Review

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

Michał Michalak \(^1,*,2\) and Wioletta Kośnik \(^2\)

\(^1\) Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
\(^2\) NanoVelos S.A., Rakowiecka 36, 02-532 Warsaw, Poland; kosnikw@yahoo.com

* Correspondence: michal.michalak@icho.edu.pl; Tel.: +48-22-343-2018

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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 carbene; 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].
The older synthetic route involved the formation of a silver complex by the action of silver oxide on catalysts. This method has been independently reported at the same time by Gimeno [57] and Nolan [58]. The formation of gold(I) complexes is observed for tetrahydrothiophene (tth) gold(I) chloride in some cases ([51]). Dimethyl sulfide gold(I) chloride is commonly applied. However, higher yields are achieved with the application of this method. 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 NaAuCl₄ in 3-chloropyridine [55] or N-heterocyclic hydrogen carbonate salt [56] with AuCl•SMe₂ 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•SMe₂ with chloride salts of N-heterocyclic carbene precursors 1 in the presence of K₂CO₃ in DCM or acetone. Recently, the application of NBu₄(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

![Figure 1](image_url). 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 carbene 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 (tth) 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].
mixture of NaH/KO\textsubscript{t}Bu [61] (NaH is used as the stoichiometric base, whereas KO\textsubscript{t}Bu acts as a phase transfer catalyst) in ethereal solvents. The combination of AuCl\textbullet SM\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{4}Cl 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, imidazolinium 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).
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 2. The synthesis of C$_2$-symmetric gold(I) complexes from chiral amines.
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 KOtBu.

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

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$_2$CO$_3$. 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.
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 6. The synthesis of NHCAuCl complexes based on a binaphthyl skeleton fused with an eight-membered ring.

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 KOtBu.

![Scheme 8. The synthesis of $N$-heterocyclic carbene precursors bearing a biphenyl subunit.](image)

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 KOtBu.
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 \(\pi\)-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.

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 \(\pi\)-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.

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 stereochromically 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<sub>a</sub>,S) isomer 69b than for (R<sub>a</sub>,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-dichloroisquinoline (70) with boronic acid 71. Then, 2-chloroisquinoline 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]quinoxaline 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]quinoxaline 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] (Tf₂O/Et₃N), 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 Tf₂O and Et₃N [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 %Vbur. For examples, %Vbur 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).
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 \(S\)-isomer 103b into \(R\)-isomer 104b was detected by \(^1\)H NMR after 3 h at 80 °C (See Scheme 15). In contrast, when \(R\)-isomer...
104b was heated to 80 °C for 24 h, only 8% of isomer 103b formed, confirming better thermodynamic stabilization of the Ra 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 C1-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.
A straightforward approach to imidazolium salts \(\text{112}\) and gold(I) complexes \(\text{113}\) 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 \(\beta\)-amino alcohols \(\text{29}\), mesityl amine \(\text{110}\), glyoxal \(\text{30}\), and paraformaldehyde \(\text{31}\). 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 minutes 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 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 \(\text{116}\) was reported by Espinet in 2010 (Scheme 18) \[43\]. The authors proved that chiral amine \(\text{114}\) undergoes smooth addition to achiral gold(I) isonitrile complex \(\text{115}\) to form the acyclic carbene complex \(\text{116}\) which is additionally stabilized by an intramolecular hydrogen bond.
Chiral, mononuclear, C₁-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 18](image)

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

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.
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 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].

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.
were alkylated with Meerwein’s salt to provide bistriazolium salts
was treated with terminal alkynes under click conditions. The respective
bis
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Catalysts
2.4.2. Acyclic Bis-NHC Gold(I) Complexes
by Espinet et al. (Scheme 24) [93]. This pioneering work in the area of chiral gold(I) complexes
interactions were confirmed by X-ray analysis, whereas no Au-Au interaction has been detected in
gold complexes
139
139
case.
interactions were confirmed by X-ray analysis, whereas no Au-Au interaction has been detected in
binuclear
141
bearing a hydrogen bonded heterocyclic carbene (HBHC), starting from chiral amine
revealed that the respective complexes could be easily generated by the reaction of amine
A similar approach to C2-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 22. The synthesis of a 12-membered macrocyclic gold(I) complex.

