ChemComm

RSCPublishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 8869

Received 27th June 2013,
Accepted 1st August 2013

DOI: 10.1039/c3cc44828b

www.rsc.org/chemcomm

Bis-cyclometallated gold(III) complexes as efficient catalysts for synthesis of propargylamines and alkylated indoles†

Hok-Ming Ko, Karen Ka-Yan Kung, Jian-Fang Cui and Man-Kin Wong*

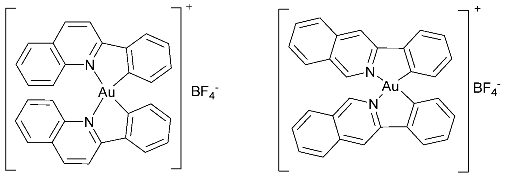
Stable bis-cyclometallated gold(III) complexes were developed as efficient catalysts for organic transformation reactions by using two strategies: (1) construction of distorted square planar gold(III) complexes and (2) dual catalysis by gold(III) complexes and silver salts.

Gold catalysis has attracted significant attention in catalysis research due to its superior reactivity, excellent selectivity and high functional group tolerance.[1] Studies on the use of simple gold salts (*e.g.* AuCl and $AuCl_3$) as catalysts for organic synthesis have been widely reported.[2] However, the instability of simple gold salts in catalytic cycles leading to low product turnovers is an unresolved issue.[3] In this connection, gold(I) complexes have been largely developed as efficient catalysts to achieve novel synthetic transformations.[1,4] However, the development of gold(III) complexes for catalysis remains largely unexplored.

Gold(III) complexes have a square planar geometry with four coordination sites, and in principle the reactivity of the gold(III) reaction centre can be easily fine-tuned by diverse ligand design in a modular approach.[5] However, a significant challenge in the development of gold(III) complexes as efficient catalysts is to strike a balance between stability and reactivity. In general, the stability of gold(III) ions significantly increases upon complexation with ligands. However, stable gold(III) complexes generally exhibit poor catalytic activity. We envision that novel ligand design and substrate activation strategies are of importance in the pursuit of gold(III) catalysis for organic synthesis.

Over the years, we have been developing gold catalysis for organic transformation reactions.[6] In particular, we are interested in employing cyclometallated gold(III) complexes[7] as catalysts for organic synthesis.[8] Recently, we found that stable bis-cyclometallated gold(III) catalysts are able to exhibit high catalytic activity in organic synthesis through two novel strategies: (1) formation of coordinatively saturated distorted square planar gold(III) complexes using bulky C,N donor ligands and (2) gold–silver dual catalysis for substrate activation.

Bis-cyclometallated gold(III) complexes $[Au(C^\wedge N)_2][BF_4]$ **1** ($HC^\wedge N$ = 2-phenylquinoline) and **2** ($HC^\wedge N$ = 3-phenylisoquinoline) were synthesized by transmetallation of $KAuCl_4$ with their corresponding organomercury complexes in 75% and 42% yields, respectively (Fig. 1). Notably, a distorted square planar geometry[9] of **1** was revealed by X-ray crystallography (Fig. 2). The two 2-phenylquinoline ligands in **1** were tilted to give a dihedral angle of 43°. The Au–N bond length is elongated (up to 0.141 Å) when compared with literature-known square planar cyclometallated gold(III) complexes[10] (Table S2, ESI†). Probably due to the steric repulsion between the quinoline rings, the Au–N bond length is elongated and a non-planar geometry is adopted in order to maintain coordination of ligands to the gold(III) centre. On the basis of NMR spectroscopy and literature reports, a typical square planar geometry is expected for complex **2**. The gold(III) complexes **1** and **2** were characterized by ^1H NMR, ^{13}C NMR, and ESI-MS, and were found to be air- and water-stable.



1 **2**

Fig. 1 Bis-cyclometallated gold(III) complexes **1** and **2**.

