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Chiral Au(I)- and Au(III)-Isothiourea Complexes: Synthesis, Characterization and Application

Danila Gasperini,[a] Mark D. Greenhalgh,[a] Rehan Imad,[b] Shezaib Siddiqui,[b] Anum Malik,[b] Fizza Arshad,[b] Muhammad Iqbal Choudhary,[b,c] Abdullah M. A. Al-Majid,[e] David B. Cordes,[a] Alexandra M. Z. Slawin,[a] Steven P. Nolan*[d,e], Andrew D. Smith*[a]

Dedication ((optional))

Abstract: During an investigation into the potential union of Lewis basic isothiourea organocatalysis and gold catalysis, the formation of gold-isothiourea complexes was observed. These novel gold complexes were formed in high yield and were found to be air- and moisture stable. A series of neutral and cationic chiral gold(I) and gold(III) complexes bearing enantiopure isothiourea ligands was therefore synthesized and fully characterized. The steric and electronic properties of the isothiourea ligands was assessed through calculation of their percent buried volume and the synthesis and analysis of novel iridium(I)-isothiourea carbonyl complexes. The novel gold(I)- and gold(III)-isothiourea complexes have been applied in preliminary catalytic and biological studies, and display promising preliminary levels of catalytic activity and potency towards cancerous cell lines and clinically-relevant enzymes.

1. Introduction

The concept of combining transition metal catalysis and organocatalysis is attractive due to the potential for achieving novel transformations impossible with either catalytic system alone.[1] This approach offers many advantages, in particular for the development of enantioselective transformations, where an appropriate combination of chiral catalysts can be used to achieve unprecedented levels of stereocontrol. Despite this great promise, a number of significant challenges exist. The reaction conditions must be compatible with both catalytic manifolds and each catalyst must be able to selectively activate a specific substrate and/or intermediate. Most significantly, the two catalysts must not engage exclusively in an interaction that inhibits one or both of the catalytic manifolds. This is a particular concern when combining a Lewis acidic transition metal and a Lewis basic organocatalyst.

Based on the collective expertise of our research groups, we envisaged the combination of isothiourea organocatalysis and gold catalysis may be productive for the development of novel enantioselective transformations.[2,3] Chiral isothioureas have been widely-applied as Lewis base organocatalysts, capable of promoting a diverse set of enantioselective transformations *via* acyl isothiouronium, isothiouronium enolate and α,β-unsaturated acyl isothiouronium intermediates.[2] Key to effective enantio-induction in these processes is the proximity of an sp^3-hydribrized stereogenic carbon adjacent to the catalytically-active Lewis basic sp^2-hybridized nitrogen (Figure 1).[4]

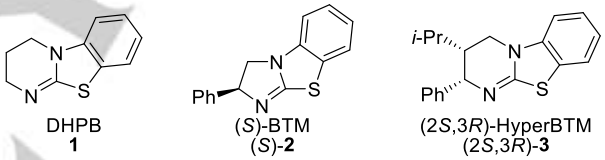

Figure 1. Selected achiral and chiral Lewis basic isothiourea organocatalysts.

Recent developments in isothiourea catalysis have focused on combining the nucleophilic isothiouronium enolate intermediate with an electrophile that is catalytically-generated by a transition metal (Scheme 1a).[5] Snaddon was first to report this successful union by using a combination of BTM **2** and a palladium catalyst for the enantioselective α-allylation of aryl acetic acid esters (Scheme 1b).[5a-f] Shortly afterwards, Hartwig reported a complementary iridium-catalyzed method to provide the related branched products (Scheme 1c).[5h] Significantly, through variation of the enantiomer of the isothiourea and iridium catalysts applied, all four stereoisomers of the product could be accessed with excellent diastereo- and enantioselectivity. More recently, Gong, and Cao and Wu have exploited the merger of isothiourea catalysis with copper catalysis, through the generation of electrophilic copper-allenylidene intermediates[5i,j] (Scheme 1d) or diaziridinone activation.[5k] In each example it has been assumed that the Lewis base and transition metal-catalyzed cycles operate independently, with no direct interaction between the Lewis basic isothiourea and transition metal required.

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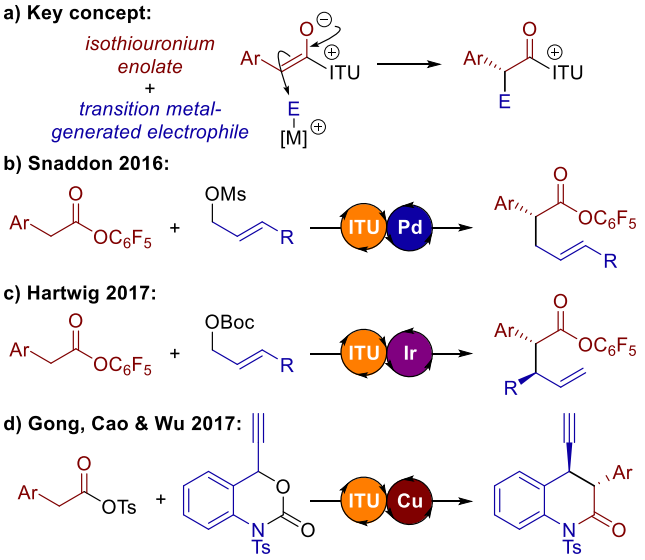
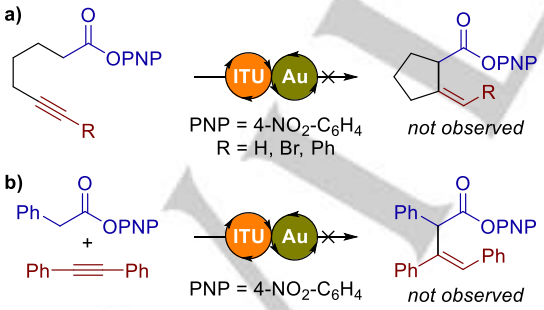


Scheme 1. Recent examples of combining isothiourea and transition metal catalysis.

We reasoned that the ability of gold catalysts to activate alkenes and alkynes could be exploited through combination with isothiourea catalysis for the enantioselective α-alkylation and α-vinylation of esters. The combination of gold with primary and secondary amine catalysts has previously been explored,[6,7] but to the best of our knowledge the use of tertiary amine catalysts has not been reported. Initial studies into the potential of this dual catalytic manifold found that despite screening a range of gold complexes, solvents and reaction temperatures, neither intra- nor intermolecular processes were successful (Scheme 2).[8] In each case only starting materials or hydrolysis products were observed. Control studies identified rapid and irreversible binding between the Lewis basic isothiourea and the Lewis acidic gold catalyst. In contrast to previous methods using primary and secondary amines, the addition of acid could not be used to circumvent this deactivation pathway due to the necessity of basic conditions for successful isothiouronium enolate formation.



Scheme 2. Initial studies into the union of isothiourea and gold catalysis.

A survey of the literature at this point revealed that although gold complexes containing simple alkylamine, nitrile, imine and pyridine ligands have been explored,[9,10] the use of other neutral sp^2-hybridized nitrogen-based ligands has been less thoroughly investigated. Schmidbaur and Cronje have reported the synthesis and characterization of neutral and cationic gold(I)-guanidine and isothiourea complexes **3** and **4** (Figure 2);[11,12] however, these studies were mostly limited to the solution and solid-state behavior of the complexes. Cronje also applied these novel gold complexes in antitumoral and antimalarial screening, however only minimal activity was observed.[12] Even more scarce are reports on the synthesis of gold complexes bearing chiral sp^2-hybridized nitrogen-based ligands. Peters synthesized and characterized dinuclear gold(I) and gold(II) ferrocenyl oxazoline complexes **6**,[13] however no applications of these novel chiral complexes were disclosed.

