Chiral Cyclometalated Oxazoline Gold(III) Complexes Catalyzed Asymmetric Carboalkoxylation of Alkynes

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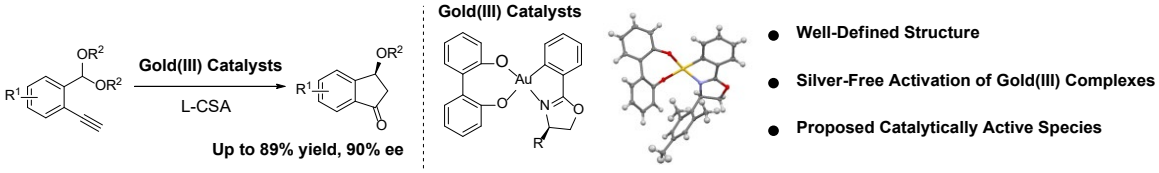


ABSTRACT: Asymmetric catalysis by using novel chiral O,O'-chelated 4,4'-biphenol cyclometalated oxazoline gold(III) complexes has been developed. High yield (up to 89%) and enantioselectivity (up to 90% ee) were achieved in asymmetric carboalkoxylation of alkynes. Enantioselectivity could be significantly improved from 19% ee to 90% ee by increasing the steric size of the substituent on the chiral oxazoline ligand. Catalytically active Au^{III} species and origin of chiral induction are proposed.

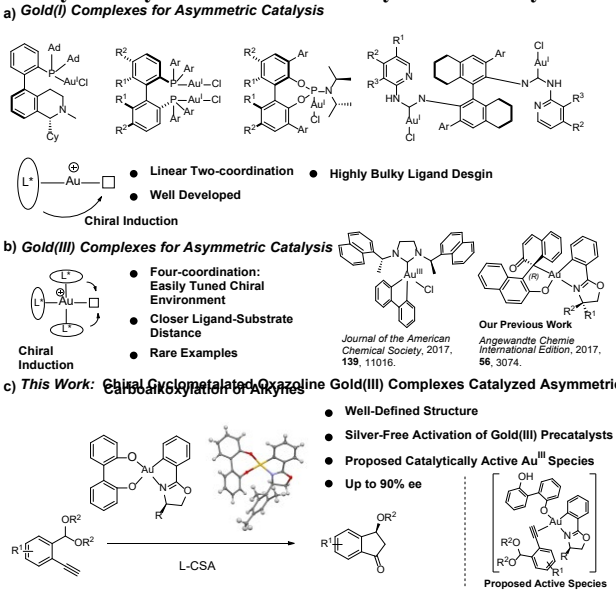
Gold catalysis has attracted significant attention in the past decade owing to the distinguished reactivity, excellent selectivity and high functional group compatibility in diverse organic transformations.[1] Meticulous ligand design and synthesis provides opportunities to overcome the decomposition of gold salts in catalytic cycles and facilitates fine-tuning of catalytic activity and selectivity.[1f, 2]

For gold(I) catalysis, complexes with diverse structure have been designed for highly enantioselective transformations of unsaturated C-C bond,[2b, 3] including bifunctional phosphine gold(I) complexes,[3] binuclear phosphine gold(I) complexes, chiral phosphoamidite gold(I) complexes and acyclic diaminocarbene-Au(I) complexes[2a, 2b] (Scheme 1a). However, the limitation comes from the linear coordination of Au(I) with ligands and substrates. When binding to Au(I) center, the substrate was placed on the opposite side of the chiral ligand. Thus, the resulting long distance between the substrate and the chiral ligand brings significant challenges in chiral induction.[1d, 1g, 2a]

