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Gold(I) catalysed asymmetric hydroamination of alkenes: a silver and solvent dependent enantiodivergent reaction.

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Dedicated to Professor Jérome Lacour at the occasion of his 50th birthday.

Abstract: In the present study, we report the first silver dependent enantiodivergent gold catalysed reaction. The asymmetric intramolecular hydroamination of alkenes catalysed by the combination of a single chiral binuclear gold(I) chloride complex and silver perchlorate can afford both enantiomers of the products by a simple solvent change from toluene to methanol. Such an enantiodivergent reaction is strictly independent of the reaction temperature or of the nature of the catalyst anion and displays the same first-order kinetic rate law with respect to substrate concentration in both solvents. Beyond a simple solvent effect, the enantioinversion is controlled by gold-silver chloride adducts which occur only in methanol and allow a dual activation of the reagent. While one single gold atom activates the alkene moiety, the other gold atom forms an oxophilic gold-silver chloride adduct which is likely to interact with the carbamate function. By comparison with toluene which affords (*S*)-enantiomer, this proximal and bimetallic activation would allow an opposite stereodifferentiation of the two diastereomeric intermediates during the final protodeauration step and lead therefore to the (*R*)-enantiomer.

Introduction

The hydroamination of unactivated alkenes is the shortest synthetic route to secondary and tertiary amines.[1] For the enantioselective synthesis of optically pure amines, the most studied and privileged hydroamination method is metal catalysis.[1] Throughout recent years, gold catalysts have been successfully applied to various C-C multiple bond substrates like alkynes, alkenes, allenes, and dienes for both intra- and intermolecular hydroamination reactions.[2,3] As high temperatures, long reaction times, and strict conditions are generally required, the gold catalysed hydroamination of alkenes has been less studied in its asymmetric version.[1p,3,4] To the best of our knowledge, only seven reports have been published so far on this topic.[4] First, binuclear gold(I) catalysts based on BIPHEP ligands were found to be active for intermolecular hydroamination of ethylene and 1-alkenes with cyclic ureas leading to high yields and enantioselectivities.[4a] Latter, *tropos* BIPHEP-binuclear gold(I) species combined with chiral anions were shown to catalyse intramolecular hydroamination of *N*-alkenyl ureas at room temperature with good yields and average enantioselectivities.[4b] Thereafter, the use of several mononuclear gold(I) complexes based on axially-chiral ligands was reported to catalyse intramolecular hydroamination of *N*-alkenyl tosylates. Moderate yields and enantioselectivities were obtained at quite high temperatures and reaction times.[4c] In 2014, Widenhoefer et al. reported the intramolecular hydroamination of *N*-4-pentenylcarbamates and ureas catalysed by the combination of a mono- or binuclear gold complex and AgOTf (5 mol%) in methanol.[4d] While using a binuclear gold(I)-(*S*)-DTBM-MeO-BIPHEP catalyst, average to high yields and enantioselectivities were obtained at room temperature, 0 °C or -20 °C within 2 or 3 days of reaction. Besides the axially chiral bidentate BIPHEP ligands, monodentate phosphines derivatised from MOP ligand skeleton led to active mononuclear gold catalysts which allowed quantitative reactions but low enantioselectivities.[4d] At the meantime, following our ongoing interest in hydroamination reactions,[5] we recently reported on mononuclear gold(I)- phosphoramidite complexes which led to valuable catalysts for the intramolecular hydroamination of several alkenes at mild temperatures, providing good yields and average enantioselectivities.[4e] We subsequently studied various binuclear gold(I)-diphosphine catalysts. When combined with selected silver salts, a binuclear gold(I) chloride species built on a specific SEGPHOS diphosphine ligand proved to perform efficiently the intramolecular hydroamination of alkenes at mild temperatures with high yields and enantioselectivities.[4f,g] Interestingly, both enantiomers of the products were obtained through the use of the same chiral gold catalyst by simply switching from toluene to methanol (Scheme 1).

Like many organometallics, most gold complexes require the combined use of silver salts to be activated through abstraction of halides from neutral complexes. In the past years, several groups have reported on the silver salt effects in gold catalysis.[6] Positive or negative impacts on yields and selectivities were observed.

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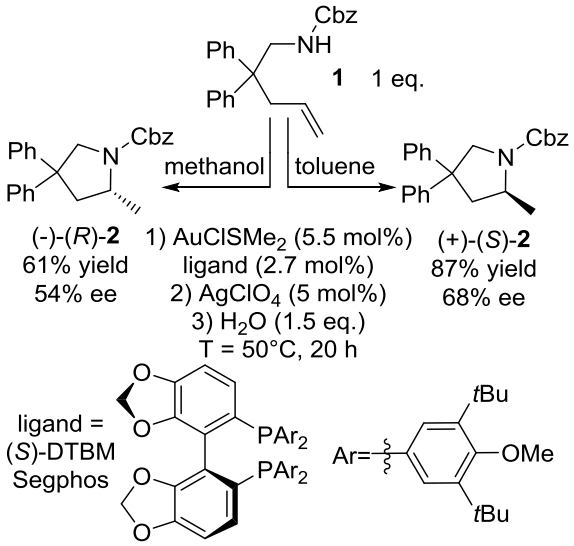


Scheme 1. Enantiodivergent intramolecular hydroamination of alkenes catalysed by gold(I) cationic complex.

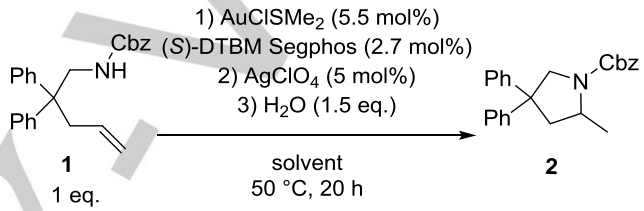
Whether the interference of silver and chloride has been highlighted by several bonding modes for cationic monomeric and oligomeric phosphine gold chloride complexes,[7] the catalytic behaviour of such gold-silver chloride species was, to the best of our knowledge, never rationalised before.

Along our studies on gold catalysed hydroamination reactions, we noticed a positive silver effect for binuclear gold(I) catalysts but none for mononuclear ones.[4e-g,5c] Indeed, a phosphoramidite mononuclear gold(I) cationic species led to an unchanged reaction outcome while removing AgCl by filtration through Celite™ or a PTFE filter prior to the catalysis. However, a significant decrease of yields and enantioselectivities was observed when a binuclear gold(I) catalyst was filtered in a similar way. Hence, we assumed one gold atom of the binuclear catalyst may interfere positively with silver chloride within the catalytic process depending on the solvent used. Though various enantiodivergent reactions using a single chiral catalyst have been reported,[8] their mechanisms remain not well understood. However, some previous studies demonstrated through kinetic analyses and calculations the origin of solvent-dependent stereodiscrimination was often controlled by an enthalpy-entropy compensation.[9] Regarding gold catalysed enantiodivergent reactions, solvent, temperature or counterion proved to induce the enantioinversion alone or in combination with one another.[10-12] Herein, we report the first silver and solvent dependent enantiodivergent gold(I) catalysed reaction.