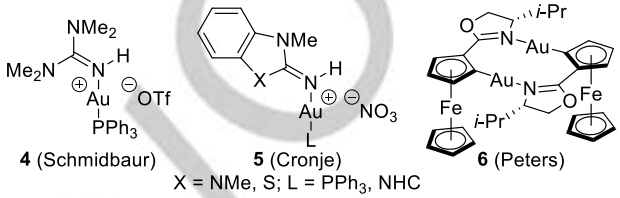


Figure 2. Cationic and neutral gold(I)-guanidine and chiral dinuclear gold(I)-oxazoline complexes.

Due to the wide variety of applications of gold complexes,[1,14] where the nature of the ligands are pivotal for imparting stability and functionality,[15] we pursued the synthesis of gold complexes bearing novel isothiourea ligands. Beyond gold chemistry, the use of isothiourea ligands for transition metal catalysts in general has been somewhat overlooked. An example from Doyle has demonstrated the addition of a chiral isothiourea to the cobalt-catalyzed hydrofluorination of epoxides has a positive effect.[16] It was proposed, based on spectroscopic studies, that the isothiourea acts as a ligand to facilitate complex dimer dissociation and enhance reactivity, however no isolated complexes were reported. Considering this precedent, and the current interest in combining isothiourea- and transition metal catalysis, we believed that a fundamental study on the potential for isothioureas to act as ligands for transition metals would be of significant interest. Herein we report the synthesis, characterization and preliminary applications of a range of novel cationic and neutral chiral gold(I) and gold(III) isothiourea complexes. The inherent steric and electronic properties of the isothiourea ligands are assessed through computation and the synthesis of novel iridium(I) isothiourea complexes, and their catalytic and biological activities are evaluated in some preliminary studies.

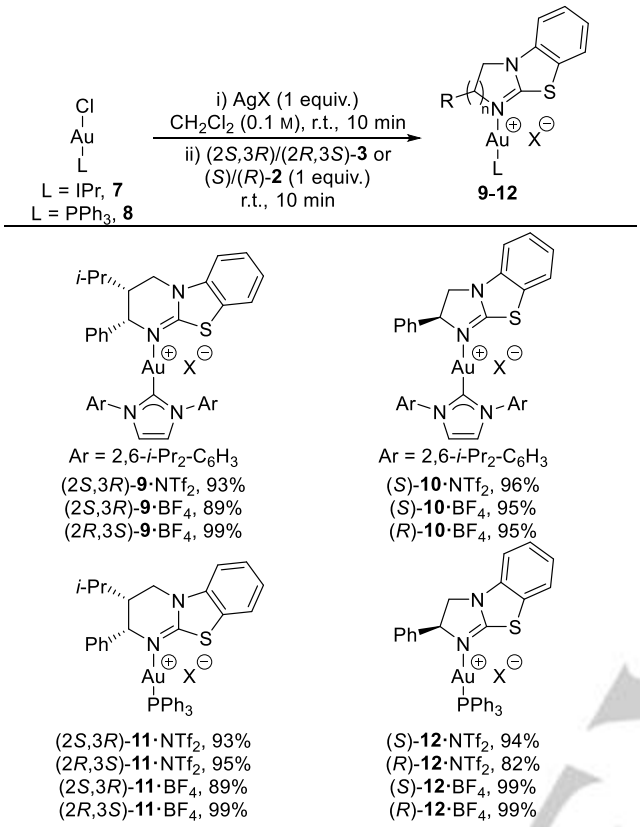
2. Results and Discussion

2.1. Cationic Heteroleptic Gold(I)-Isothiourea Complexes

2.1.1. Synthesis

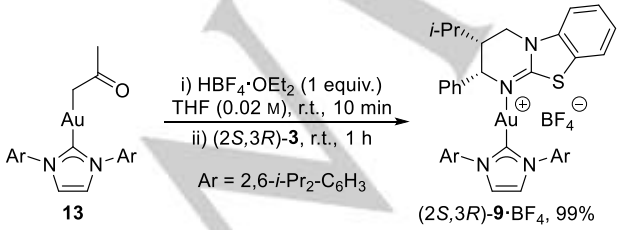
The synthesis of cationic heteroleptic gold(I)-isothiourea complexes was explored using easily-accessed gold(I) chloride NHC and phosphine precursors. Halide abstraction from either [Au(IPr)(Cl)] (IPr = *N*,*N*′-bis(2,6-di*iso*propylphenyl)imidazol-2-ylidene) **7** or [Au(PPh_3)(Cl)] **8** using $AgNTf_2$ or $AgBF_4$, followed by addition of an isothiourea led to rapid and quantitative conversion to new gold(I)-isothiourea complexes **9**–**12** (Scheme 3). Recrystallization of the crude products from pentane afforded pure, air- and moisture-stable microcrystalline gold(I) complexes.

Using this simple synthetic approach, a series of cationic gold(I) complexes containing triflimide or tetrafluoroborate counterions were synthesized in excellent yield (82–99%).



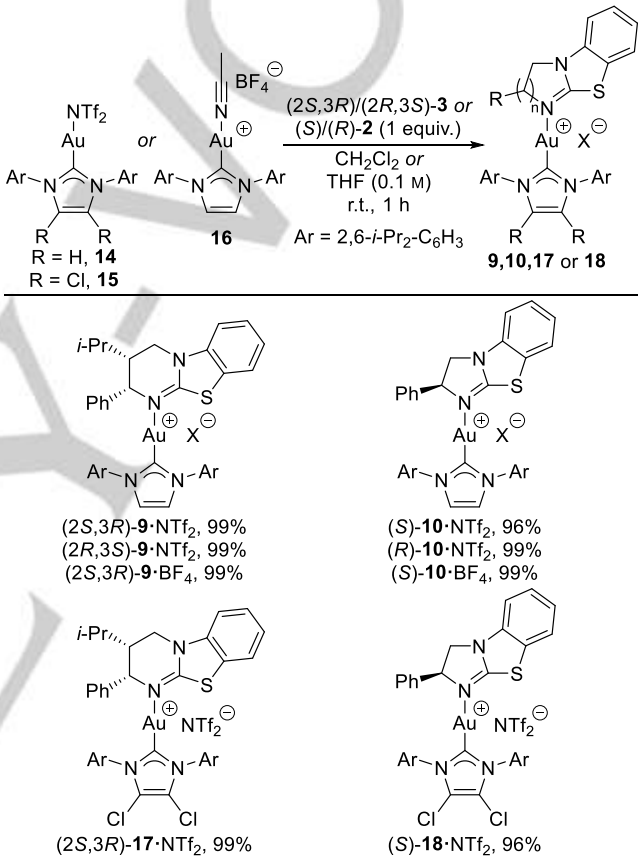
Scheme 3. Synthesis of cationic heteroleptic gold(I)-isothiourea complexes from gold(I) chloride precursors using silver-mediated halide abstraction. IPr = *N*,*N*′-bis(2,6-di*iso*propylphenyl)imidazol-2-ylidene.

Due to the commonly-observed non-innocent role of silver in gold catalysis,[17] alternative methods for the synthesis of these complexes was investigated. We recently reported the silver-free preparation of gold(I)(NHC)(acetonyl) complexes from [Au(SMe$_2$)(Cl)], an NHC·HCl salt and acetone in the presence of potassium carbonate.[18] These gold(I)(NHC)(acetonyl) complexes proved excellent precursors to a range of gold complexes. Applying this approach to the current study, activation of [Au(IPr)(CH$_2$C(O)CH$_3$)] **13** using HBF$_4$·OEt$_2$, followed by the addition of isothiourea (2*S*,3*R*)-**3** gave (2*S*,3*R*)-**9**·BF$_4$ in quantitative yield (Scheme 4).