Compared with gold(I) catalysts, gold(III) complexes have four coordination sites with square planar geometry (Scheme 1a and 1b). This four-coordination geometry positions ligands much closer to the catalytic vacant site, which facilitates ligand-induced stereoselectivity in catalysis.[4] Nonetheless, homogenous catalysis by gold(III) complexes remains much undeveloped due to the inadequate approaches to high oxidation state with mild conditions,[2c, 5] and the subtle balance between stability and catalytic activity.[4a, 6] The gold(III) complexes are mainly developed for luminescent[7] and therapeutic applications[8]. For asymmetric gold(III) catalysis, examples are even rare.[4] Pioneered by Toste and co-workers, enantioconvergent kinetic resolution of 1,5-enynes was catalyzed by well-defined chiral gold(III) complexes.[4b]

In most of the reported gold catalyzed organic transformations, gold complexes generally functioned as precatalysts. In particular, for gold(III) catalysis, the catalytic active species remains to be investigated.[9] Thus, to achieve high stereoselec-

Scheme 1. a and b) Previously Reported Chiral Gold Complexes for Asymmetric Catalysis. c) This Work: Chiral Cyclometalated Oxazoline Gold(III) Complexes Catalyzed Asymmetric Carboalkoxylation of Alkynes.

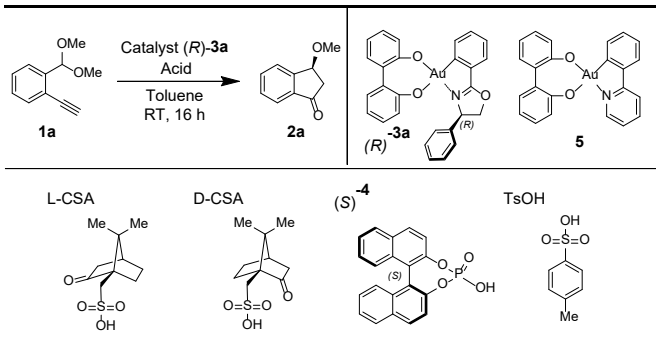


tivity in gold(III) catalyzed reactions, insights on the catalytically active species and origin of asymmetric induction are of great importance.

Over the years, our group has been developing gold(III) complexes as catalysts with good catalytic activity.[4a, 6, 10] Recently, we developed a series of novel C,O-chelated cyclometalated oxazoline gold(III) complexes. The cyclometalated gold(III) complexes can be synthesized in wide scope, and one of the chiral cyclometalated gold(III) complexes achieved asymmetric catalysis of 41% ee.[4a] Given this discovery, we further explore their potential in asymmetric catalysis. The modular synthesis of these gold(III) complexes allows structure fine-tuning to study their ligand effect and catalytic mechanism. Their air and moisture stability enables facile reaction under mild conditions. The activation by camphorsulfonic acid[4a] instead of silver species permits silver-free catalysis since silver effect in gold catalysis was commonly observed.[11] Here we first report chiral O,O'-chelated 4,4'-biphenol cyclometalated oxazoline gold(III) complexes catalyzed asymmetric carboalkoxylation of alkynes with enantioselectivity up to 90% ee. Studies on catalytically active Au^{III} species and origin of chiral induction are also reported in this work (Scheme 1c).

We began with the optimization of reaction conditions for carboalkoxylation reaction of alkyne **1a** affording 3-methoxyindanone **2a** catalyzed by O,O'-chelated cyclometalated oxazoline gold(III) catalyst (*R*)-**3a** (Table 1). We were delightful to obtain the promising result (76% yield, 67% ee) with 10 mol% catalyst (*R*)-**3a** and 5.0 mol% L-camphorsulfonic acid (L-CSA) as activator (Entry 1). Note that changing the Cat / Acid ratio (2 : 1, 1: 1 and 1 : 2, Entries 1-3) affected the resulting yield (54 – 76%) and enantioselectivity (38 – 67% ee), indicating that increasing the ratio of Cat / Acid improved yield and ee.

