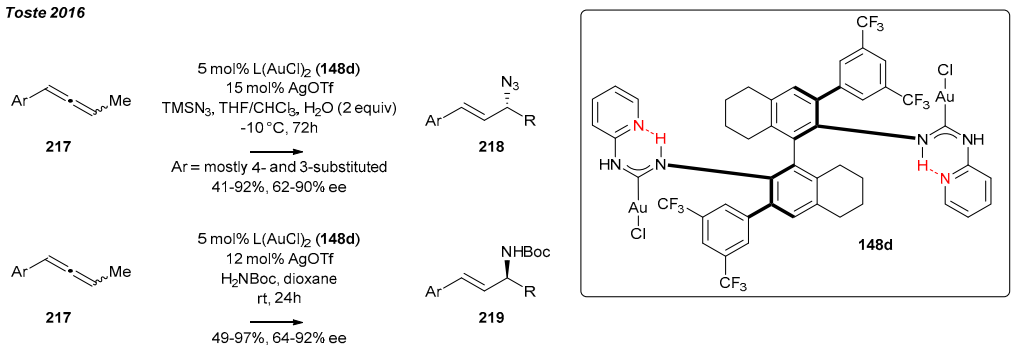
has been introduced by Díez et al. [85]. Unfortunately, enantioselectivity appeared to be low, no more than 30%; however, the yield was quite good. Recently, Zhang [90] has also examined atropoisomeric gold(I) complexes **103b** and **104b** in this transformation. However, low to moderate enantioselectivities were achieved, leaving room for further improvements. In contrast to C_1-symmetric NHCAuCl complexes **82**, **88**, **103b**, and **104b** (See Scheme 44), ferrocene-based gold(I) complex **216** appeared to be the ligand of choice for the formation of cyclobutene **215**. Echevarren group presented an efficient protocol leading to the product **215** with the high enantioselectivityp [130].



Scheme 44. The synthesis of disubstituted cyclobutene derivatives as a result of [2+2]-cycloaddition.

Hydroamination and Hydroazidation of Allenes

Exploring the potential of acyclic diaminocarbene gold(I) complexes, Toste and co-workers have presented an enantioselective approach to essential building blocks such as allylic amines [94]. This goal was accomplished by the hydroazidation of allenes catalyzed by the bimetallic complex **148d**. As a source of the amine function, $TMSN_3$ was used which generated HN_3 under the reaction conditions through the addition of a small amount of water. The yield of allylic azides and the enantioselectivity were usually high. In search of an alternative source of nitrogen, the authors utilized *t*-butyl carbamate (H_2NBoc). Surprisingly, the configuration of the newly formed stereogenic center was opposite in comparison to allylic azides **218** (See Scheme 45). This rare enantiodivergent approach offers easy access to both enantiomers using the same catalyst, only through changing the nitrogen nucleophile. It should be mentioned that the configuration of the disubstituted allenes did not influence the outcome of the reaction. Enantioselective version of the hydroazidation has not been developed with gold-phosphine complexes or related ligands. Muñoz and co-workers reported hydroazidation of allene catalyzed by achiral $(PhO)_3PAuCl$ complex [131].

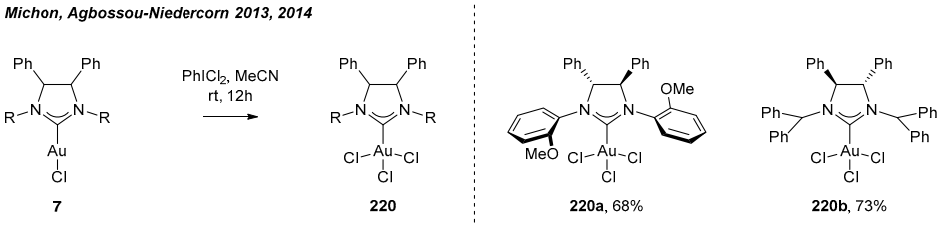


Scheme 45. Intermolecular asymmetric hydroazidation and hydroamination of allenes.