Results and Discussion

The influence of solvents on the enantiodivergent hydroamination of alkenes was studied first (Table 1). Whether coordinative solvents like tetrahydrofurane (THF) and 1,4-dioxane led to poor yields (entries 1-2), apolar aromatic solvents allowed the reaction to proceed in high yields and good enantioselectivies for the (*S*)-enantiomer, toluene being the best (entries 3-7). Interestingly, the addition of water to the reaction mixture significantly improved yields and to a lesser extent enantioselectivities (entries 5-7). The combined use of toluene and 1.5 equivalent of water offered the best compromise for yield and enantioselectivity. While using polar solvents, rather mixed results were obtained. Whether 1,1,2,2-tetrachloroethane (TCE) did not allow any reaction (entry 8), ethylenecarbonate afforded product **2** in good yield and low enantioselectivity (entry 9). Surprisingly, the use of nitromethane (entry 10) or several alcohols (entries 11-16) resulted in an enantioinversion, (*R*)-enantiomer being obtained in average to high yields. Methanol appeared as the best alcohol solvent affording (*R*)-**2** in 54% ee while using 1.5 equivalent of water (entries 15-17). In addition, we noticed the use of either toluene or methanol led to similar enantioinversions for *N*-alkenyl BOC, urea and methylester substrates (Table S1).

Table 1. Effect of the solvent on the hydroamination of **1**.

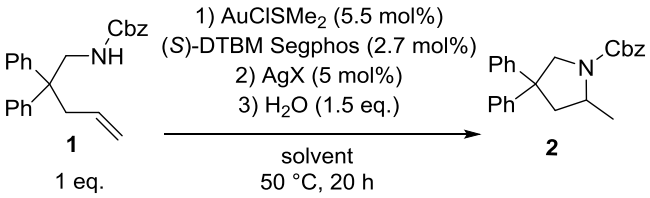


Entry	Solvent	Yield (%)[a]	Ee (%)
1	THF	35	21 (*S*)
2	1,4-dioxane	< 5	-
3	*m*-xylene	78	67 (*S*)
4	Benzene	90	65 (*S*)
5	Toluene	87	68 (*S*)
6	Toluene + no H_2O	71	63 (*S*)
7	Toluene + 10 eq. H_2O	94	67 (*S*)
8	1,1,2,2-tetrachloroethane (TCE)	< 5	-
9 [c]	ethylene carbonate	71	18 (*S*)
10	NO_2Me	> 95	5 (*R*)
11	*t*-BuOH	38	1 (*R*)
12	*i*-PrOH	43	27 (*R*)
13	CF_3CH_2OH	90	14 (*R*)
14	Ethanol	36	44 (*R*)
15	Methanol	61	54 (*R*)
16	Methanol + no H_2O	76	52 (*R*)
17	Methanol / H_2O (1/1)	< 5	-

[a] measured by ^1H NMR. [b] From HPLC.

We next focused on the influence of the anion and the dehalogenating cation on the yield and enantiomeric excess (Table 2). Among the various salts screened, perchlorate and tetrafluoroborate anions appeared to be the most appropriate (entries 1−2, 9-10). When product **2** was formed, the enantioselectivity and the nature of the ion pairing[13] were unrelated under our reaction conditions. The catalyst proved to be unreactive when associated with $BArF_{24}$ anion or chiral TRIP phosphate, even with stronger reaction conditions (entries 16-22). Finally, the chloride abstraction of the gold(I) pre-catalyst and therefore the reaction needed a silver cation to proceed.

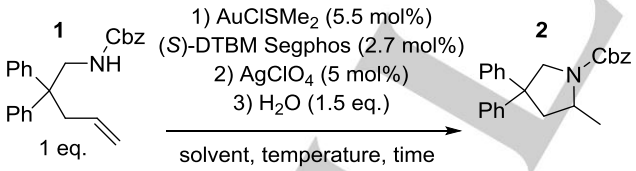
Table 2. Effect of the anion on the reaction of **1**.



Entry	AgX	Solvent	Yield (%)[a]	Ee (%)[b]
1	$AgClO_4$	Toluene	87	68 (*S*)
2	$AgClO_4$	Methanol	61	54 (*R*)
3	AgOTf	Toluene	21	67 (*S*)
4	AgOTf	Methanol	65	58 (*R*)
5	AgOTs	Toluene	0	-
6	AgOTs	Methanol	15	54 (*R*)
7	$AgSbF_6$	Toluene	>95	48 (*S*)
8	$AgSbF_6$	Methanol	86	52 (*R*)
9	$AgBF_4$	Toluene	>95	62 (*S*)
10	$AgBF_4$	Methanol	49	55 (*R*)
11[c]	$AgNTf_2$	Toluene	61	41 (*S*)
12	$AgNTf_2$	Methanol	64	54 (*R*)
13	$KNTf_2$	Toluene	0	-
14	$KNTf_2$	Methanol	0	-
15[d]	AgPNB	Toluene	0	-
16[e,f]	(*R*)-AgTriP	Toluene	0	-
17[f,g]	(*R*)-AgTriP	Methanol	17	53 (*R*)
18[e,f]	(*S*)-AgTriP	Toluene	0	-
19[f,g]	(*S*)-AgTriP	Methanol	10	52 (*R*)
20[h]	$AgBArF_{24}$	Toluene	10	5 (*S*)
21[h]	$NaBArF_{24}$	Toluene	0	-
22[h]	$NaBArF_{24}$	Methanol	0	-

[a] measured by ^{1}H NMR and average of 2 runs. [b] From HPLC. [c] NTf_2: trifluoromethanesulfonimide. [d] PNB: paranitrobenzoate. [e] same result at 100 °C for 67 h. [f] TriP: 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl-phosphate. [g] at 65°C, 96 h. [h] $BArF_{24}$: tetrakis[(3,5-trifluoromethyl)phenyl]borate.

Table 3. Effect of the reaction temperature on the enantioselectivity of **2**.



Entry	Solvent	Temperature	time	Yield	Ee of **2**
1	Toluene	50	20	94	69 (*S*)
2	Toluene	30	20	47	75 (*S*)
3	Toluene	30	110	90	75 (*S*)
4	Toluene	0	68	19	68 (*S*)
5	Methanol	50	20	61	54 (*R*)
6	Methanol	30	20	25	58 (*R*)
7	Methanol	30	110	58	59 (*R*)
8	Methanol	0	68	0	-

[a] From ^{1}H NMR. [b] From HPLC.

Furthermore, we noticed any modification of the reaction procedure[6e] resulted in a significant fall-off in yields and a slight decrease of the enantioselectivity. The same trend was observed when catalyst was filtered through a PTFE filter before the reaction (Table S2).