Table 1. Screening of Reaction Conditions for O,O'-chelated Cyclometalated Gold(III) Catalyzed Carboalkoxylation[a]



Entry	Catalyst Loading (mol%)	Acid (mol%)	Cat / Acid ratio	Solvent	Yield[b] (%)	ee[c] (%)
1	10	L-CSA (5)	2 : 1	Toluene	76	67
2	5	L-CSA (5)	1 : 1	Toluene	62	55
3	5	L-CSA (10)	1 : 2	Toluene	54	38
4	10	MsOH (5)	2 : 1	Toluene	52	45
5	10	TsOH (5)	2 : 1	Toluene	74	59
6	10	(*S*)-**4** (5)	2 : 1	Toluene	49	44
7[d]	10	(*S*)-**4** (5)	2 : 1	Toluene	48	–50
8[e]	10	L-CSA (5)	2 : 1	Toluene	45	8
9	10	L-CSA (2.5)	4 : 1	Toluene	83	75
10	10	D-CSA (2.5)	4 : 1	Toluene	77	69
11	10	L-CSA (1)	10 : 1	Toluene	22	63
12	10	L-CSA (2.5)	4 : 1	CHCl3	61	62
13	10	L-CSA (2.5)	4 : 1	ACN	56	12

[a]Reaction Conditions: Catalyst (*R*)-**3a**, different acids, 0.2 mmol substrate **1a**, 2 mL solvent. Work-up: 4 mL 1.0 M HCl, 2 mL DCM, 10 min. CSA = camphorsulfonic acid. [b]Isolated yield. [c]Determined by Chiral HPLC. [d]Catalyst (*S*)-**3a** was used. [e]Catalyst **5** was used.

Then, we fixed catalyst (*R*)-**3a** (10 mol%) and screened different organic acids with a loading of 5 mol% (Entries 4-6). Compared with L-CSA (76% yield, 67% ee, Entry 1), methenesulfonic acid (MsOH), toluenesulfonic acid (TsOH) and binaphthyl-2,2'-diyl hydrogenphosphate ((*S*)-**4**) afforded slightly reduced enantioselectivity (45%, 59% and 44%, respectively, Entries 4-6) with moderate yield (52%, 74% and 49%, respectively). Notably, adoption of catalyst (*S*)-**3a** of opposite chirality with (*S*)-**4** afforded similar enantioselectivity of opposite side (–50% ee) (Entry 7). The combination of chiral L-CSA and racemic catalyst **5** gave low enantioselectivity (8% ee) with moderate yield (45%) (Entry 8), indicating the chirality of the acid activators have little effect on enantioselectivity. The screening of organic acids indicated that L-CSA is the ideal activator to obtain good enantioselectivity.

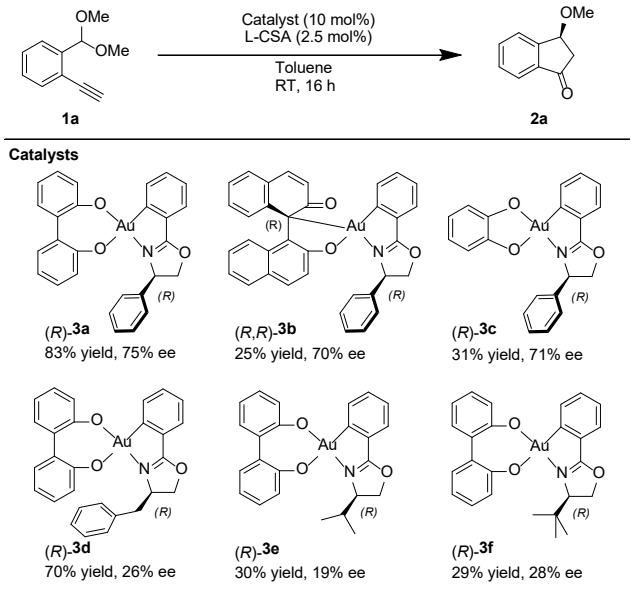
Given L-CSA as the optimized activator, we further examined higher Cat / Acid ratio by keeping catalyst loading (10 mol%) and reducing L-CSA loading. With 2.5 mol% L-CSA (Cat / Acid = 4 : 1), the yield and enantioselectivity was further improved (83% yield, 75% ee) (Entry 9). The adoption of D-CSA (2.5 mol%, Cat / Acid = 4 : 1) instead of L-CSA also afforded comparable yield (77% yield) and enantioselectivity (69% ee) (Entry 10), again indicating the chirality of the acid activator exerted little effect on enantioselectivity. When the L-CSA loading was further reduced to 1.0 mol% (Cat / Acid = 10 : 1), the product yield was significantly decreased (22% yield) with comparable enantioselectivity (63% ee) (Entry 11). The screening indicated the optimized catalyst loading (10 mol%) and acid loading (2.5 mol%) with the ratio of Cat / Acid = 4 : 1 for the present asymmetric carboalkoxylation of alkynes.