Scheme 4. Synthesis of cationic heteroleptic gold(I) complex (2*S*,3*R*)-**9**·BF$_4$ from Au(I)-acetonyl complex **13**.

The isolated Gagosz-type complexes **14** and **15**,[19] which contain a labile inner-sphere triflimide ligand, can also be synthesized from gold(I)(NHC)(acetonyl) complexes.[18a] Reaction of these gold(I) triflimide complexes with isothioureas (2*S*,3*R*)-**3**, (2*R*,3*S*)-**3**, (*S*)-**2** or (*R*)-**2** provided cationic gold(I)-isothiourea complexes in uniformly excellent yields (96–99%) (Scheme 5). Using this synthetic approach, the formation of (*S*)-**17**·NTf$_2$ and (2*S*,3*R*)-**18**·NTf$_2$ bearing a chlorinated NHC ligand could also be obtained in excellent yield. As a final alternative approach, the heteroleptic cationic gold(I) acetonitrile complex, [Au(IPr)(NCCH$_3$)][BF$_4$] **16**,[20] was applied for the synthesis of gold(I)-isothiourea BF$_4$ adducts, (2*S*,3*R*)-**9**·BF$_4$ and (*S*)-**10**·BF$_4$, which were both obtained in quantitative yield (Scheme 5).



Scheme 5. Synthesis of cationic heteroleptic gold(I)-isothiourea complexes from gold(I) triflimide complexes **14** and **15** and gold(I) acetonitrile BF$_4$ adduct **16**.

2.1.2. Characterization

Several distinguishing features of the cationic heteroleptic gold(I)-isothiourea complexes were observed by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy in CDCl$_3$ (Table 1).[21] The C(2) proton of HyperBTM **3** (N1-C*H*Ph) was observed to undergo a significant upfield shift ($\Delta\delta_H \approx -0.65$ ppm) upon coordination to the NHC-Au$^+$ fragments of heteroleptic complexes **9** and **17** (entries 1–3). In contrast, for [Au(PPh$_3$)(HyperBTM)][NTf$_2$] **11** the C(2) proton of HyperBTM appeared in a more deshielded environment ($\Delta\delta_H$ = +0.20 ppm) (entry 4). The same trends were observed for the analogous gold(I)-BTM complexes (entries 6–8), with the C(2) proton of BTM **2** shielded when in combination with an NHC ligand ($\Delta\delta_H \approx -0.30$ ppm); and deshielded when combined with PPh$_3$ ($\Delta\delta_H$ = +0.34 ppm). These variations in the effective

Table 1. Selected spectroscopic characterization of cationic heteroleptic gold(I) isothiourea complexes

entry	Compound	δ_H(N−C*H*Ph) (ppm)	δ_C(N=*C*−N) (ppm)	δ_C(carbenic) (ppm)	ν(N=C−N) (cm^{-1})
1	HyperBTM **3**	4.93	158.5	-	1627
2	[Au(IPr)(HyperBTM)][NTf_2] **9**	4.31 (**−0.62**)[a]	167.9 (**+9.4**)[a]	170.6	1578 (**−49**)[a]
3	[Au(IPr^{Cl})(HyperBTM)][NTf_2] **17**	4.27 (**−0.66**)[a]	168.1 (**+9.6**)[a]	170.7	1576 (**−51**)[a]
4	[Au(PPh_3)(HyperBTM)][NTf_2] **11**	5.13 (**+0.20**)[a]	166.8 (**+8.3**)[a]	-	1570 (**−57**)[a]
5	BTM **2**	5.67	166.6	-	1593
6	[Au(IPr)(BTM)][NTf_2] **10**	5.36 (**−0.31**)[b]	172.2 (**+5.6**)[b]	171.7	1560 (**−33**)[b]
7	[Au(IPr^{Cl})(BTM)][NTf_2] **18**	5.37 (**−0.30**)[b]	172.4 (**+5.8**)[b]	171.8	1565 (**−28**)[b]
8	[Au(PPh_3)(BTM)][NTf_2] **12**	6.01 (**+0.34**)[b]	171.6 (**+5.0**)[b]	-	1570 (**−23**)[b]

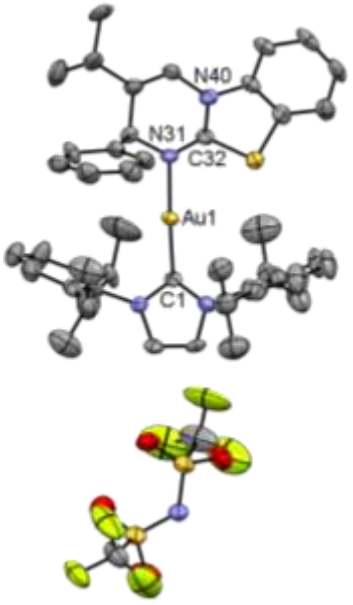
[a] value in parentheses relative to free HyperBTM **3**. [b] value in parentheses relative to free BTM **2**.

shielding of the C(2) proton of the isothiourea ligand may reflect differences in ion pairing between the heteroleptic complex and the triflimide counterion influenced by the nature of the ancillary ligand.[22] Another interesting feature observed by ^{1}H NMR spectroscopy was that the C*H* signals of the *iso*-propyl groups of the NHC ligands in [Au(IPr)(HyperBTM)][NTf_2] **9** and [Au(IPr^{Cl})(HyperBTM)][NTf_2] **17** appear as two sets of septets centred at ~2.35 ppm. This is consistent with a non-symmetrical environment around the gold centre and indicate that rotation around the Au–N is slow on the NMR timescale.

Analysis by $^{13}C\{^1H\}$ NMR spectroscopy revealed that the central isothiouronium carbon (N=*C*–N) was shifted downfield in all complexes, relative to the parent isothiourea ($\Delta\delta_C$ = +5–10 ppm). The magnitude of this downfield shift is consistent with those previously reported for gold(I)-isothiourea complexes,[12] and indicates that the positive charge is delocalized into the isothiourea ligand, and at least partially centralized on the isothiouronium carbon. The carbenic carbons of the NHC-Au-isothiourea complexes **9**, **10**, **17**, and **18** were observed at 171–172 ppm (Table 1, entries 2,3,6,7). These carbenic carbon chemical shifts are downfield relative to analogous cationic homoleptic and heteroleptic gold(I)-NHC complexes bearing ancillary NHC and phosphine ligands {e.g. [Au(IPr)$_2$][BF_4]: δ_C = 184.2 ppm; [Au(IPr)(PPh_3)][BF_4]: δ_C = 188.2 ppm},[23] but upfield relative to cationic heteroleptic complexes bearing other neutral nitrogen-based ligands {e.g. [Au(IPr)(NCMe)][BF_4]: δ_C = 165.9 ppm; [Au(IPr)(pyridine)][PF_6]: δ_C = 167.1 ppm; [Au(NHC)(ylideneamine)][NO_3]: δ_C = 165.6 ppm}.[9f,12] This suggests that the gold centres in the heteroleptic complexes bearing isothiourea ligands are more Lewis acidic than the homoleptic and heteroleptic gold(I)-NHC complexes bearing ancillary NHC and phosphine ligands; but less Lewis acidic than those bearing alternative nitrogen-based ligands. This latter observation could be rationalized by the high Lewis basicity of isothioureas translating to their efficacy as σ-donating ligands.