Regarding the effect of the reaction temperature on enantioselectivity, the hydroamination reactions in toluene and methanol were significantly slowed down or inhibited by decreasing the temperature to 30 and 0°C without any further inversion of the enantioselectivity (Table 3). Through kinetic analyses in both solvents, we observed the same first-order kinetic rate law with respect to substrate concentration in methanol and toluene at 50°C (Figures S1-S5). Moreover, by using deuterated methanol, we observed a strong isotopic effect: t = 20 h, 25 % conv. in MeOH-d^4 / 61% conv. in MeOH. Though a deuterium-proton exchange between the methanol and the amine was likely to proceed during the reaction, the steps involving a proton migration/transfer appeared as the rate limiting ones.[14] Furthermore, no non-linear effects were observed (Figure 1) and enantiomeric excesses proved to be stable along time (Figure 2).

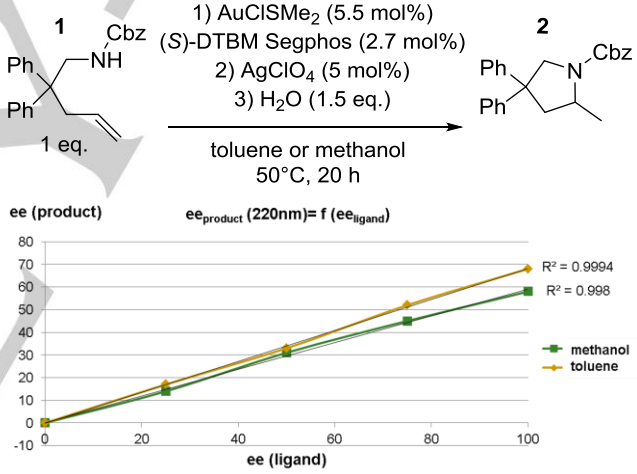


Figure 1. Study of non-linear effects on the hydroamination of **1**.

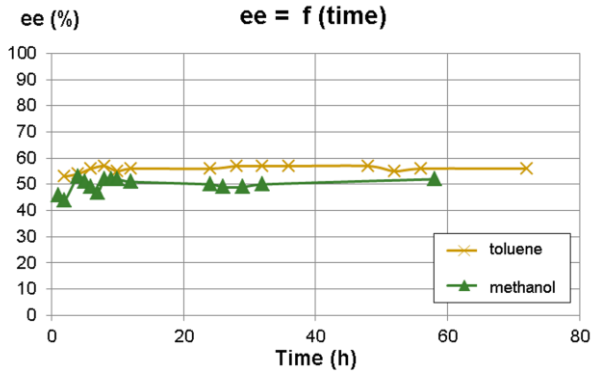
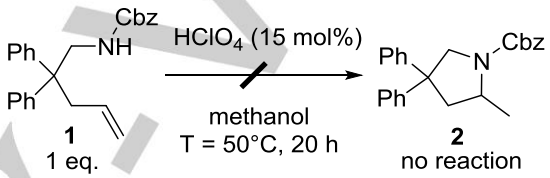


Figure 2 Stability of enantiomeric excess of **2** along time.

Though the structure of the catalyst resting state was not confirmed, we could consider the nuclearity of the gold active species remained unchanged during the whole

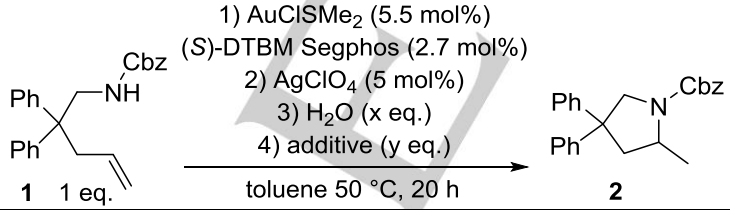
catalytic process[15] and excluded also any involvement of an in-situ kinetic resolution.[16] Finally, in spite of previous examples in the field of gold catalysis,[4c,17,18] our results ruled out the contribution of anion and cation π-interactions[17-20] between the catalyst and toluene along the enantiodivergent reaction.

At that stage, we focused again on the reactivity of the present gold catalysed hydroamination reaction and studied a series of control experiments through the use of several additives (Table 4). First, we performed control experiments in order to check the activity of monocationic gold complexes (entries 2,3). While the enantioselectivities decreased slightly, yields in product **2** were much lower using monocationic binuclear complex (entry 2) or cationic mononuclear complex (entry 3) instead of the dicationic binuclear complex (entry 1). The reaction was not catalysed by $AgClO_4$ itself in toluene or methanol, the cyclised amine **2** being not formed (entries 1,4,5). Moreover, because gold(I) cationic catalyst was formed prior to the addition of the reagent, any background reaction catalysed by $AgClO_4$ was unlikely (see experimental section). We next observed the reaction could be stopped by the addition of an inorganic base like Cs_2CO_3 (entry 8). However, the use of a non-coordinative base like 2,6-di-tert-butyl-pyridine didn't have any effect (entry 9). That trend was confirmed by the addition of a proton trap like $PhSi(Me)_3$ (entry 7) which didn't alter the reaction course. A last control experiment proved the reaction was not catalysed by perchloric acid (Scheme 2). Hence, the presence of free protons in the reaction medium was here unlikely. However, the use of an alcohol along with a cationic binuclear gold complex was reported by Toste et al.[21] to generate an acidic species which catalysed the hydroamination reaction of 4,6-heptadienyl sulfonamides following a Brønsted acid catalysed pathway. We performed a series of reactions by adding 1.5 equivalents of an alcohol to the reaction mixture in toluene (entries 10-18). Depending on the nature of the alcohol used, the yields could be improved, but no global trend was noticed. Enantioselectivities were either stable or reduced and no enantioinversion were observed. Finally, the use of (+)-phenylethanol, (-)-menthol or methanol increased slightly the ee values to 67% ee, whereas yields were respectively 88, 67, and 97 % (entries 11, 12, 18). On the basis of these results, we concluded any Brønsted acid catalysis[21] was unlikely.



Scheme 2. Control experiments regarding the use of $HClO_4$ as catalyst for the hydroamination of aminoalkene **1**.

Table 4. Effect of additives on the hydroamination of aminoalkene **1**.