Meanwhile, we examined different solvents with the optimized catalyst loading (10 mol%) and L-CSA addition (2.5 mol%). Using toluene afforded higher yield and enantioselectivity (83% yield, 75% ee, Table 1, Entry 9) than chloroform (61% yield, 62% ee, Entry 12). The use of acetonitrile resulted in moderate yield (56%) and low ee (12%). The results indicated that toluene is the optimized solvent.

With the optimized conditions in hand, we then investigated catalysts with different structures (Scheme 2). Catalysts with the same phenyl ring-containing oxazoline ligand with different O,O'- or C,O-chelated components ((*R*)-**3a**, (*R*,*R*)-**3b** and (*R*)-**3c**) afforded comparable enantioselectivity (70 – 75% ee) with a large difference in yields (25 – 83%). However, reducing the steric bulkiness of the substituents on the chiral oxazoline ((*R*)-**3d** (benzyl), (*R*)-**3e** (*iso*-propyl), and (*R*)-**3f** (*tert*-butyl) afforded significantly lower enantioselectivity (19 – 28% ee). These results suggested that the enantioselectivity was mainly determined by the substituent on the chiral oxazoline ligand.

Aiming to obtain higher enantioselectivity, we decided to further increase the steric bulkiness of the substituent on the chiral oxazoline. In this regard, we synthesized novel phenyl-containing oxazoline ligands with different alkyl substituents

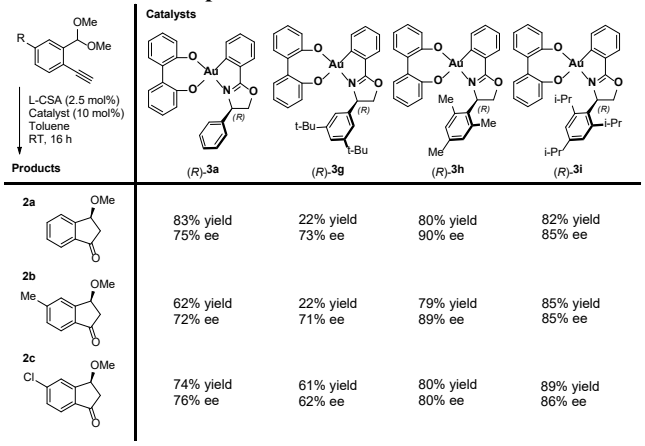
Scheme 2. Catalyst Structure Scope of Cyclometalated Gold(III) Complexes[a]



[a]Reaction Conditions: 10 mol% Catalyst, 2.5 mol% L-CSA, 0.2 mmol substrate **1a**, 2 mL toluene. Work-up: 4 mL 1.0 M HCl, 2 mL DCM, 10 min. Isolated yields are presented, ee's were determined by chiral HPLC. CSA = camphorsulfonic acid.