Infrared spectroscopic analysis of the cationic heteroleptic complexes revealed a lower stretching frequency of the N=C–N unit in all complexes relative to the free isothiourea (Table 1). This effect was most pronounced for complexes containing HyperBTM (entries 1–4, $\Delta\nu$ = −49−57 cm^{-1}). This indicates that the C=N bond of the isothiouronium is weakened upon complexation, and could be consistent with an increased contribution from resonance bonding structures within the isothiourea ligand. The complexes did not exhibit any luminescence and therefore their photophysical properties were not assessed further.

The structure of the heteroleptic complex (2*R*,3*S*)-**9**·NTf_2 was unambiguously established by single crystal X-ray diffraction analysis (Figure 3).[24] The isothiourea binds as expected through the nitrogen atom, with the complex adopting a near linear geometry, with an N−Au−C angle of 176.2(5)°. The length of the Au−N bond (2.053(11) Å) is slightly longer than those reported for heteroleptic ylideneamine and acetonitrile complexes (Δ = 0.02–0.04 Å),[12,9f,20] but similar in length to heteroleptic tetramethylguanidine and pyridine complexes.[11,9f] The Au−C distance of 1.979(13) Å is similar to that found in heteroleptic gold(I)-NHC complexes bearing pyridine and acetonitrile ligands, but shorter than in cationic homoleptic and heteroleptic gold(I)-NHC complexes bearing ancillary NHC and phosphine ligands. The N31−C32 and C32−N40 distances of 1.288(16) and 1.367(18) Å within the isothiourea ligand, reveal a slight extension of the N31−C32 bond (+0.01 Å) and contraction of the C32−N40 bond (−0.02 Å) relative to the free isothiourea. This increase in N31−C32 bond length upon complexation is consistent with the observed reduction in IR stretching frequency of this fragment.



(2*R*,3*S*)-**9**·NTf$_2$

Au–N31	Au–C1	N31–C32	C32–N40	N31–Au–C1
2.053(11) Å	1.979(13) Å	1.288(16) Å	1.367(18) Å	176.2(5)°

Figure 3. Thermal ellipsoid representation of (2*R*,3*S*)-**9**·NTf$_2$ at 50% probability. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (°) given.

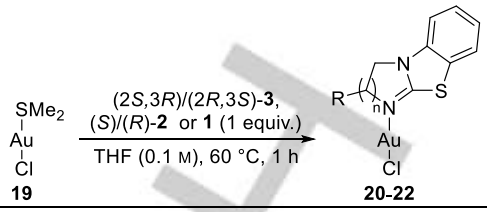
2.2. Neutral Gold(I)-Isothiourea Complexes

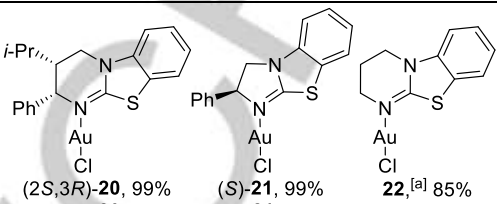
2.2.1. Synthesis

The synthesis of neutral gold(I)-isothiourea chloride complexes was next targeted. Mixing [Au(SMe$_2$)(Cl)] **19** and (*S*)-BTM (*S*)-**2** in THF resulted in no conversion after 3 days at r.t.; however, upon heating the same reaction mixture at 60 °C [Au((*S*)-BTM)(Cl)] (*S*)-**21** was obtained in quantitative yield within 1 h (Scheme 6). The method was also applied to the synthesis of gold(I) complexes bearing the (*R*)-enantiomer of BTM (*R*)-**2**; racemic and both enantiomers of HyperBTM **3**; and the achiral isothiourea DHPB **1**. The neutral gold(I) complexes bearing BTM and HyperBTM ligands, **21** and **20**, were obtained in quantitative yield, while complex **22**, bearing the achiral DHPB ligand, was obtained in 85% yield. For the synthesis of **22** the use of K_2CO_3, and an extended reaction time of 16 h, was required to obtain high yields. All six complexes were obtained as bench-stable solids. This is in contrast to previously-reported gold(I)-guanidine chloride and bromide complexes, which were observed to undergo rapid decomposition to give gold metal within a few hours.[11]

2.2.2. Characterization

^{1}H Spectroscopic analysis of the neutral gold(I)-isothiourea complexes revealed the C(2) proton of all isothiourea ligands had undergone a small downfield shift relative to the corresponding free isothiourea (Scheme 6, $\Delta\delta_H$ = +0.06–0.18 ppm). A much more significant effect was observed by ^{13}C{^{1}H} NMR spectroscopy, with substantial upfield shifts observed for the isothiouronium carbons (N=C–N) relative to the free isothioureas ($\Delta\delta_C$ = −18–27 ppm). The IR stretching frequencies





(2*S*,3*R*)-**20**, 99%
(2*R*,3*S*)-**20**, 99%
(±)-**20**, 99%

(*S*)-**21**, 99%
(*R*)-**21**, 99%

22,[a] 85%

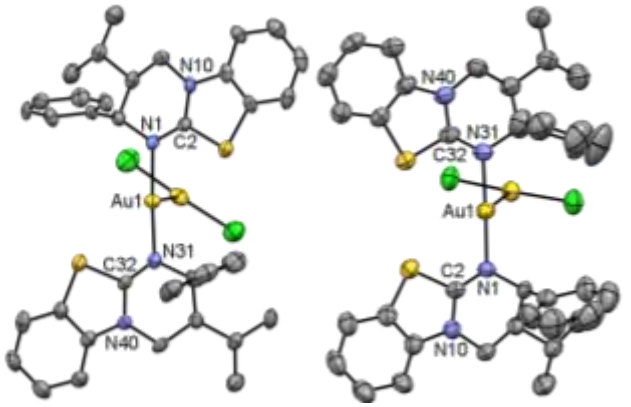
δ_H (N−C*H*Ph) (ppm)	5.09 (**+0.18**)[b]	5.73 (**+0.06**)[c]	3.90 (**+0.11**)[d]
δ_C (N=C−N) (ppm)	140.6 (**−17.9**)[b]	140.0 (**−26.6**)[c]	nd (−)[e]
ν (N=C−N) (cm^{-1})	1575 (**−52**)[b]	1564 (**−29**)[c]	1580 (**−36**)[d]

Scheme 6. Synthesis and selected spectroscopic characterization of neutral gold(I)-isothiourea chloride complexes **20**–**22**. [a] 16 h reaction time. [b] value in parentheses relative to free HyperBTM **3**. [c] value in parentheses relative to free BTM **2**. [d] value in parentheses relative to free DHPB **1**. [e] not determined.

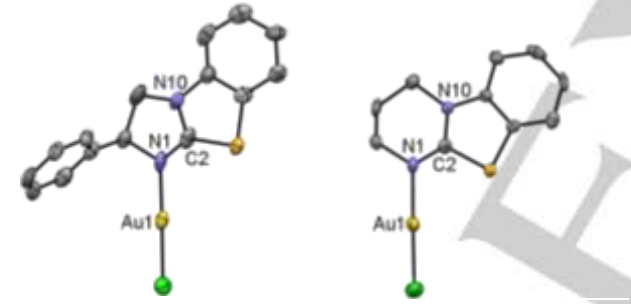
of the isothiouronium units (N=C–N) were reduced in all complexes relative to the free isothiourea ($\Delta\nu$ = −39−52 cm^{-1}). This trend is consistent with that observed for the cationic heteroleptic series, and may indicate increased contribution from resonance bonding structures within the isothiourea ligand. It may be pertinent to note that this apparent increased delocalization in bonding does not necessarily correlate with an increase in positive charge on the isothiourea ligand, as evidenced by the shielding (rather than deshielding) of the isothiouronium carbon. Once again, the complexes did not exhibit luminescence and therefore their photophysical properties were not assessed.