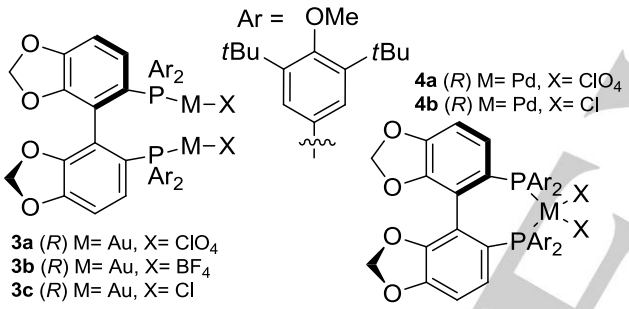


Entry	Water	Additive	Yield (%)[a]	Ee (%)
1	1.5 eq.	None	87	68 (*S*)
2	1.5 eq.	None, ligand + 5.5 mol% $AuClSMe_2$ + 2.5 mol% of $AgClO_4$	40	61 (*S*)
3	1.5 eq.	None, ligand + 2.7 mol% $AuClSMe_2$ + 2.5 mol% $AgClO_4$	29	66 (*S*)
4[b]	1.5 eq.	None, only $AgClO_4$ was used in toluene	0	-
5[b]	1.5 eq.	None, only $AgClO_4$ was used in methanol	0	-
6[c,d]	1.5 eq.	None, only ligand and $AgClO_4$ were used	0	-
7	1.5 eq.	PhTMS (1 eq.)	84	64 (*S*)
8	1.5 eq.	Cs_2CO_3 (5.5 mol%)	0	-
9	1.5 eq.	2,6-di(terbutyl)pyridine (5.5 mol%)	54	57 (*S*)
10	None	None	81	64 (*S*)
11	None	(1*R*,2*S*,5*R*)-(-)-menthol (1.5 eq.)	67	67 (*S*)
12	None	(*R*)-(+)-phenylethanol (1.5 eq.)	88	67 (*S*)
13	None	*t*-BuOH (1.5 eq.)	76	62 (*S*)
14	None	guaiacol (1.5 eq.)	61	57 (*S*)
15	None	CF_3CH_2OH (1.5 eq.)	92	42 (*S*)
16	None	cyclohexanol (1.5 eq.)	83	64 (*S*)
17	None	phenol (1.5 eq.)	73	41 (*S*)
18	None	methanol (1.5 eq.)	97	67 (*S*)

[a] measured by ^1H NMR. [b] performed without ligand and $AuClSMe_2$. [c] performed without $AuClSMe_2$. [d] same result in methanol.

In order to define the bonding mode of our cationic gold(I) species in solution, DOSY ^{1}H NMR experiments were performed on several gold catalysts using palladium complexes as references (Table 5). We found a good agreement between diffusion coefficient D and hydrodynamic radius rH of all species. This therefore confirmed the presumed nuclearity and coordination of our catalysts, i.e. two gold atoms coordinated to one diphosphine ligand, and tended to prove any chloride and/or silver bridged species[6d-e] was unlikely. Indeed, compounds with higher molecular volumes and weights would have displayed lower diffusion coefficient D and higher hydrodynamic radius rH. As water was required in the catalytic medium,[4g] we followed by NMR the reaction of substrate **1** with a stoichiometric amount of pre-formed gold complex **3a** in order to check if **3a** was likely to be hydrolysed or not.[22] NMR analyses of aliquots showed unchanged ^{31}P spectra were obtained along all the reaction and no hydrate or hydroxide species were present on ^{1}H spectra (Figures S2-S5), suggesting a strong Brønsted basic gold species was not observed at the NMR time scale and was rather unlikely to be formed.[22c]

Table 5. Results of DOSY ^{1}H NMR experiments.



3a (*R*) M= Au, X= ClO_4
3b (*R*) M= Au, X= BF_4
3c (*R*) M= Au, X= Cl
4a (*R*) M= Pd, X= ClO_4
4b (*R*) M= Pd, X= Cl

Compound	D(^{1}H) (10^{-10}m^2 s^{-1})	rH (Å)
(*S*)-DTBM-Segphos	5.03	8.1
(*R*) 3a	4.98	8.2
(*R*) 3b	4.85	8.4
(*R*) 3c	4.96	8.2
(*R*) 4a	4.91	8.3
(*R*) 4b	4.96	8.2

At the solid state, the structure of pre-catalyst **3c** and catalyst **3b** were confirmed by X-ray diffraction analysis (Figures 3, S6-S7). The data were refined using a rigid body approach because *t*Butyl substituents were disordered. For complex **3b**, anions, i.e. tetrafluoroborate here, proved to be coordinated to the gold atoms which were not bound to each other being 4.390(19) Å apart. Hence, by using weakly coordinative tetrafluoroborate anions, complex **3b** could be considered as a neutral species like it was previously observed for other complexes with NTf_2 anion.[23] We measured for **3b** a molecular radius of 8.989(19) Å (Figures 3,S6) which was close from its rH value calculated from the DOSY ^{1}H NMR experiments. On the whole, the molecular structure of the gold(I) binuclear complexes was confirmed, two gold atoms being coordinated to one DTBM Segphos diphosphine ligand.

The structure of gold perchlorate catalyst **3a** was also studied at the solid state. Whether no crystals were obtained when complex **3a** was prepared in toluene, it was isolated and characterised by liquid NMR as well as elemental analysis on solids without any doubt. However, X-ray diffraction analyses on crystals obtained from **3a** in methanol-diethyl ether mixtures revealed different species which were likely to arise out of a partial decomposition of **3a** (Scheme 3, Figures 4-5 and S8-S10). Among the several possible mono- and dicationic complexes, species **3d** and **3e** were observed by X-ray diffraction.

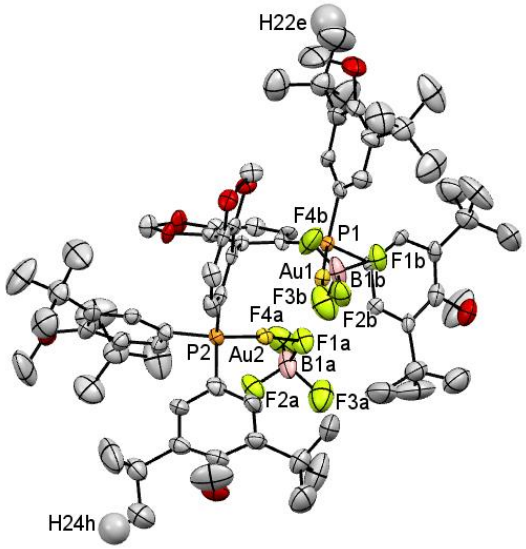
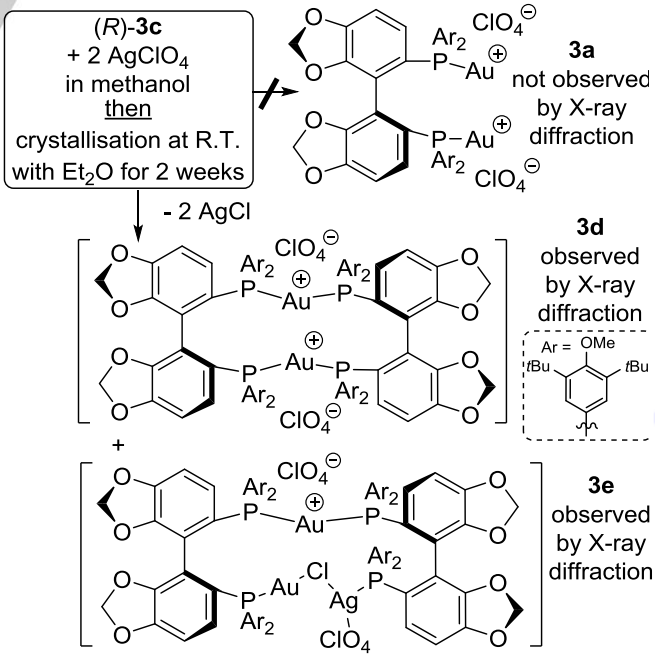


Figure 3. Molecular structure of catalyst **3b** at the solid state. Thermal ellipsoids are shown at the 50% probability level. Hydrogens atoms and 2 molecules of toluene were omitted for clarity. Selected bond lengths (Å): Au1-Au2 4.390(19), P1-Au1 2.213(2), P2-Au2 2.205(2), Au1-F3b 2.101(15), Au2-F1a 2.095(15). CCDC 995301.



