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

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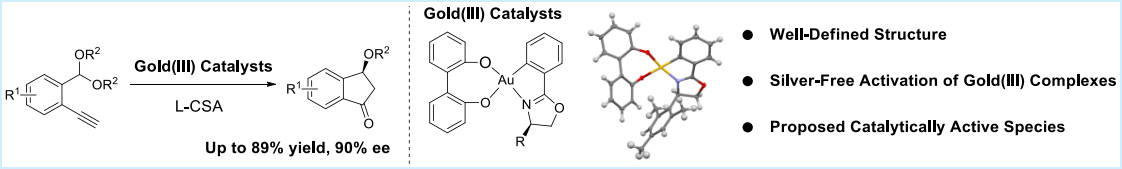
Supporting Information



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

Gold catalysis has attracted a significant amount of 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 provide opportunities to overcome the decomposition of gold salts in catalytic cycles and facilitate 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 an 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,b] (Scheme 1a). However, the limitation comes from the linear coordination of Au(I) with ligands and substrates. When binding to the 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 presents significant challenges in chiral induction.[1d,g,2a]

Compared with gold(I) catalysts, gold(III) complexes have four coordination sites with square planar geometry (Scheme 1a,b). This four-coordination geometry positions ligands much closer to the catalytic vacant site, which facilitates ligand-induced stereoselectivity in catalysis.[4] Nonetheless, homogeneous catalysis by gold(III) complexes remains quite undeveloped due to the inadequate approaches to the 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]

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

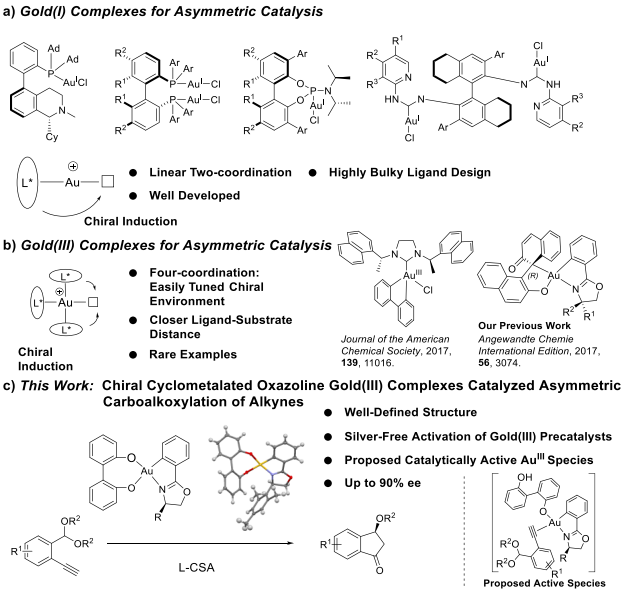


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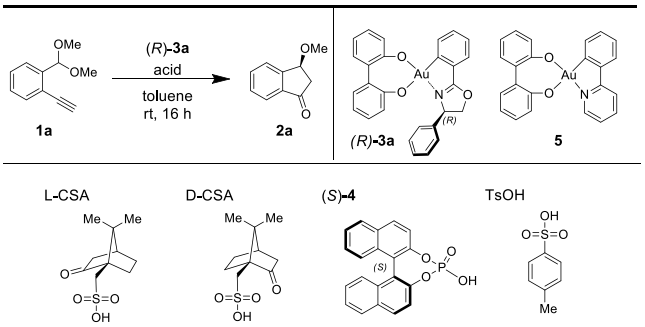
Table 1. Screening of Reaction Conditions for O,O′-Chelated Cyclometalated Gold(III)-Catalyzed Carboalkoxylation[a]



entry	catalyst loading (mol %)	acid (mol %)	catalyst: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	$CHCl_3$	61	62
13	10	L-CSA (2.5)	4:1	ACN	56	12

[a]Reaction conditions: catalyst (*R*)-**3a**, different acids, 0.2 mmol of substrate **1a**, 2 mL of solvent. Workup: 4 mL of 1.0 M HCl, 2 mL of 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.

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 stereoselectivity in gold(III)-catalyzed reactions, insights into the catalytically active species and the 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 a wide scope, and one of the chiral cyclometalated gold(III) complexes achieved an 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 structural fine-tuning for studying 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 because the effect of silver in gold catalysis was commonly observed.[11] Here we first report chiral O,O′-chelated 4,4′-biphenol cyclometalated oxazoline gold(III) complex-catalyzed asymmetric carboalkoxylation of alkynes with an enantioselectivity of ≤90% ee. Studies of catalytically active Au^{III} species and the origin of chiral induction are also reported herein (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 delighted 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 the activator (entry 1). Note that changing the catalyst:acid ratio (2:1, 1:1, and 1:2, entries 1−3, respectively) affected the resulting yield (54−76%) and enantioselectivity (38−67% ee), indicating that increasing the catalyst:acid ratio improved the yield and ee.