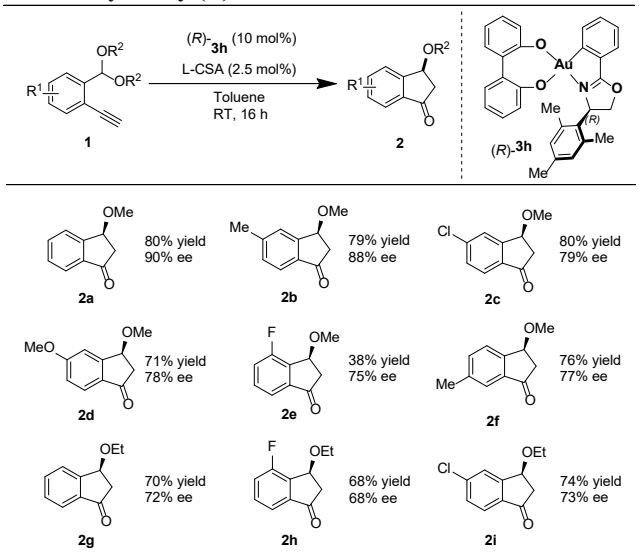
on the phenyl ring. The corresponding O,O'-chelated cyclometalated oxazoline gold(III) catalysts ((*R*)-**3g**, (*R*)-**3h** and (*R*)-**3i**) were then prepared. We used the newly synthesized chiral catalysts for the asymmetric catalysis of substrates **1a**, **1b** and **1c** (Scheme 3). Compared with (*R*)-**3a**, catalyst (*R*)-**3g** with 3,5-di(*tert*-butyl)phenyl group afforded lower yield and similar enantioselectivity for **2a** (22% yield, 73% ee) and **2b** (22% yield, 71% ee). Additionally, **2c** was also afforded with catalyst (*R*)-**3g** with moderate yield (61%) and enantioselectivity (62% ee). As (*R*)-**3g** with modification on the two *meta* positions of chiral phenyl substituent on oxazoline ring, we set out to test the modification on *ortho* and *para* positions. (*R*)-**3h** with 2,4,6-trimethylphenyl group afforded remarkably

Scheme 3. Asymmetric Catalysis by O,O'-chelated Cyclometallated Complexes[a]



[a]Reaction Conditions: 10 mol% Catalyst, 2.5 mol% L-CSA, 0.2 mmol substrate, 2 mL toluene. Work-up: 4 mL 1.0 M HCl, 2 mL DCM, 10 min. Isolated yields are presented, ee's were determined by chiral HPLC. CSA = camphorsulfonic acid.

Scheme 4. Substrate Scope of Asymmetric Carboalkoxylation Catalyzed by (*R*)-3h[a]



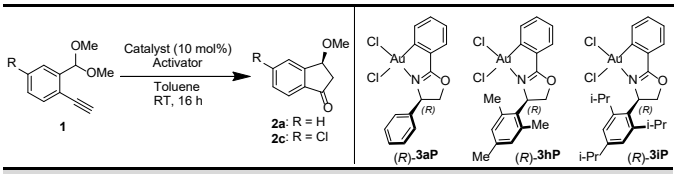
[a]Reaction Conditions: 10 mol% Catalyst (*R*)-**3h**, 2.5 mol% L-CSA, 0.2 mmol substrate, 2 mL toluene. Work-up: 4 mL 1.0 M HCl, 2 mL DCM, 10 min. Isolated yields are presented, ee's were determined by chiral HPLC. CSA = camphorsulfonic acid.

improved enantioselectivity of 90% ee for product **2a**. Product **2b** (79% yield, 89% ee) and **2c** (80% yield, 80% ee) was also afforded with improved enantioselectivity by (*R*)-**3h**. (*R*)-**3i** with *ortho* and *para* positions substituted by more bulky isopropyl groups afforded comparable enantioselectivity for **2a** (82% yield, 85% ee), **2b** (85% yield, 85% ee) and **2c** (89% yield, 86% ee). These results further supported that the sterically bulky substituent on the chiral oxazoline ring predominantly influences the chiral induction.