Scheme 3. Crystallisation in methanol of gold(I) cationic complexes **3d** and **3e**.

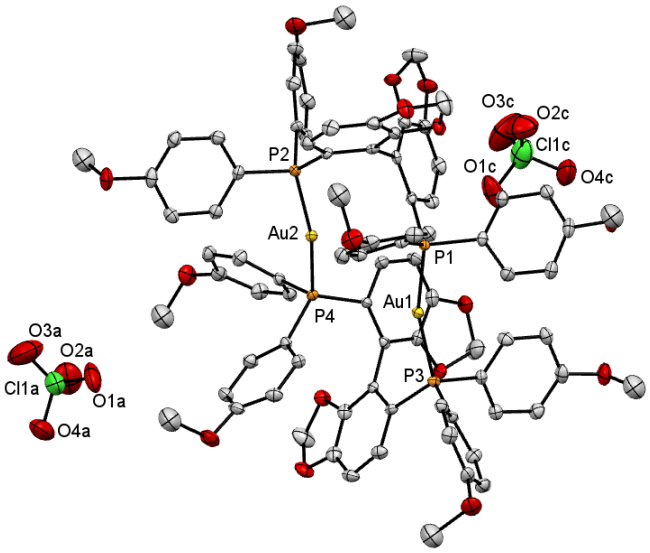


Figure 4. Molecular structure of complex **3d** at the solid state. Thermal ellipsoids are shown at the 50% probability level. Hydrogens atoms, *t*Bu groups and a disorder on one of the ClO_4 anions were omitted for clarity. Selected bond lengths (Å): Au1-Au2 3.930(19), P1-Au1 2.318(3), P2-Au1 2.320(3), P3-Au2 2.311(2), P4-Au2 2.301(3). CCDC 1539521 (ClO_4) and CCDC 1539523 (SbF_6).

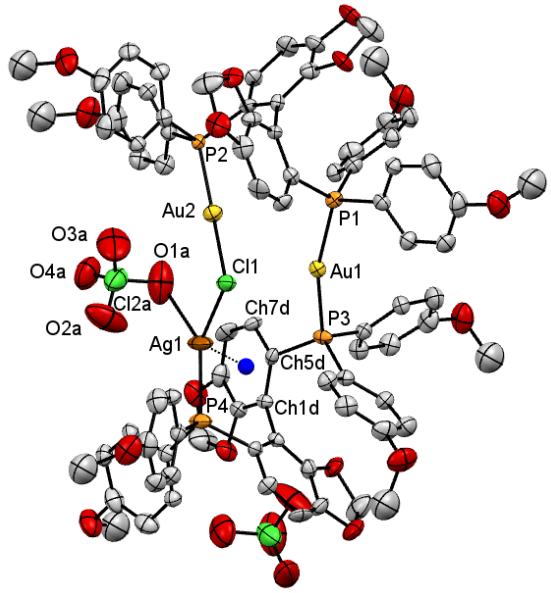
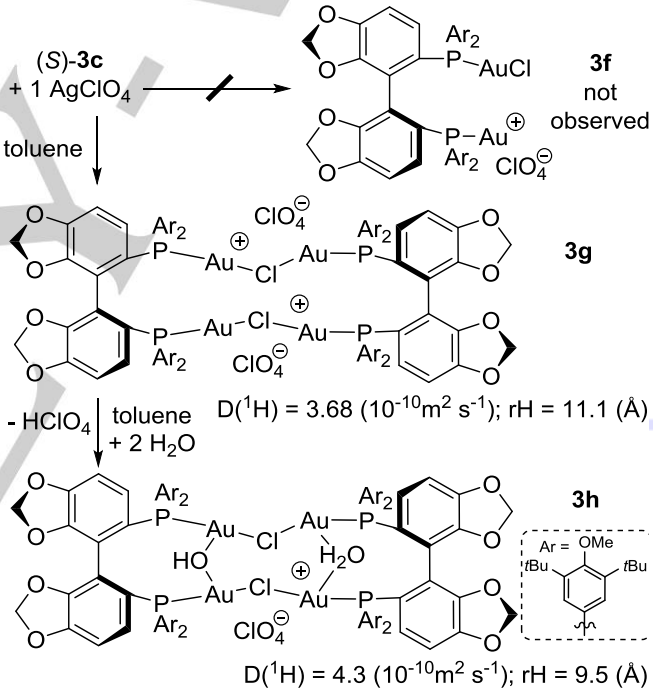


Figure 5. Molecular structure of complex **3e** at the solid state. Thermal ellipsoids are shown at the 50% probability level. Hydrogens atoms and *t*Bu groups were omitted for clarity. Selected bond lengths (Å): Au1-Au2 3.552(19), P1-Au1 2.314(2), P2-Au2 2.242(2), P3-Au1 2.321(3), Au2-Cl1 2.345(2), Cl1-Ag1 2.552(3), Ag1-P4 2.373(2), Ag1-O1a 2.464(19), Au1-Ag1 4.160(19), Ag1-Ch1d 3.233(19), Ag1-Ch5d 2.705(19), Ag1-Ch7d 2.901(19), Ag1-blue centroid 3.100(19). CCDC 1539524.

Both complexes had two gold atoms which were not coordinated to each other or to perchlorate anions, and whose coordination appeared to be different from **3b** (Figures 4-5, Figures S8 and S10). Indeed, we observed two (*S*)-DTBM-Segphos ligands were coordinated to the two gold atoms in a trans-fashion. It was worth to note a similar species was formed while using silver hexafluoroantimonate (Figure S9). As compared to complex **3d**, X-ray diffraction analysis of species **3e** showed an additional silver chloride molecule inserted into one of the phosphorous-gold bonds (Figures 5 and S10). Whereas silver chloride was once shown to form a triangular fragment with a gold(I) NHC complex,[7f] species **3e** highlighted for the first time a rather linear adduct, gold and silver being connected through a μ-chloro bridge and coordinated to two distinct phosphorous atoms. It was worth to note the coordination geometry of the silver centre was likely trigonal pyramidal as this metal was also bound to an oxygen of a perchlorate anion and to aromatic carbons through pi-stacking interactions, a silver-centroid distance of average 3.100(19) Å being measured (Figure 5). In the past, several silver chloride adducts were characterised for gold(I),[6,7f] iridium(I)[24] and platinum(II) complexes.[25]

As monocationic binuclear complexes were shown to be preferred in the case of the intramolecular hydroalkoxylation of allenes,[26] we subsequently investigated the synthesis of monocationic binuclear gold complex **3f** through the use of a single equivalent of silver perchlorate (Scheme 4, Figures S11-S13).