3. Chiral *N*-Heterocyclic Gold(III) Complexes

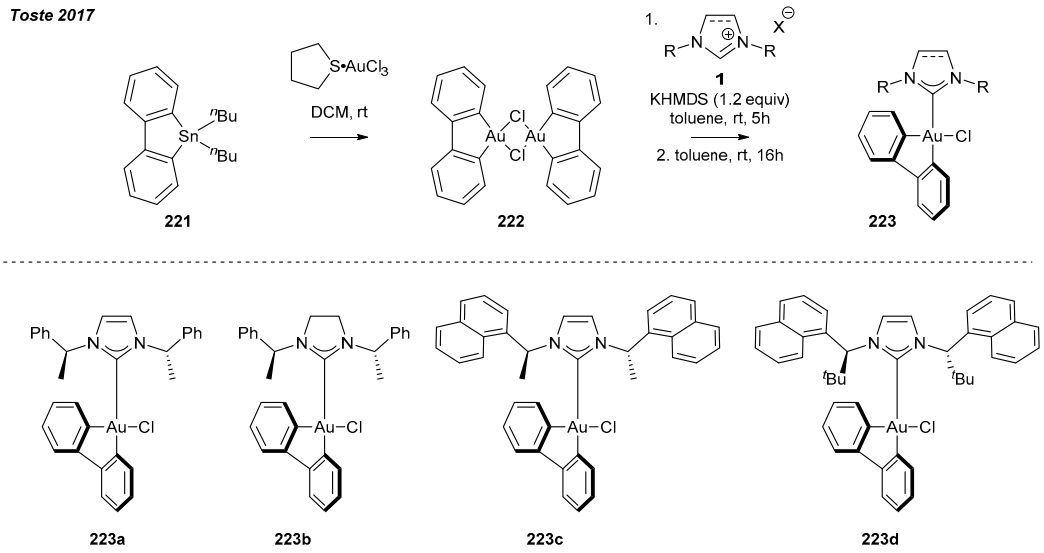
3.1. The Synthesis of Gold(III) Complexes

In contrast to gold(I) complexes, the synthetic efforts leading to their gold(III) counterparts have met with little success to date and there have only been two reports devoted to chiral gold(III) complexes. The seminal work of Michon and Agbossou-Niedercorn [115,118] proved that chiral gold(III) complexes are readily available by a protocol initially developed by Nolan et al. [61]. Gold(I) complexes **7** were oxidized by the action of $PhICl_2$ at rt to afford stable products **220a** and **220b** with quite good yields (See Scheme 46).



Scheme 46. The synthesis of gold(III) complexes via oxidation with $PhICl_2$.

Further examples of chiral gold(III) complexes come from Toste et al. [47]. Inspired by the work of Chicote [132], the authors have prepared a series of chiral complexes **223** directly from C_2-symmetric *N*-heterocyclic carbene precursors by initial deprotonation of the salt with KHMDS and subsequent reaction with dimeric cyclometalated gold(III) **222** (See Scheme 47). Unfortunately, no yield was provided by the authors, which would be necessary for further discussion. The corresponding gold(III) dimer **222** was synthesized from stannole **221** and $AuCl_3$•tht complex. It should be noted that metal complexes developed by Toste constitute one of the rare examples of Au(III) complexes merging intrinsic stability with catalytic activity.

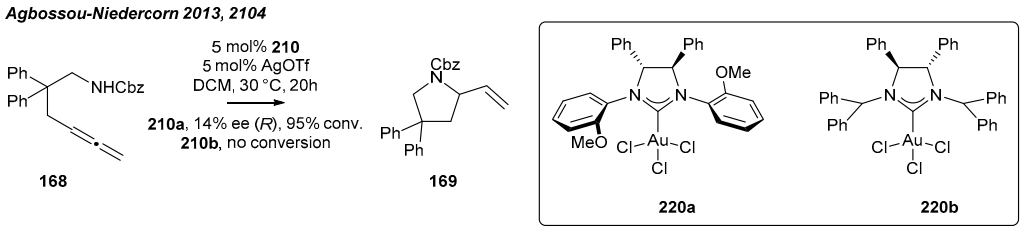


Scheme 47. The synthesis of cyclometalated gold(III) complexes.