Colourless crystals of (2*R*,3*S*)-**20**, (±)-**20**, (*S*)-**21** and **22** were grown by slow diffusion of pentane or hexane into saturated solutions in CH_2Cl_2, and their structures were unambiguously determined by single crystal X-ray diffraction analysis (Figure 4).[25] All complexes are virtually linear along the N1–Au–N31/N1–Au–Cl axes (177.3–179.5°), with Au–N bond lengths within the range of 2.003–2.021 Å. These Au–N bond lengths are considerably shorter than that observed for the heteroleptic complex (2*R*,3*S*)-**9**·NTf$_2$ (2.053 Å).

In complexes (2*R*,3*S*)-**20** and (±)-**20** bearing the HyperBTM ligand, distortions in the nitrogen-carbon bond lengths were consistent with the data obtained for the heteroleptic complex (2*R*,3*S*)-**9**·NTf$_2$. In both cases, slight extension of the N1−C2/N31−C32 bond (+0.013 Å on average) and contraction of the C2−N10/C32−N40 bond (−0.03 Å on average) relative to the free isothiourea was observed. The enhanced extension of the N1−C2/N31−C32 bond, relative to that observed for the heteroleptic complex (2*R*,3*S*)-**9**·NTf$_2$, is consistent with the lower stretching frequency of the N=C−N fragment observed by IR spectroscopy.



	(2*R*,3*S*)-**20**	(±)-**20**
Au–N1	2.011(8) Å	2.003(5) Å
Au–N31	2.006(8) Å	2.010(5) Å
N1–C2	1.297(14) Å	1.280(6) Å
N31–C32	1.288(14) Å	1.301(7) Å
C2–N10	1.358(13) Å	1.358(8) Å
C32–N40	1.355(13) Å	1.349(8) Å
N1–Au–N31	177.3(4)°	178.69(15)°



	(*S*)-**21**	**22**
Au–N1	2.016(16) Å	2.021(9) Å
N1–C2	1.31(2) Å	1.316(15) Å
C2–N10	1.34(2) Å	1.341(13) Å
Au–Cl	2.248(5) Å	2.255(3) Å
N1–Au–Cl	179.5(4)°	178.7(3)°

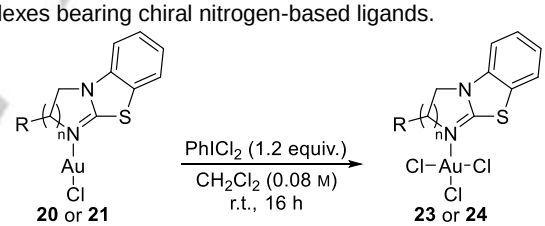
Figure 4. Thermal ellipsoid representations of (2*R*,3*S*)-**20**, (±)-**20**, (*S*)-**21** and **22** at 50% probability. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (°) given.

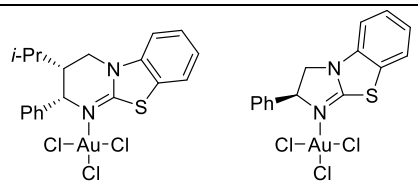
The X-ray crystal structures of the neutral gold(I)-isothiourea complexes also reveal some striking differences. Whilst (*S*)-**21** and **22** crystallize as linear gold(I)-isothiourea chloride complexes, (2*R*,3*S*)-**20** and (±)-**20** crystallize in a cation-anion arrangement, consisting of a cationic homoleptic gold(I)-diisothiourea component and an anionic gold(I)-dichloride counterion.[11] An interesting feature of the homoleptic enantiopure complex (2*R*,3*S*)-**20** is that the isothiourea ligands are arranged in a head-to-tail configuration, whilst the racemic version (±)-**20** crystallizes in a heterochiral head-to-head arrangement. In both cases, the isothiourea ligands are effectively co-planar with one another. It is worth noting that all four complexes appear similar by NMR spectroscopic analysis, with only a single species observed in each case. This indicates that the solid state structures may not be an accurate representation of the complexes in the solution phase, and have therefore been simply represented as gold(I)-isothiourea chloride complexes in Scheme 6.

2.3. Gold(III)-Isothiourea Complexes

2.3.1. Synthesis

Having prepared and characterized a range of neutral and cationic gold(I)-isothiourea complexes, the synthesis of gold(III)-isothiourea analogues was investigated.[10j,26] The attempted oxidation of (2*S*,3*R*)-**20** and (*S*)-**21** using Br_2 or $PhI(OAc)_2$ resulted in the formation of several species which could not be fully analyzed or isolated. In contrast, the use of 1.2 equiv. of $PhICl_2$ led to the corresponding gold(III)-isothiourea trichloride complexes (2*S*,3*R*)-**23** and (*S*)-**24** as purple and magenta solids in quantitative yield (Scheme 7). Notably, oxidation of sulfur in either isothiourea ligand, or the oxidative aromatization of BTM **2** was not observed. The same method was successfully applied to the opposite enantiomers of **20** and **21**, however the attempted oxidation of **22** led to a complex mixture of products. In addition, oxidation of the cationic heteroleptic complex (*S*)-**10**·NTf_2 gave a complex mixture of gold(I) and gold(III) species, with [Au(IPr)Cl_3] identified as the major product.[26b] To the best of our knowledge, these complexes represent the first gold(III) complexes bearing chiral nitrogen-based ligands.





(2*S*,3*R*)-**23**, 96%
(2*R*,3*S*)-**23**, 98%
(*S*)-**24**, 99%
(*R*)-**24**, 99%

δ_H (N–C*H*Ph) (ppm)	5.32 (**+0.39**)[a]	6.36 (**+0.69**)[b]
δ_C (N=*C*–N) (ppm)	165.1 (**+6.6**)[a]	169.7 (**+3.1**)[b]
ν (N=C–N) (cm^{-1})	1574 (**−53**)[a]	1560 (**−33**)[b]

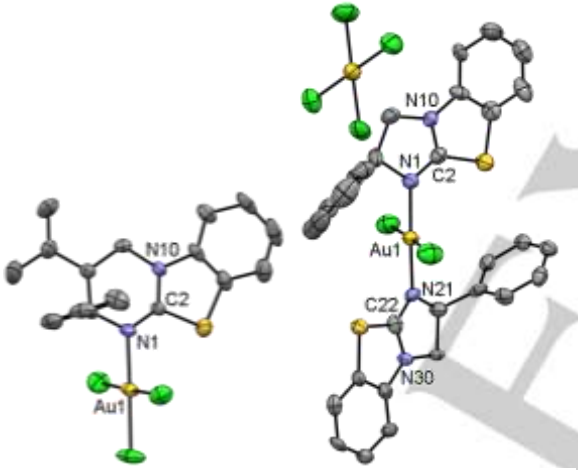
Scheme 7. Synthesis and selected spectroscopic characterization of gold(III)-isothiourea trichloride complexes. [a] value in parentheses relative to free HyperBTM **4**. [b] value in parentheses relative to free BTM **5**.

2.3.2. Characterization

^{1}H Spectroscopic analysis of the gold(III)-isothiourea trichloride complexes **23** and **24** revealed that the C(2) proton of both isothiourea ligands had undergone a large downfield shift relative to the corresponding free isothiourea (Scheme 7, $\Delta\delta_H$ =

+0.39–0.69 ppm). This downfield shift was significantly enhanced relative to that observed for the corresponding gold(I) chloride complexes **20** and **21**, and is consistent with the increased Lewis acidity of the d^8 gold(III) centre. In both complexes there is also a similar substantial downfield shift for the isothiouronium carbons (N=C–N) relative to the gold(I) chloride complexes ($\Delta\delta_C$ = +25-30 ppm) (cf. Scheme 6). The IR stretching frequencies of the isothiouronium units (N=C–N) were also reduced in both complexes relative to the free isothiourea ($\Delta\nu$ = −33−53 cm^{-1}), and to a similar extent to that observed for the corresponding neutral and cationic gold(I) complexes. Once again, the complexes did not exhibit any luminescence and therefore their photophysical properties were not assessed.