Scheme 4. Synthesis of gold(I) cationic complexes **3g** and **3h**.

To our surprise, we isolated complexes **3g** and **3h** as the result of a self-assembly of two species **3f**.[27] For **3g**, both (*S*)-DTBM-Segphos ligands were respectively coordinated to two gold atoms and the resulting complexes were connected to each other through two μ-chloro bridges. Compound **3h** had a related but more rigid molecular structure than **3g** thanks to the additional hydroxyl and aquo bridges linking the gold atoms. Whether we were unable to get any suitable crystals for X-ray diffraction analysis, DOSY ^{1}H NMR experiments confirmed clearly compounds with higher molecular volumes and weight than **3f** were formed. Indeed, lower diffusion coefficients D and higher hydrodynamic radii rH were observed for **3g** and the rigid **3h** as compared to **3f** whose D and rH values would have been close from complexes **3a-c** (Scheme 4, Table 5).

Mass spectrometry and other analyses confirmed **3g** and **3h** complexes were obtained and, similar species were formed while using silver hexafluoroantimonate (Figure S13 and other supporting informations). Finally, it was worth to note complexes **3g** and **3h** were far less efficient catalysts for the hydroamination of amino-alkene **1** (Figure S12).

Following these rather unexpected results, dinuclear gold perchlorate catalyst complex **3a** was analysed in methanol by ESI-FT mass spectrometry (Figure 4, figures S14-S19). Two monocationic gold complexes, respectively binuclear and mononuclear, were first identified along with some oxidised ligand. We further noticed a good agreement of experimental and simulated isotopic ratios for the chlorinated binuclear species (Figures S16-S19). Moreover, the expected dicationic gold species was not detected at m/z 786.745 and a silver–chloride adduct of a binuclear monocationic gold complex was observed. In order to check whether the observed species could be affected by the solvent and the ionisation mode, additional analyses of complex **3a** were performed in toluene using a mass spectrometer coupled with an additional Liquid Injection Field Desorption Ionization (LIFDI) source (Figures S20-S21).[28]

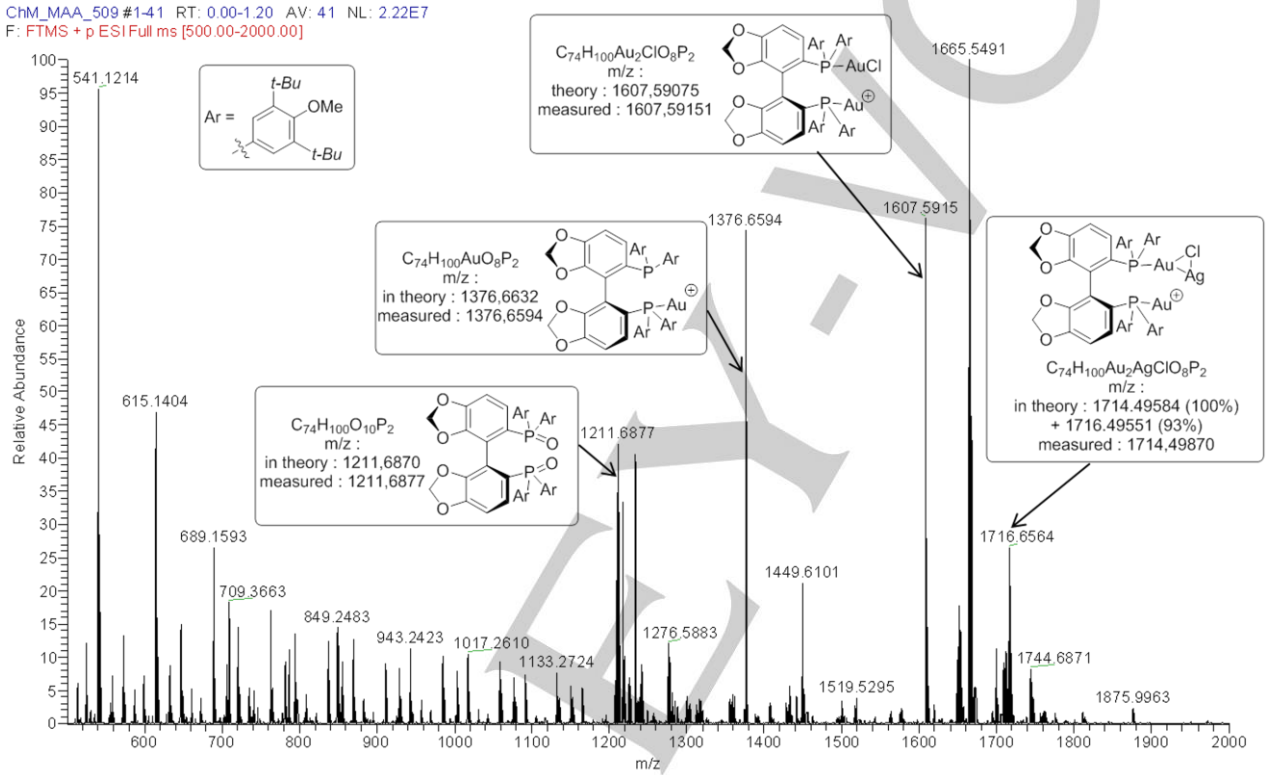


Figure 6. Mass spectrum of compound **3a** in methanol.