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
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).

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 24. The synthesis of acyclic gold(I) complexes based on the BINAM scaffold.](image-url)
2.5. Applications of Chiral N-Heterocyclic Carbene Gold(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-enzyme 149, which was studied by Tomioka [62], Kündig [104], Haasmi [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-enzyme 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-enzyme 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 terms of yield and enantioselectivity [105]. It should be mentioned that direct comparison of NHCAuCl and phosphine-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 PtCl2/(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.

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-enzyme 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 enantioselectivity [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.

### 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 tetrahydrofuran derivatives 165 with high enantioselectivity [114].

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

### Scheme 31. The synthesis of a vinylfuran derivative via alkoxy cyclization.
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 C2-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.](image)

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)-bispshophine 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 alkyn 182. Although the enantioselectivity level was far from practical (Scheme 35), especially in comparison to the bispshophine 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].
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 \( \text{179} \) 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 \( \text{181} \) led to the product with very low enantiomeric excess. Application of chiral phosphines for this transformation has not been reported thus far.

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

Further studies of Zhang et al. [90] have revealed that structurally similar NHCAuCl complexes \( \text{103b} \) and \( \text{104b} \) can also catalyze the formation of indanone \( \text{183} \) via carboalkoxylation of alkyne \( \text{182} \).

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 \( \text{183} \) could be catalyzed by the cyclometalated gold(III) complexes \( \text{184} \) [123].

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 \( \Delta \Delta G^\ddagger \) 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 \( \text{148f} \)). 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].
The authors applied monodentate and bidentate complexes to the cyclopropanation reaction between styrene proposed by Czekelius et al. [72]. The authors utilized highly sterically demanding gold(I) complexes [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 36. The synthesis of indole derivatives bearing a fused ring system.

#### Diynamide Desymmetrization

A unique approach to substituted oxazepines featuring a quaternary stereocenter has been proposed by Czekelius et al. [72]. The authors utilized highly sterically demanding gold(I) complexes based on a bis(tetrahydroisoquinoline) skeleton for the desymmetrization of 1,4-diynes 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].

### 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].
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 38.** Enantioselective cyclopropanation.

**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 H₂, 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].
[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 biphenyl 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].

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 alkenes) 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.
A practical approach to the synthesis of tri- and tetrasubstituted alkylidene cyclobutane derivatives has been recently proposed by Chen et al. [102]. The corresponding cyclobutane derivatives were easily accessible by [2+2] cycloaddition of oxazolidinone and N-sulfonyl allene amide with styrene or stilbene derivatives. A different substitution pattern in allene amide or olefin partner 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 bearing chiral sulfoxide structural motif appeared to be excellent ligand leading to the product of type with comparable enantioselectivities.

Regarding the possible formation of a cyclobutene bearing an internal double bond [2+2] cycloaddition of terminal alkynes and 1,1-disubstituted alkenes has also been developed (See Scheme 44). The first example of this transformation, catalyzed by NHC-gold(I) complexes and ,
has been introduced by Diez 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 C1-symmetric NHCAuCl complexes 82, 88, 103b, and 104b (See Scheme 44), ferrocene-based gold(I) complex 215 appeared to be the ligand of choice for the formation of cyclobutene 215. Echevarren presented an efficient protocol leading to the product 215 with the high enantioselectivity [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, TMSN3 was used which generated HN3 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 (H2NBoc). 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)2PAuCl 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 PhICl2 at rt to afford stable products 220a and 220b with quite good yields (See Scheme 46).

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 222 directly from C2-symmetric N-heterocyclic carbene precursors by initial deprotonation of the salt with KHMD 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 AuCl3•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.

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 C2-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 fulfill 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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