Colourless crystals of (2*R*,3*S*)-**23** and (*S*)-**24** were grown by slow diffusion of pentane or hexane into saturated solutions in CH_2Cl_2, and their structures were unambiguously determined by single crystal X-ray diffraction analysis (Figure 5).[27] (2*R*,3*S*)-**23** crystallized in the expected square planar configuration, in which the Cl_{cis}–Au–Cl_{cis} plane was close to perpendicular to the plane of the isothiourea ligand (77.1°). Extension of the N1−C2 bond(+0.015 Å) and contraction of the C2−N10 bond (−0.045 Å), relative to the free isothiourea, was consistent with the trend observed for the heteroleptic and neutral gold(I) complexes, and with the reduction in stretching frequency of the N=C−N fragment observed by IR spectroscopy. In contrast, (*S*)-**24** crystallized in a cation-anion arrangement, similar to those observed for (2*R*,3*S*)-**20** and (±)-**20**. In this case however, the cationic gold(III) diisothiourea dichloride complex and $[AuCl_4]^-$ counterion exist as a loose ion pair with no close Au−Au contacts. As before, it is possible that the solid state structure may not necessarily reflect the arrangement in solution.



	(2*R*,3*S*)-**23**	(*S*)-**24**
Au–N1	2.022(5) Å	1.988(11) Å
Au–N21	-	1.992(10) Å
N1–C2	1.294(7) Å	1.323(18) Å
N21–C22	-	1.306(18) Å
C2–N10	1.341(8) Å	1.321(18) Å
C22–N30	-	1.310(17) Å
Au–Cl_{trans}	2.264(2) Å	-
Au–Cl_{cis}	2.276 Å[a]	2.275 Å[a]
N1–Au–Cl3/N21	179.20(15)°	177.5(4)°
N1–Au–Cl_{cis}	87.73(15)/90.68(15)°	89.2(3)/92.5(3)°

Figure 5. Thermal ellipsoid representations of (2*R*,3*S*)-**23** and (*S*)-**24** at 50% probability. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (°) given. [a] Average value given.

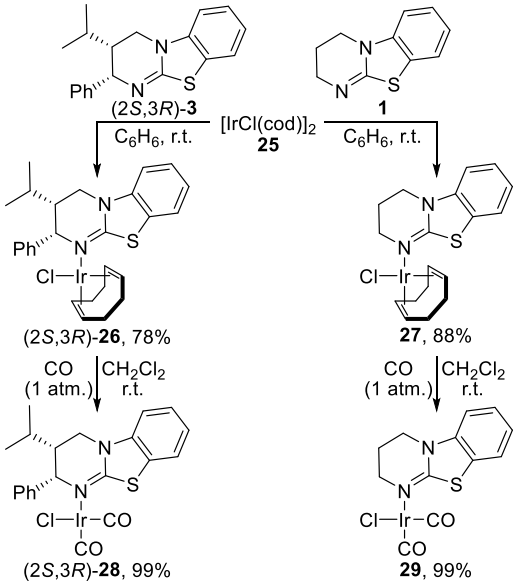
2.4. Steric and Electronic Properties of Isothiourea Ligands

To provide an improved fundamental understanding of isothiourea ligands in transition metal complexes, we next appraised the steric and electronic parameters of the novel isothiourea ligands used in this study. The steric properties of the three isothiourea ligands was first investigated using the percent buried volume (%V_{Bur}) metric.[28] Modelling the neutral gold(I) complexes synthesized in this study, we obtained %V_{Bur} values of 28.7% for (2*R*,3*S*)-**20**; 27.5% for (*S*)-**21**; and 25.1% for **22**.[8] These steric parameters suggest that the isothiourea ligands are quite small, with these %V_{Bur} values coinciding with the lower range of %V_{Bur} values reported for common carbene ligands (%V_{Bur} = 26–51%), and below the range reported for phosphines (%V_{Bur} = 38–64%).[28]

The electronic effect of the isothiourea ligands was assessed using the Tolman Electronic Parameter (TEP).[29] To determine this parameter, the synthesis of iridium(I)-isothiourea carbonyl complexes was undertaken. The reaction of $[IrCl(cod)]_2$ **25** with either (2*S*,3*R*)-HyperBTM (2*S*,3*R*)-**4** or DHPB **6** gave mono-coordinated [IrCl{(2*S*,3*R*)-HyperBTM}(cod)] (2*S*,3*R*)-**26** and [IrCl(DHPB)(cod)] **27** as yellow solids in good to excellent yield.[30] In contrast, the reaction of $[IrCl(cod)]_2$ **25** with BTM **5** led to a complex inseparable mixture of products. Reaction of the iridium(I) isothiourea complexes (2*S*,3*R*)-**26** and **27** with 1 atm of carbon monoxide gave [IrCl{(2*S*,3*R*)-HyperBTM}$(CO)_2$] (2*S*,3*R*)-**28** and [IrCl(DHPB)$(CO)_2$] **29** as off-white solids in quantitative yield. (2*S*,3*R*)-**26** and **27** and their carbonylated analogues, (2*S*,3*R*)-**28** and **29**, were all produced as air- and bench-stable complexes. It is interesting to note that in the methodology reported by Hartwig on the union of isothiourea and iridium catalysis, a pre-formed iridium phosphoramidite complex was used.[5h] When *in situ* formation of the complex from $[IrCl(cod)]_2$ **25** and free ligand in the presence of the isothiourea catalyst was attempted, only minimal product formation was achieved. This result may be consistent with the effective binding we have observed between isothioureas and iridium(I).

IR spectroscopic analysis was used to obtain the CO stretching frequencies [ν(CO)] for the iridium(I)-isothiourea complexes, (2*S*,3*R*)-**28** and **29** (Scheme 8). Two variations of a linear regression equation have been reported for the calculation of TEPs of phosphine and NHC ligands bound to Ir(L)(Cl)$(CO)_2$ complexes by Crabtree[31a] and Nolan,[31b] respectively. Applying these two methods to the isothiourea ligands reported in this study provide values of 2052.4 and 2048.1 cm^{-1} for HyperBTM **4**, and 2044.1 and 2038.3 cm^{-1} for DHPB **6**. This analysis suggests that these isothiourea ligands are significantly more electron-donating than phosphine ligands (TEP of PCy_3 = 2056.4 cm^{-1};

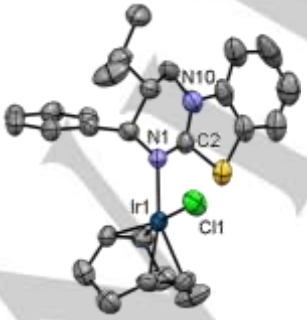
PPh_3 = 2068.9 cm^{-1}) and similarly or more electron-donating than NHC ligands (TEP of IAd = 2049.5 cm^{-1}; IPr = 2051.5 cm^{-1}). This indicates that the isothiourea ligands used in this study are highly efficient σ-donor ligands.