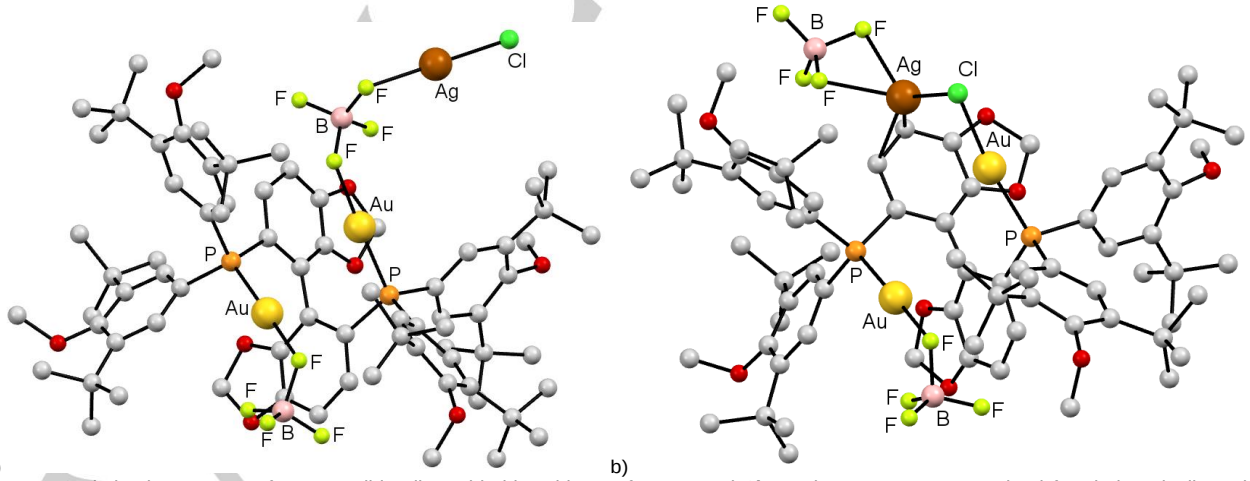


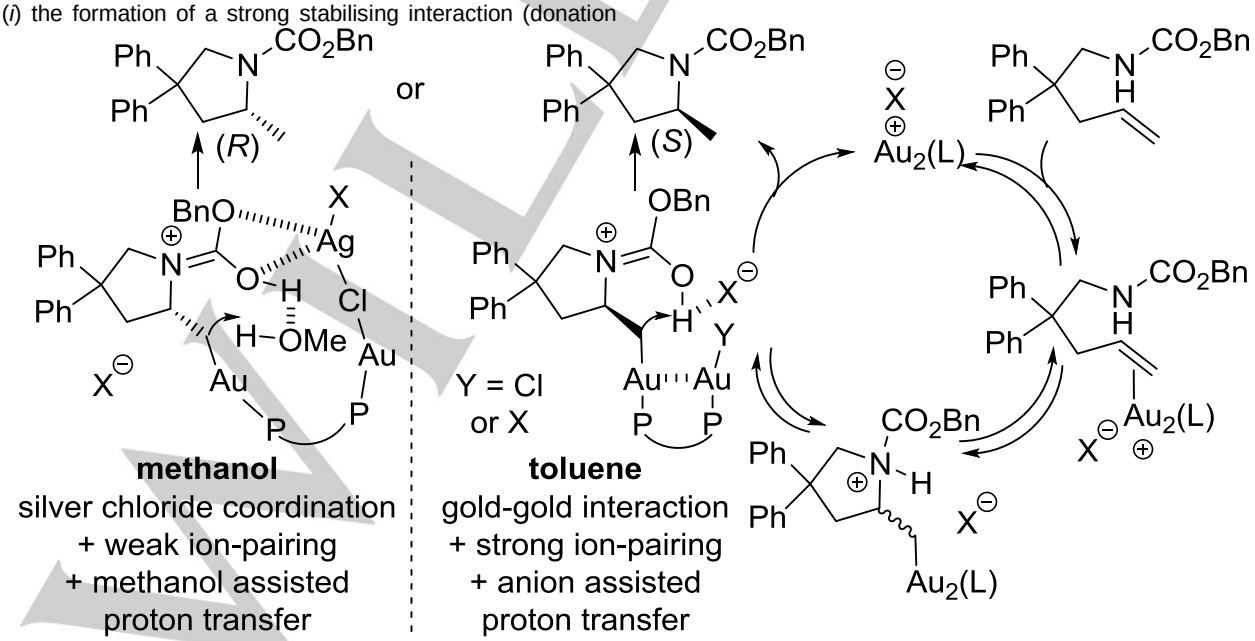
Figure 7. Optimized structures of two possible silver chloride adducts of compound **3b**. Hydrogen atoms are omitted for clarity. a) silver chloride interacting only with one of the tetrafluoroborate anions; b) silver coordinating to a tetrafluoroborate anion and to two aromatic carbons of the phosphine ligand as well as direct bonding of the chloride atom to one of the gold centres.

The resulting mass spectra were in good agreement with the ESI-MS data as two binuclear monocationic gold complexes were observed, one gold atom being bound either to a chloride, either to a perchlorate anion. In addition, similar isotope distributions were observed for measured and simulated spectra. At that stage, though mass spectrometry had already allowed identification of several transient gold species,[29] we remained careful about drawing a parallel between a mass analysis and a solution phase synthesis or catalysis.

Two possible silver chloride adducts of complex **3b** (Figure 7) were investigated by DFT calculations at the B3PW91 level of theory. A first adduct showed silver chloride interacting only with one of the tetrafluoroborate anions (Figure 7a). A second adduct was found more stable by 12.3 kcal.mol^{-1} (Gibbs free energy) as the result of the direct bonding of the chloride atom to one of the gold centres together with the coordination of the silver atom to a tetrafluoroborate anion (Figure 7b). The energy difference between these two complexes could be explained by the second-order perturbation of the NBO's analysis which highlights the formation of two stabilising interactions, between the chloride atom and the gold atom (donation from a chloride lone pair to an anti-bonding Au-P orbital) and between the silver atom and two aromatic carbons of the phosphine ligand (donation from the π C-C bond to an empty *s* orbital of silver). These stabilising interactions counterbalanced the breaking of the interaction between a tetrafluoroborate anion and a gold atom. By comparison, the interaction mode of silver chloride in complex **3e** (Figure 5) was also theoretically studied. In this case, a decrease of the interaction between Ag and Cl is observed as evidenced by the elongation of the Ag-Cl bond in **3e** with respect to the most stable adduct **3b** (2.552 and 2.438 Å resp.). This was in agreement with the decrease of the donation of the chloride lone pairs to an empty *s* orbital of the silver atom (18 kcal.mol^{-1} for **3e** *vs.* 47 kcal.mol^{-1} for **3b**). According to second order perturbation NBO analysis, this difference was due to: (*i*) the formation of a strong stabilising interaction (donation from a chloride lone pair to one of the gold centres, yielding to a stabilisation energy of 83 kcal.mol^{-1} which was slightly higher than the 70 kcal.mol^{-1} found for **3b**); (*ii*) the stabilisation of the silver atom in complex **3e** due to the donation from a phosphorous lone pair to an empty *s* orbital of the silver atom (85 kcal.mol^{-1}) and from a lone pair of one of the oxygen atoms of a perchlorate anion to an empty *s* orbital of the silver atom (14 kcal.mol^{-1}).

Analyses by X-ray fluorescence spectrometry were performed on catalyst **3a** solutions after decantation of silver chloride residues (Figures S22-S23). Whether no silver was present in toluene, methanol solutions of catalyst **3a** proved to contain silver and gold in a 1:2 ratio. Hence, the use of methanol allowed the solvation of silver chloride and could favour the formation of a silver adduct on the basis of catalysts **3a** or **3b** (Figure 7) or like complex **3e** (Scheme 3, Figure 5).