We selected (*R*)-**3h** as the catalyst to further expand the substrate scope (Scheme 4). Catalyzed by (*R*)-**3h**, most substrates (**2a**-**2d** and **2f**-**2g**) were smoothly reacted to give the corresponding products in good yield of 70-80%, except **2e** was afforded with yield of 38%. Substrates with 5-methyl, 5-chloro and 5-methoxy substitution afforded **2b**, **2c** and **2d** with good enantioselectivity ranging from 78% to 88% ee. In addition, substrates with 6-fluoro and 4-methyl substituents also afforded **2e** and **2f** with good enantioselectivity of comparable ee value (75% ee and 77% ee respectively). When diethyl acetal instead of dimethyl acetal was used as substrate, enantioselectivity was afforded (**2g** (72% ee), **2h** (68% ee) and **2i** (73% ee)) with yields of 68-74%. We have conducted the carboalkoxylation of the corresponding internal alkyne analogue of **1a** with a phenyl group under the same reaction conditions. However, no product was found.

Considering that the sterically bulky substituent would be the origin of enantioselectivity, we inferred that the catalytic vacant site was generated by the detachment of the biphenol ligand. With this idea, we set out to examine the catalytic activity of cyclometalated oxazoline gold(III) dichloride complexes (i.e., the precursors of the O,O'-chelated gold(III) complexes) (Table 2). With $AgBF_4$ as activator and chloroform as solvent, using (*R*)-**3aP** afforded complex reaction mixture with only 15% yield of desired product **2a** in 20% ee (Entry 1). When sodium L-camphorsulfonate (L-CSNa) (10 mol%) was added to the reaction with lowered $AgBF_4$ addition (10 mol%), both product yield and enantioselectivity were signifi-

Table 2. Asymmetric Catalysis by Cyclometalated Oxazoline Gold(III) Dichloride Complexes[a]



Entry	Product	Catalyst	Activator (mol%)	Solvent	Yield[b] (%)	ee[c] (%)
1	**2a**	(*R*)-**3aP**	$AgBF_4$ (20)	$CHCl_3$	15	20
2	**2a**	(*R*)-**3aP**	$AgBF_4$ (10) + L-CSNa (10)	$CHCl_3$	81	61
3	**2a**	(*R*)-**3hP**	$AgBF_4$ (10) + L-CSNa (10)	$CHCl_3$	50	54
4	**2a**	(*R*)-**3iP**	$AgBF_4$ (10) + L-CSNa (10)	$CHCl_3$	59	48
5	**2c**	(*R*)-**3aP**	$AgBF_4$ (10) + L-CSNa (10)	$CHCl_3$	78	61
6	**2c**	(*R*)-**3hP**	$AgBF_4$ (10) + L-CSNa (10)	$CHCl_3$	74	77
7	**2c**	(*R*)-**3iP**	$AgBF_4$ (10) + L-CSNa (10)	$CHCl_3$	75	69
8	**2a**	(*R*)-**3aP**	$AgBF_4$ (10) + L-CSNa (10)	Toluene	82	29

[a]Reaction Conditions: 10 mol% catalyst, different addition of activators, 0.2 mmol substrate, 2 mL solvent. Work-up: 4 mL 1.0 M HCl, 2 mL DCM, 10 min. L-CSNa = sodium L-camphorsulfonate. [b]Isolated yield. [c]Determined by Chiral HPLC.

cantly improved (81% yield and 61% ee, Entry 2). With this optimized condition, combining different catalysts ((*R*)-**3aP**, (*R*)-**3hP** and (*R*)-**3iP)** and substrates (**1a** and **1c**) afforded products with good yield (50 – 75%) and enantioselectivity (48 – 77%) (Entries 2-7). Using toluene as solvent, (*R*)-**3aP** afforded product **2a** with comparable yield (82%) and enantioselectivity of 29% ee (Entry 8). Notably, $AgBF_4$ activated cyclometalated oxazoline gold(III) dichloride provided higher enantioselectivity in chloroform than toluene, while toluene is the optimized solvent for O,O'-chelated gold(III) catalysts, indicating different solvent effects. In addition, the catalysis of cyclometalated gold(III) dichloride complexes requires shorter reaction time (2 h) compared with O,O'-chelated complexes (16 h). The enantioselectivity obtained by cyclometalated oxazoline gold(III) dichloride complexes further proved the significant role of the oxazoline ring on chiral induction. However, the different solvent effects and short reaction time with oxazoline gold(III) dichloride catalysts suggested that the catalytically active species of O,O'-chelated gold(III) complexes and oxazoline gold(III) dichloride might be different.