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 hydrogen phosphate [(*S*)-**4**] afforded slightly reduced enantioselectivity (45%, 59%, and 44%, respectively, entries 4−6) with moderate yields (52%, 74%, and 49%, respectively). Notably, adoption of catalyst (*S*)-**3a** with a chirality that is the opposite of that of (*S*)-**4** afforded similar enantioselectivity of opposite side (−50% ee) (entry 7). The combination of chiral L-CSA and racemic catalyst **5** gave a low enantioselectivity (8% ee) with a moderate yield (45%) (entry 8), indicating the chirality of the acid activators has little effect on enantioselectivity. The screening of organic acids indicated that L-CSA is the ideal activator for obtaining good enantioselectivity.

Given L-CSA as the optimized activator, we further examined a higher catalyst:acid ratio by maintaining the catalyst loading (10 mol %) and reducing the L-CSA loading. With 2.5 mol % L-CSA (4:1 catalyst:acid), the yield and enantioselectivity were further improved (83% yield and 75% ee) (entry 9). The adoption of D-CSA (2.5 mol %, 4:1 catalyst:acid) instead of L-CSA also afforded a 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 % (10:1 catalyst:acid), the product yield was significantly decreased (22%) with comparable

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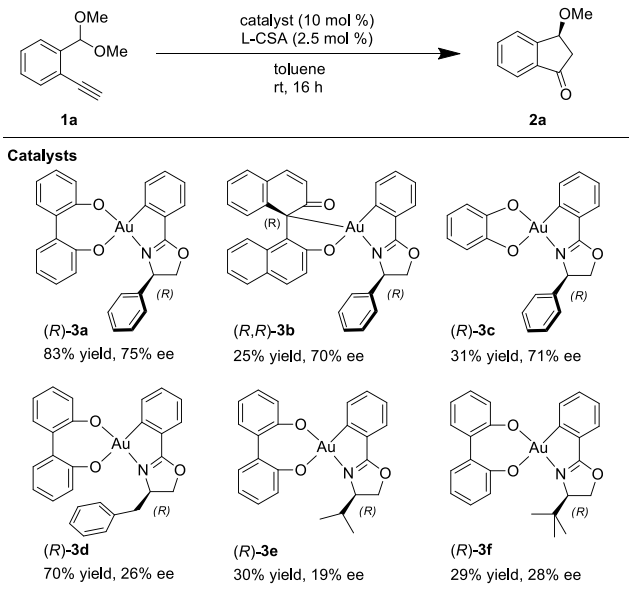
enantioselectivity (63% ee) (entry 11). The screening indicated the optimized catalyst loading (10 mol %) and acid loading (2.5 mol %) with a 4:1 catalyst:acid ratio for the present asymmetric carboalkoxylation of alkynes.

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

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

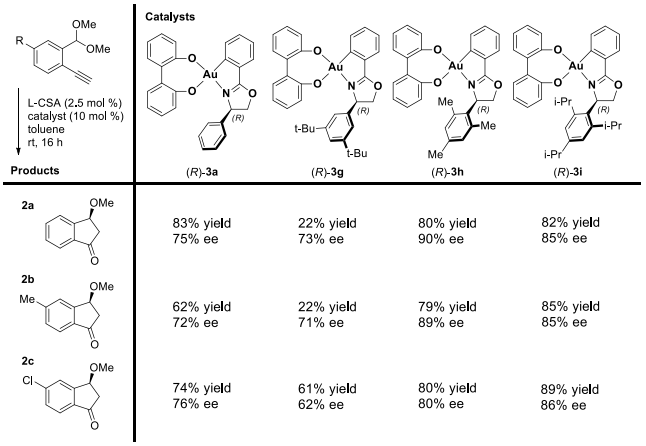


[a]Reaction conditions: 10 mol % catalyst, 2.5 mol % L-CSA, 0.2 mmol of substrate **1a**, 2 mL of toluene. Workup: 4 mL of 1.0 M HCl, 2 mL of DCM, 10 min. Isolated yields are presented; ee's were determined by chiral HPLC. CSA = camphorsulfonic acid.

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** (isopropyl), and (*R*)-**3f** (*tert*-butyl)] afforded significantly lower enantioselectivities (19−28% ee). These results suggested that the enantioselectivity was mainly determined by the substituent on the chiral oxazoline ligand.