3.2. Applications of Chiral N-Heterocyclic Carbene Gold(III) Complexes in Asymmetric Catalysis

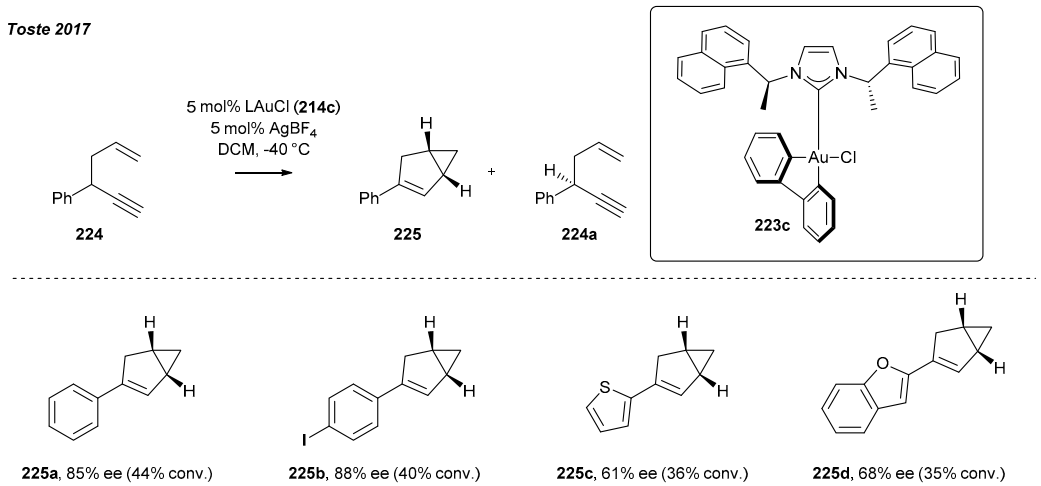
The above-described gold(III) chloride complexes **220** were used as an efficient catalyst for intramolecular hydroamination of protected allenylamine **168** [118]. Complex **220a** resulted vinyl pyrrolidine **169** with low enantioselectivity, although high conversion was observed. In contrast, complex **220b** displayed no activity (See Scheme 48). The enhanced activity of **220a** was attributed

by the authors to the coordination of the methoxy group to the gold center [133]. It should be underlined that presented hydroamination of allene **168** constitutes the first examples of gold(III) catalyzed enantioselective process. Pyrrolidine **169** could also be synthesized by the silver- or gold(I)-catalyzed [116,117] process with the high enantioselectivity.



Scheme 48. An application of gold(III) complexes in intramolecular hydroamination.

Further studies of Toste have proved that C_2-symmetric cyclometalated complexes **223** are useful in enantioconvergent kinetic resolution of 1,5-enynes [47]. A series of 1,5-enynes **224** resulted in bicyclic products **225** with good enantioselectivity and quite good conversion (See Scheme 49). The authors also proposed a model for the prediction of enantioselectivity in all of the transformations. It should be noted that the presented reaction could not be accomplished with gold(I) and represents the first example of the application of well-defined *N*-heterocyclic carbene gold(III) complexes in an enantioselective process.



Scheme 49. An application of gold(III) complexes in kinetic resolution.

4. Summary and Outlook

Since the discovery of *N*-heterocyclic carbenes and their introduction to transition metal catalysis almost 30 years ago, the use of chiral carbene ligands has gained significant attention of the synthetic community in the last decade. Although many transition metals are able to form stable complexes with chiral *N*-heterocyclic carbenes, gold complexes have become a subject of intense research only recently. It could be possible by the formation of stable complexes, in particular in the +1 oxidation state, allowing for effective creation of a chiral environment around the central atom. The unique π-activation of multiple C-C bonds allowing for the intra- or intermolecular attacks of nucleophile has led to an enormous development of enantioselective gold catalysis. Bearing in mind the excellent properties of chiral *N*-heterocyclic carbenes as ligands, further development requires ready access to chiral ligands for gold-catalyzed processes, which would enable their implementation in heterogeneous catalysis and fulfil the criteria of industrial applications. Furthermore, recent breakthrough reports

on the synthesis of gold (III) complexes and their catalytic activity provide a good platform for the design of tandem processes to build molecular complexity, where the course of each step depends on the oxidation state of the gold atom. This could perhaps lead to transforming enantioselective gold catalysis from a laboratory curiosity into a useful tool for organic synthesis in the near future.

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Conflicts of Interest: The authors declare no conflict of interest.

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