Considering the reaction mechanism hypothesis (Scheme 5), the first step shall be the electrophilic activation of the alkene by the gold catalyst followed by the nucleophilic attack of the amine which was previously found to be reversible.[30-33] Second, the tautomerization of the resulting carbamate intermediate is likely to be assisted by an anion (perchlorate in our case).[34,35] Finally, the stereochemical outcome of the hydroamination reaction appeared to be defined during the final protodeauration step[30] by differentiation of the two assumed diastereomeric intermediates depending on the solvent used (Scheme 5). Because the use of toluene, a low polarity solvent, would imply the absence of gold-silver chloride adducts and lead to tight ion-pairs, a single gold metal might be bound to the aminated substrate with a possible gold-gold interaction as suggested by the structure of **3c** at the solid state (Figure S7).[4b,36] As a result, the proton-transfer/protodeauration step shall be assisted by the anion[34,35] and affords the (*S*)-product.



Scheme 5. Hypothesis for the reaction mechanism.

As opposed, methanol, a high polarity solvent, might allow the presence of gold-silver chloride adducts with possible wider bite angles and weak molecular ion-pairs. Whereas methanol itself shall act as a proton transfer agent for the protodeauration step as suggested by the strong isotopic effect observed when deuterated methanol was used,[14] the aminated substrate might interact twice with a flexible gold / gold-silver species, the single gold atom being bound to the alkene moiety and the more oxophilic gold-silver adduct[32] interacting with the carbamate function. Such proximal and bimetallic activation[4b] would allow the generation of the (*R*)-product and therefore lead to the enantioinversion. Hence, the protodeauration step would imply two different intermediates by presenting the CH_2-Au group on one or the other face of the medium plane defined by the *N*-heterocycle and by taking into account steric constrains of the overall molecular structure of the catalytic intermediate. As a result, this leads to the observed opposite stereochemistries.

Conclusions

To summarise, when combined with silver perchlorate, a selected binuclear gold(I) chloride complex based on DTBM-Segphos ligand catalysed efficiently the asymmetric intramolecular hydroamination of alkenes at mild temperatures in presence of water with high yields and enantioselectivities. For the first time, both enantiomers of the products were obtained through the use of a single chiral gold catalyst by simply switching from toluene to methanol. Whereas the same first-order kinetic rate law with respect to substrate concentration was observed in methanol and toluene, analyses by X-ray fluorescence spectrometry showed only solutions of gold catalyst in methanol contained silver and gold in a 1:2 ratio. Whether several gold(I) cationic catalysts were characterised unambiguously at the solid state by X-ray analysis and in solution by diffusion NMR experiments, related silver chloride adducts were observed by ESI-MS and X-ray diffraction analysis and studied by DFT calculations. As opposed to toluene, methanol, a high polarity solvent, allows the presence of gold-silver adducts with wider bite angles and weak molecular ion-pairs. As a result, a flexible gold / gold-silver species may interact in a dual fashion with the aminated substrate. Indeed, through a double activation process, one single gold atom would be bound to the alkene moiety like in toluene and the more oxophilic gold-silver adduct would interact with the carbamate function. Hence, by comparison to toluene, methanol allows another selectivity to proceed among the two diastereomeric intermediates during the final protodeauration step and leads to the opposite enantiomer.

Experimental Section

Safety concern. Caution! Perchloric acid as well as all organic and organometallic perchlorate salts are often explosive and are thus highly dangerous.[37]

General Procedure for the catalysis

In a glovebox, $AuS(Me)_2Cl$ (0.01 mmol, 2.95 mg) and (*S*)-DTBM-Segphos (0.005 mmol, 5.90 mg) are disposed in a first Schlenk flask. Under a nitrogen atmosphere, dry dichloromethane (1 mL) is then added and the resulting mixture is stirred for 1 hour at room temperature. Afterwards, the solvent is evaporated under vacuum and the resulting solid is dried 30 minutes before addition of $AgClO_4$ (0.009 mmol, 1.87 mg) in a glovebox. Under a nitrogen atmosphere, dry toluene or methanol (1 mL) is added and the resulting solution is stirred for 30 minutes before being transferred to a second Schlenk flask containing the corresponding substrate (0.18 mmol). Finally, H_2O (0.28 mmol, 5 μL) is added under nitrogen to the reaction mixture. After 20 hours under stirring at 50 °C, the solution is filtered through a pad of silica gel using dichloromethane as solvent. After evaporation of solvents under vacuum, the resulting oil is analysed by ^1H NMR and HPLC.

Computational details

All calculations were performed with Gaussian 09.[38] Calculations were carried out at the DFT level of theory using the hybrid functional B3PW91.[39] Geometry optimizations were achieved without any symmetry restriction. Calculations of vibrational frequencies were systematically done in order to characterize the nature of stationary points. Stuttgart effective core potentials[40] and their associated basis set were used for gold, silver and chlorine. The basis sets were augmented by a set of polarization functions (ζ_f = 1.050 for Au, ζ_f = 1.611 for Ag and ζ_d = 0.6433 for Cl). Boron, fluorine, phosphorus, oxygen, carbon and hydrogen atoms were treated with 6-31G(d,p) double-ζ basis sets.[41] The electron density and partial charge distribution were examined in terms of localized electron-pair bonding units by using the NBO program implemented in Gaussian 09.[42]

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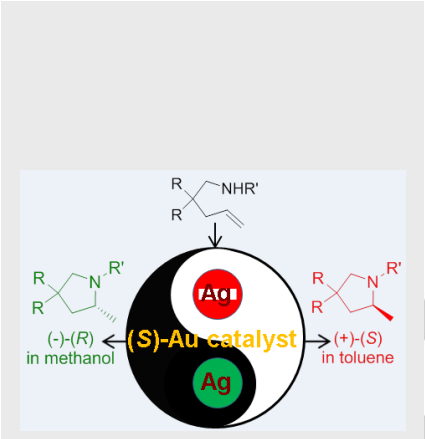
Silver and solvent dependent enantiodivergent hydroamination of alkenes using gold catalysis.

FULL PAPER

A selected diphosphine binuclear gold(I) complex catalyses efficiently the asymmetric intramolecular hydroamination of alkenes with high yields and enantioselectivities in mild and wet conditions. Both enantiomers of the products can be obtained through the use of a single chiral gold catalyst. By switching the solvent from toluene to methanol, an oxophilic gold-silver adduct is formed and allows a double activation of the *N*-alkenyl reagent.



Marc-Antoine Abadie, Xavier Trivelli, Florian Medina, Nathalie Duhal, Mostafa Kouach, Bernhard Linden, Eric Génin, Maxence Vandewalle, Frédéric Capet, Pascal Roussel, Iker Del Rosal, Laurent Maron, Francine Agbossou-Niedercorn, Christophe Michon**

Page No. – Page No.
Gold(I) catalysed asymmetric hydroamination of alkenes: a silver and solvent dependent enantiodivergent reaction.