Aiming to obtain a 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 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**−**1c** (Scheme 3). Compared with (*R*)-**3a**, catalyst (*R*)-**3g** with a 3,5-di(*tert*-butyl)phenyl group afforded a lower

Scheme 3. Asymmetric Catalysis by O,O′-Chelated Cyclometalated Gold(III) Complexes[a]



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

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 a moderate yield (61%) and a moderate enantioselectivity (62% ee). As (*R*)-**3g** with modifications at the two *meta* positions of the chiral phenyl substituent on the oxazoline ring, we set out to test the modification at the *ortho* and *para* positions. (*R*)-**3h** with a 2,4,6-trimethylphenyl group afforded a remarkably improved enantioselectivity of 90% ee for product **2a**. Product **2b** (79% yield, 89% ee) and **2c** (80% yield, 80% ee) were also produced with an improved enantioselectivity by (*R*)-**3h**. (*R*)-**3i** with the *ortho* and *para* positions substituted with more bulky isopropyl groups afforded comparable enantioselectivities for **2a** (82% yield, 85% ee), **2b** (85% yield, 85% ee), and **2c** (89% yield, 86% ee). These results further support the idea 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**, **2f**, and **2g**) were smoothly reacted to give the corresponding products in good yields of 70−80%, except **2e** was afforded with a yield of 38%. Substrates with 5-methyl, 5-chloro, and 5-methoxy substitutions afforded **2b**−**2d**, respectively, with good enantioselectivities ranging from 78% to 88% ee. In addition, substrates with 6-fluoro and 4-methyl substituents also afforded **2e** and **2f**, respectively, with good enantioselectivities of comparable ee values (75% ee and 77% ee, respectively). When diethyl acetal instead of dimethyl acetal was used as the 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)

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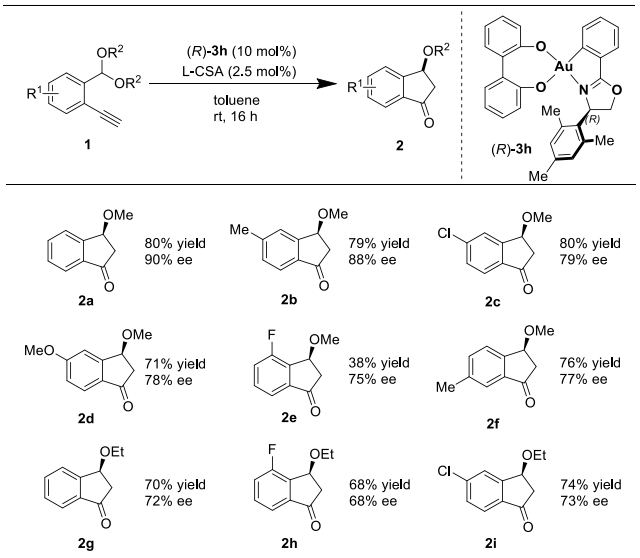
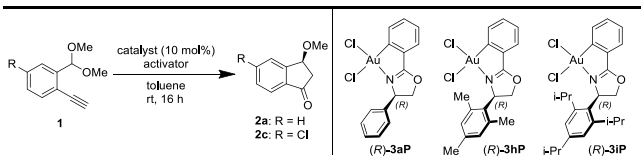
Scheme 4. Substrate Scope of Asymmetric Carboalkoxylation Catalyzed by (*R*)-3h[a]



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

complexes] (Table 2). With $AgBF_4$ as the activator and chloroform as the solvent, using (*R*)-**3aP** afforded a complex

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



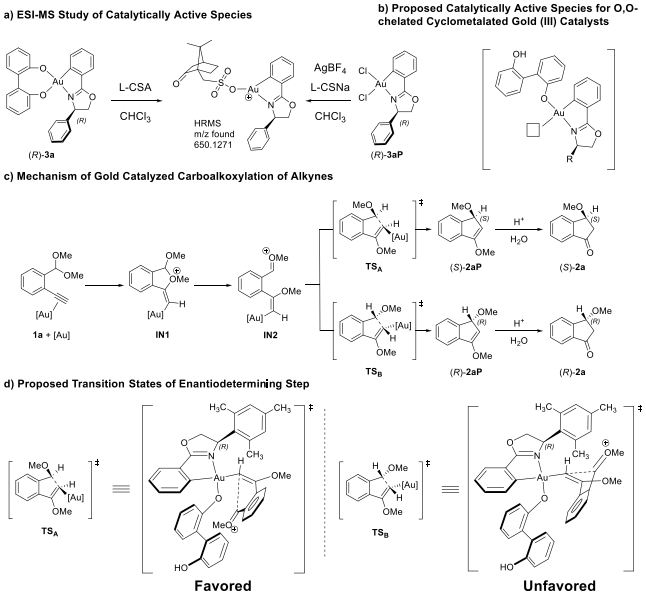
entry	product	catalyst	activator (mol %)	solvent	yield[b] (%)	ee[c] (%)
1	**2a**	(*R*)-**3aP**	$AgBF_4$ (20)	$CHCl_3$	15	20
2	**2a**	(*R*)-**3aP**	$AgBF_4$ (10) and L-CSNa (10)	$CHCl_3$	81	61
3	**2a**	(*R*)-**3hP**	$AgBF_4$ (10) and L-CSNa (10)	$CHCl_3$	50	54
4	**2a**	(*R*)-**3iP**	$AgBF_4$ (10) and L-CSNa (10)	$CHCl_3$	59	48
5	**2c**	(*R*)-**3aP**	$AgBF_4$ (10) and L-CSNa (10)	$CHCl_3$	78	61
6	**2c**	(*R*)-**3hP**	$AgBF_4$ (10) and L-CSNa (10)	$CHCl_3$	74	77
7	**2c**	(*R*)-**3iP**	$AgBF_4$ (10) and L-CSNa (10)	$CHCl_3$	75	69
8	**2a**	(*R*)-**3aP**	$AgBF_4$ (10) and L-CSNa (10)	toluene	82	29