To provide insights into the catalytically active species, we treated gold(III) catalysts with different activators for ESI-MS analysis (Details in Supporting Information). By ESI-MS analysis, the same camphorsulfonate coordinated gold(III) cationic species (m/z 650.1271) was identified in both the mixture of O,O'-chelated cyclometalated gold(III) complex (*R*)-**3a** and L-CSA (1.0 eq.) and the mixture of cyclometalated gold(III) dichloride complex (*R*)-**3aP**, $AgBF_4$ (1.0 or 2.0 eq.) and L-CSNa (1.0 eq.) in chloroform (Scheme 5a). When substrate **1a** was added to the mixtures, the signal of the camphorsulfonate coordinated gold(III) species (m/z 650.1271) was dramatically lowered, along with the appearance of trace product **2a** (m/z 163.0754) by ESI-MS analysis. Notably, for the mixture of O,O'-chelated cyclometalated gold(III) complex (*R*)-**3a** with L-CSA, lowering the acid loading significantly decreased the signal of the camphorsulfonate coordinated gold(III) cationic species. When L-CSA loading was lowered to 0.25 eq. (i.e., the optimized Cat / Acid ratio of

Scheme 5. a) ESI-MS Study of Catalytically Active Species. b) Proposed Catalytically Active Species for O,O'-chelated Cyclometalated Gold(III) Catalysts. c) Mechanism of Gold Catalyzed Carboalkoxylation of Alkynes. d) Proposed Transition States of Enantiodeterming Step.

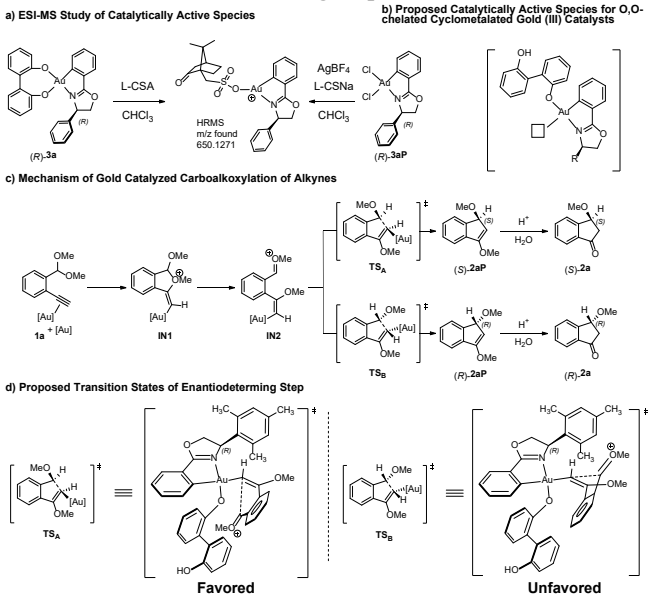


Table 1, Entry 8), only a trace amount of the sulfonate coordinated species was detected by ESI-MS.

ESI-MS analysis suggested that the sulfonate coordinated gold(III) cationic species would possibly be the catalytically active species for silver activated cyclometalated gold(III) dichloride complexes. On the other hand, for O,O'-chelated cyclometalated gold(III) complexes, we noticed that a lower acid loading decreased the ESI-MS signal of the sulfonate coordinated gold(III) species but improved the resulting enantioselectivity. We propose that upon treatment with acid the O,O'-chelated oxazoline cyclometalated gold(III) complexes go through protodeauration on one of the oxygen atoms of biphenol, generating a vacant site for substrate binding (Scheme 5b). The *trans* influence in C,N-chelated cyclometalated gold(III) complexes was reported to be the key factor to determine the vacant site formation.[12] Thus, due to the stronger *trans* effect of C than N, protodeauration could be preferred *trans* to the C of the oxazoline ligand to generate a vacant site for substrate binding that is close to the substituent on the chiral oxazoline.