ν (CO) (cm^{-1})	1980.9; 2061.9	1967.4; 2052.3
$\nu(CO)_{average}$ (cm^{-1})	2021.4	2009.8
TEP (cm^{-1})[a]	2052.4	2044.1
TEP (cm^{-1})[b]	2048.1	2038.3

Scheme 8. Synthesis and characterization of iridium(I) isothiourea complexes. [a] calculated using TEP = 0.722 × $\nu(CO)_{average}$ + 593 cm^{-1}.[31a] [b] calculated using TEP = 0.847 × $\nu(CO)_{average}$ + 336 cm^{-1}.[31b]

The structure of (2*S*,3*R*)-**26** was unambiguously determined by single crystal X-ray diffraction analysis (Figure 6).[32] The Ir−N1 distance of 2.104(8) Å, was longer than those observed for the gold(I) and gold(III) complexes (1.99–2.05 Å). The complex adopted the expected square planar configuration (N1−Ir−Cl = 87.0(2)°), with the isothiourea ligand in a perpendicular plane to the Ir−Cl bond (C2−N1−Ir−Cl = 91.1(6)°).



(2*S*,3*R*)-**26**

Ir–N1	N1–C2	C2–N10	N1–Ir–Cl	C2–N1–Ir–Cl
2.104(8) Å	1.257(13) Å	1.365(13) Å	87.0(2)°	91.1(6)°

Figure 6. Thermal ellipsoid representation of (2*S*,3*R*)-**26** at 50% probability. Hydrogens omitted for clarity. Selected distances (Å) and angles (°) given.

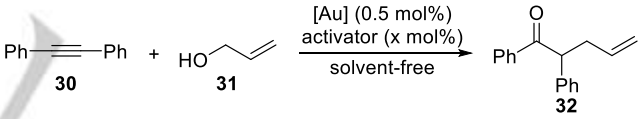
2.5. Preliminary Catalytic and Biological Studies

Having prepared and characterized a range of gold(I) and gold(III)-isothiourea complexes, preliminary investigations into their catalytic and biological activities were performed.

2.5.1. Catalytic studies

Initial studies focused on using heteroleptic gold(I) complexes as pre-catalysts for the hydroalkoxylation-Claisen rearrangement using diphenylacetylene **30** and allyl alcohol **31** to give homoallylic ketone **32**.[33] Stoichiometric studies had demonstrated that treatment of the heteroleptic gold(I) complexes with $HBF_4{\cdot}OEt_2$ would provide $[Au(IPr)]^+$ following release of the protonated isothiourea ligand. We speculated that the protonated chiral isothiourea may be able to operate as a hydrogen bond donor to catalyze the stereo-determining step of the transformation. Activation of (2*S*,3*R*)-**9**·NTf_2 (0.5 mol%) using $HBF_4{\cdot}OEt_2$ (0.5 mol%) provided homoallylic ketone **32** in quantitative yield after 5 h at 120 °C, however the product was obtained as a racemate (Table 5, entry 1). For context, the state-of-the-art pre-catalyst, $Au(IPr^{Cl})(NTf_2)$, provides **32** in quantitative yield after 20 min under analogous conditions.[33] The reaction temperature could be reduced to 60 °C using either (2*S*,3*R*)-**9**·NTf_2 or (2*S*,3*R*)-**11**·BF_4 as pre-catalyst, providing **32** as a racemate in 52–54% yield after 72 h (entries 2,3). In an attempt to generate a chiral gold(I) catalyst *in situ*, activation of the neutral gold(I) complex (2*S*,3*R*)-**20** using sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F_4$) was investigated, however in this case no conversion of the starting materials was observed (entry 4).

Table 2. Gold(I)-catalyzed hydroalkoxylation/Claisen rearrangement of diphenylacetylene using allyl alcohol.



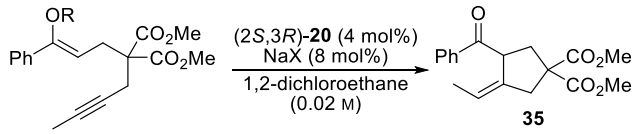
entry	[Au]	Activator (mol%)	T (°C)	t (h)	32 (%)[a]
1	(2*S*,3*R*)-**9**·NTf_2	$HBF_4{\cdot}OEt_2$ (0.5)	120	5	99
2	(2*S*,3*R*)-**9**·NTf_2	$HBF_4{\cdot}OEt_2$ (0.5)	60	72	52
3	(2*S*,3*R*)-**11**·BF_4	$HBF_4{\cdot}OEt_2$ (0.5)	60	72	54
4	(2*S*,3*R*)-**20**	$NaBAr^F_4$ (1)	60	72	0

Reaction conditions: **30** (0.25 mmol), **31** (0.75 mmol), [Au] (0.5 mol%), $HBF_4{\cdot}OEt_2$ (0.5 mol%), solvent-free. [a] Isolated yield.

The *in situ* activation of neutral gold(I) pre-catalysts was further investigated for the gold-catalyzed cyclization of silyloxyenynes.[34] Treatment of (2*S*,3*R*)-**20** (4 mol%) with $NaBF_4$ (8 mol%) at either −30 or 0 °C, did not promote cyclization of TIPS-protected enol ether **33** (Table 3, entries 1,2), indicating significantly lower activity than that previously reported using Au(I)diphosphine complexes.[34] Activity was only achieved by heating the reaction at reflux, to give cyclopentane **35** in 74% yield after 48 h (entry 3). By switching the substrate to TBS-protected enol ether **34**, activation and subsequent cyclization could be achieved at −30 °C to give cyclopentane **35** in 17%

yield (entry 4), however in both examples the product was isolated as a racemate.

Table 3. Gold(I)-catalyzed cyclization of silyloxyenynes **33** and **34**.



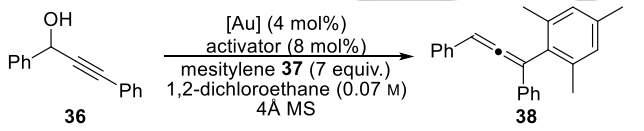
R = (*i*-Pr)$_3$Si (TIPS), **33**
(*t*-Bu)Me$_2$Si (TBS), **34**

entry	Substrate	NaX	T (°C)	t (h)	35 (%)[a]
1	**33**	$NaBF_4$	−30	16	0
2	**33**	$NaBF_4$	0	16	0
3	**33**	$NaBF_4$	84	48	76 (74)[b]
4	**34**	$NaBAr^F_4$	−30	16	17[c]

Reaction conditions: silyloxyenyne **33** or **34** (0.04 mmol), (2*S*,3*R*)-**20** (4 mol%), NaX (8 mol%), DCE (0.02 M). [a] Conversions measured by ^{1}H NMR spectroscopy. [b] Isolated yield in parentheses. [c] Major product was desilylated starting material.

Finally, the novel gold(III)-isothiourea complexes, (2*S*,3*R*)-**23** and (*S*)-**24**, were applied as catalysts for the synthesis of allene **38** from propargylic alcohol **36** and mesitylene **37** (Table 4).[35] Using (*S*)-**24** (4 mol%), activated *in situ* with $AgSbF_6$ (8 mol%), allene **38** was obtained in high conversion after 20 min at 50 °C (entry 1). Substituting $AgSbF_6$ with $NaBAr^F_4$ provided a boost in activity, with allene **38** produced in quantitative yield after only 20 min at room temperature (entry 2). The use of (2*S*,3*R*)-**23** (4 mol%), activated *in situ* with $NaBAr^F_4$ (8 mol%), proved equally effective (entry 3), however in all cases allene **38** was obtained as a racemate. The addition of mesitylene **37** to propargylic alcohol **36** was completely regioselective using both pre-catalysts, with no formation of alkyne side-products arising from C(1) addition of mesitylene.[35,36] Control reactions demonstrated that an activator was required, but that sodium or silver salts alone were not catalytically active.[8]

Table 4. Gold(III)-catalyzed synthesis of allene **38** from propargylic alcohol **36** and mesitylene **37**.