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

reaction mixture with an 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 mixture with a smaller addition of $AgBF_4$ (10 mol %), both the product yield and the enantioselectivity were significantly improved (81% yield and 61% ee, entry 2). Under this optimized condition, combining different catalysts [(*R*)-**3aP**, (*R*)-**3hP**, and (*R*)-**3iP**] and substrates (**1a** and **1c**) afforded products with good yields (50−75%) and enantioselectivities (48−77% ee) (entries 2−7). Using toluene as a solvent, (*R*)-**3aP** afforded product **2a** with a comparable yield (82%) and an enantioselectivity of 29% ee (entry 8). Notably, $AgBF_4$-activated cyclometalated oxazoline gold(III) dichloride provided a higher enantioselectivity in chloroform than in 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 a shorter reaction time (2 h) compared with that of 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 the 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 equiv) and the mixture of cyclometalated gold(III) dichloride complex (*R*)-**3aP**, $AgBF_4$ (1.0 or 2.0 equiv), and L-CSNa (1.0 equiv) in chloroform (Scheme 5a). When substrate **1a** was added to the mixtures, the intensity of the signal of the camphorsulfonate-coordinated gold(III) species (m/z 650.1271) was dramatically decreased, along with the appearance of trace product **2a** (m/z 163.0754) by ESI-MS analysis. Notably, for the mixture of O,O′-chelated

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, and (d) Proposed Transition States of the Enantiodetermining Step



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cyclometalated gold(III) complex (*R*)-**3a** with L-CSA, decreasing the acid loading significantly decreased the intensity of the signal of the camphorsulfonate-coordinated gold(III) cationic species. When the L-CSA loading was decreased to 0.25 equiv (i.e., the optimized catalyst:acid ratio of 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 intensity of 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 for determining 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 density functional theory calculation.[13] The cyclization by nucleophilic addition of intermediate **IN2** to afford **2aP** is believed to be the enantiodetermining step of this reaction (Scheme 5c). The cyclization of **IN2** by nucleophilic addition allows the approach 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**, respectively. According to the previous mechanistic 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 a *cis* relationship on the pseudo-five-membered ring (Scheme 5c). Considering the rotation around the Au−vinyl bond, we propose a steric arrangement in which the benzene ring of the substrate is away from the bulky substituent on the chiral oxazoline to minimize the steric hindrance (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. Compared with C_2-symmetric pybox ligands, examples of a C_1-symmetric phenyl oxazoline ligand achieving a high enantioselectivity have been infrequently reported.[15] Our work demonstrated the great potential of chiral gold(III) complexes in asymmetric catalysis that comes from the short 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 for acquiring 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 co-workers[13a] gave an excellent yield (≤97%) and an excellent enantioselectivity (99% ee). In this work, we employed chiral O,O′-chelated 4,4′-biphenol cyclometalated oxazoline gold(III) complexes to catalyze the carboalkoxylation providing a high yield (≤89%) and enantioselectivity (≤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 a catalytic efficiency and an enantioselectivity not far from those achieved by gold(I) catalysis. It is envisioned that more advancements from asymmetric gold(I) and gold(III) catalysis will be achieved in the future.

In summary, we have developed asymmetric catalysis by using novel O,O′-chelated 4,4′-biphenol cyclometalated gold(III) complexes with an enantioselectivity of ≤90% ee. This work would open up new directions for chiral ligand design and a 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 at DOI: 10.1021/acs.orglett.9b02171.

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

Accession Codes

CCDC 1836528, 1921831, and 1922039 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 emailing 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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Author Contributions

§J.-J.J. and J.-F.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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