The mechanism of carboalkoxylation reaction of alkynes was previously studied and supported by DFT calculation.[13] The cyclization by nucleophilic addition of Intermediate **IN2** to afford **2aP** is believed to be the enantiodeterming step of this reaction (Scheme 5c). The cyclization of **IN2** by nucleophilic addition allows the approaching of the oxonium (–$CH(OMe)^+$) from two directions, i.e., through two different transition states $\mathbf{TS_A}$ and $\mathbf{TS_B}$, which finally lead to enantiomers of products, (*S*)-**2a** and (*R*)-**2a**. According to the previous mechanism study,[13] in the structure of transition states ($\mathbf{TS_A}$ and $\mathbf{TS_B}$), the gold(III) center (–[Au]) and the oxonium (–$CH(OMe)^+$) have *cis* relationship on the pseudo five-membered ring (Scheme 5c). Considering the rotation around the Au-vinyl bond, we propose a steric arrangement that the benzene ring of the substrate is away from the bulky substituent on chiral oxazoline to minimize the steric hin-

drance (Scheme 5d). The cyclization through $\mathbf{TS_B}$ is unfavored due to a higher steric hindrance caused by the bulky substituent, and hence the reaction favorably proceeds through the less hindered $\mathbf{TS_A}$ to afford (*S*)-**2a**.[14]

In this work, the enantioselectivity could be increased from 19% ee to 90% ee by simply increasing the steric size of the substituent on the C_1-symmetric chiral oxazoline ligand, which is in line with the proposed species in Scheme 5d. Comparing with C_2-symmetric pybox ligands, examples of C_1-symmetric phenyl oxazoline ligand achieving high enantioselectivity were less reported.[15] Our work demonstrated the great potential of chiral gold(III) complexes in asymmetric catalysis that comes from the close distance between substrates and chiral ligands in a square-planar geometry. Meanwhile, the activation of O,O'-chelated cyclometalated gold(III) catalysts by L-CSA represents a novel silver-free approach to acquire the catalytic activity of gold(III) complexes under mild reaction conditions.

The carboalkoxylation of 2-ethynylbenzaldehyde acetals catalyzed by binuclear phosphine chiral gold(I) complexes developed by Toste and coworkers[13a] gave excellent yield and enantioselectivity (up to 97% yield and 99% ee). In the present work, we employed chiral O,O'-chelated 4,4'-biphenol cyclometalated oxazoline gold(III) complexes to catalyse the carboalkoxylation providing high yield (up to 89%) and enantioselectivity (up to 90% ee). Despite the great difference in the catalytic systems (gold(I) vs gold(III); chiral binuclear phosphine ligands vs chiral oxazoline ligands), the chiral gold(III) catalysis exhibited catalytic efficiency and enantioselectivity not far away from that achieved by the gold(I) catalysis. It is envisioned that more advancements from asymmetric gold(I) and gold(III) catalysis would be achieved in the coming future.

In summary, we have developed asymmetric catalysis by using novel O,O'-chelated 4,4'-biphenol cyclometalated gold(III) complexes with enantioselectivity up to 90% ee. This work would open up new directions on chiral ligand design and catalyst activation strategy for asymmetric gold(III) catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Details on the synthesis procedures, extended data about the reaction, NMR data, and characterization (PDF)

Accession Codes

CCDC 1836528, 1922039 and 1921831 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful for the financial support of Hong Kong Research Grants Council (PolyU 153006/15P), State Key Laboratory of Chemical Biology and Drug Discovery, and Department of Applied Biology and Chemical Technology.

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