36 **38**

entry	[Au]	Na or Ag salt	T (°C)	t (min)	38 (%)[a]
1	(*S*)-**24**	$AgSbF_6$	50	20	83
2	(*S*)-**24**	$NaBAr^F_4$	r.t.	20	100
3	(2*S*,3*R*)-**23**	$NaBAr^F_4$	r.t.	20	100

Reaction conditions: **36** (0.1 mmol), **37** (0.7 mmol), [Au] (4 mol%), $NaBAr^F_4$ or $AgSbF_6$ (8 mol%), DCE (0.07 M). [a] Conversions determined by ^{1}H NMR spectroscopy.

These preliminary studies have demonstrated a range of disparate transformations can be catalyzed by using all three classes of the novel gold(I) and gold(III)-isothiourea complexes. The isothiourea may either be used as a semi-labile ancillary ligand or used as the sole ligand to provide stabilization of the active gold catalyst. The isothioureas used in this study are representative Lewis basic organocatalysts, and it is therefore expected that rational modulation of ligand design will provide isothioureas with improved properties as ligands. Such modifications could include increasing the size of the stereodirecting substituent on the isothiourea, and the introduction of a second point of ligation to provide bidentate ligand designs. This latter approach could be used for the preparation of enantiopure digold complexes,[37] or for the development of enantioselective Au(III) catalysis.[38] Beyond the use of Au, complexation of these second generation ligands with other transition metals may also provide catalysts, which could be applied for a broad range of enantioselective transformations.

2.5.2. Biological studies

All three classes of the newly-synthesized cationic and neutral gold(I) and gold(III)-isothiourea complexes were next examined in some preliminary biological studies.[14a–c,39] Some significant results are provided below, with full details available in the Supporting Information.

Screening for antitumoral potency was performed against breast cancer cell line MCF-7 and cervical cancer cell line HeLa, with cytotoxicity evaluated using mouse fibroblast cell line 3T3 (up to 30 μM).[8] The most potent complexes were the heteroleptic complexes bearing the BTM ligand: (*R*)-**10**·BF_4, (*S*)-**10**·BF_4 and (*S*)-**12**·BF_4, with IC_{50} values down to 0.3±0.01 μm (HeLa) and 0.6±0.2 μm (MCF-7) obtained. These activities are comparable with those reported for the anti-cancer reference drug Doxorubicin [IC_{50} (HeLa) = 0.3±0.02 μM; IC_{50} (MCF-7) = 0.92±0.01 μM], however all three complexes were also found to be cytotoxic. The most promising compound tested was gold(III) complex (*S*)-**24**, which displayed significant activity against both HeLa and MCF-7 cell lines (IC_{50} values of 10±1 μM and 11±1 μM, respectively), but did not exhibit cytotoxicity. In contrast, the enantiomeric gold(III) complex (*R*)-**24** displayed no activity against HeLa or MCF-7.

Inhibition activities towards a range of enzymes including β-glucuronidase,[40] carbonic anhydrase,[41] lipase,[42] phosphodiesterase (PDE I),[43] tyrosinase[44] and dipeptidyl peptidase were assessed next.[8] All complexes displayed exceptionally-high β-glucuronidase inhibition, with (*S*)-**12**·BF_4 proving the most potent (IC_{50} = 0.11±0.001 μM). (*S*)-**24**, which is not cytotoxic, was also a highly potent inhibitor of β-glucuronidase (IC_{50} = 0.19±0.09 μM) and compares favorably with the commercially-available standard inhibitor, D-saccharic acid 1,4-lactone (IC_{50} = 47±2 μM). Inhibition of the other enzymes assayed was much less general. Three of the heteroleptic gold(I) complexes [(*R*)-**10**·BF_4, (*R*)-**12**·BF_4, and (*S*)-**12**·BF_4] displayed potent activity against phosphodiesterase (PDE I), however all other complexes were inactive. Four of the neutral gold(I) complexes [(2*R*,2*S*)-**20**, (2*S*,2*R*)-**20**, (*R*)-**21** and (*S*)-**21**)] were potent for the inhibition of lipase, but only moderate inhibition of carbonic anhydrase, tyrosinase and dipeptidyl peptidase was observed with some of the complexes.

These preliminary studies demonstrate that gold-isothiourea complexes display promising potency against cancer cell lines and for the inhibition of enzymes. Further research is currently underway to identify the mechanism of action in each example, with this information expected to direct further modulation of ligand design to provide more active and selective complexes.

3. Conclusions

The attempted combination of gold catalysis and isothiouronium enolate catalysis resulted in the formation of gold-isothiourea complexes. These complexes proved to be air- and moisture-stable for several months, and therefore their synthesis was investigated in more detail. A range of gold(I), gold(III) and iridium(I)-isothiourea complexes were synthesized in high yield using chiral and achiral isothiourea ligands, with these novel complexes characterized both in solution and in the solid state. The chiral gold(III)-isothiourea complexes reported here represent the first gold(III) species synthesized bearing chiral nitrogen-based ligands. The inherent steric and electronic properties of the isothiourea ligands have been analyzed using the percent buried volume (%V_{Bur}) and Tolman Electronic Parameter (TEP) descriptors. Based on this analysis, the isothioureas used in this study are highly effective σ-donor ligands. To the best of our knowledge this is the first appraisal of steric and electronic parameters of isothioureas as ligands, and thus should provide inspiration for the wider use of related ligands for complexation with transition metals.

The gold(I) and gold(III) complexes were also applied as pre-catalysts for several gold-catalyzed transformations. Promising activities were found; however as the isothiourea ligands used were based on those developed as organocatalysts, rational modulation of ligand design will undoubtedly lead to further improvements in the future. Finally, these complexes also showed promising biological activity towards specific cancer cell lines (MCF-7 and HeLa) and for the inhibition of clinically-important enzymes (β-glucuronidase and phosphodiesterase). Elaboration of these preliminary studies is currently underway to identify mechanisms of action, which will inform future work to develop more highly active and selective complexes.[45]

Experimental Section

Detailed experimental procedures, characterization data, spectra and X-ray crystallographic methods and data are available in the supporting information.

Acknowledgements

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Keywords: gold • coordination chemistry • N ligands • homogeneous catalysis • bioinorganic chemistry

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[25] Crystallographic data for (2*R*,3*S*)-**20** (CCDC 1587862), (±)-**20** (CCDC 1587863), (*S*)-**21** (CCDC 1587861) and **22** (CCDC 1587864) is available free of charge from the Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk/structures.

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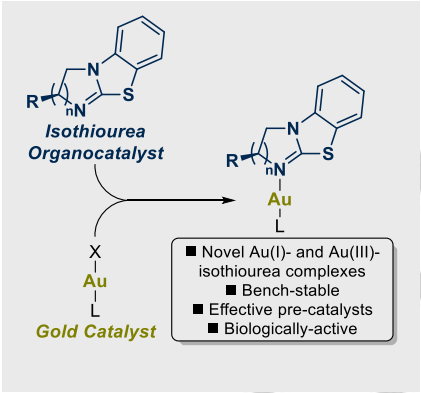
An investigation into the union of isothiourea organocatalysis and gold catalysis led to the discovery of bench-stable gold-isothiourea complexes. A series of neutral and cationic chiral gold(I) and gold(III) complexes bearing enantiopure isothiourea ligands have been synthesized, with the steric and electronic properties of the isothiourea ligands also assessed. The novel complexes have also been applied in preliminary catalytic and biological studies.



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Chiral Au(I)- and Au(III)-Isothiourea Complexes: Synthesis, Characterization and Application

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