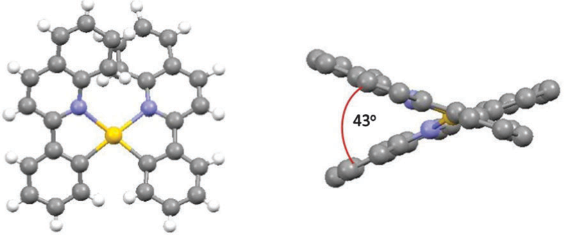
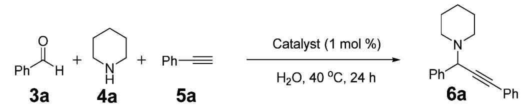


Fig. 2 Crystal structure of **1** in top view (left) and side view (right). Anions were omitted for clarity.

State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China. E-mail: mankin.wong@polyu.edu.hk; Fax: +852 2364-9932

† Electronic supplementary information (ESI) available: Experimental details, NMR spectra of new compounds, and crystallographic data of complex **1**. CCDC 946727. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44828b

Table 1 Bis-cyclometallated gold(III) complex-catalyzed three-component coupling reaction for propargylamine synthesis[a]



Entry	Catalyst (mol%)	Isolated yield (%)
1	**1** (1)	83
2	**1** (0.1)	60
3[b]	**1** (1)	25
4	**2** (5)	8
5	**2** (1)	0

[a] Reaction conditions: **3a** (0.5 mmol), **4a** (0.55 mmol) and **5a** (0.75 mmol) in H_2O (1 mL). [b] Room temperature.

Results of studies on the catalytic activities of **1** and **2** in the three-component coupling reaction of aldehydes, amines and alkynes for propargylamine synthesis[11] are given in Table 1. Using 1 mol% of complex **1** with a distorted square planar geometry, propargylamine **6a** was obtained in 83% isolated yield at 40 °C in 24 h under air (entry 1). As shown in entry 2, **6a** was obtained in 60% isolated yield even with 0.1 mol% of **1**, which was found to be comparable with our previous studies.[6a,8a,c] Note that complex **1** (1 mol%) was able to catalyze the reaction at room temperature (entry 3). In contrast, complex **2** exhibited poor catalytic activity. Using 5 mol% of **2** only gave 8% isolated yield (entry 4) while no reaction was observed with 1 mol% of **2** (entry 5).

The significantly higher catalytic activity of **1** than that of **2** could be attributed to their difference in geometry. Complex **1** has a distorted square planar geometry with elongated bond lengths. Hence, ligand dissociation of **1** to generate a highly reactive gold(III) reaction centre for alkyne activation would be more favorable than that of complex **2**. It is envisioned that such design of distorted gold(III) complexes would be applicable in catalyzing other classes of organic reactions.

Next, complex **1** was used in stereoselective synthesis of propargylamines **6b–6h** with 70–90% isolated yields and diastereomeric ratio (dr) of up to >99 : 1 (Fig. 3). In addition, complex **1** was able to promote selective modification of D-raffinose aldehyde with 85% aldehyde conversion.[8b]

In the next section, a gold–silver cooperative dual catalysis strategy[12] was used in bis-cyclometallated gold(III) complex-catalyzed indole alkylation[13] (Table 2). According to the proposed reaction mechanism,[14] alkylated indole **9a** was formed by metal-catalyzed cyclization of alkynyl alcohol **7a** to generate enol ether *in situ* followed by C–H addition of indole **8a** to the enol ether. Through systematic screening, we found that silver salts are able to work synergistically with bis-cyclometallated gold(III) complexes in the indole alkylation.

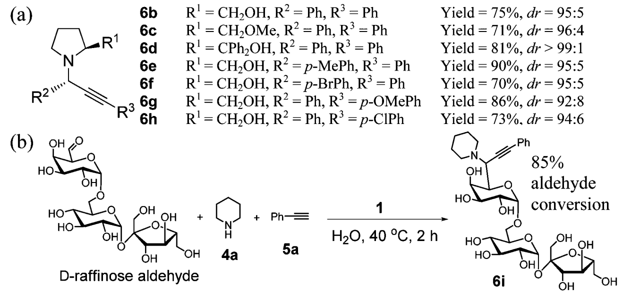
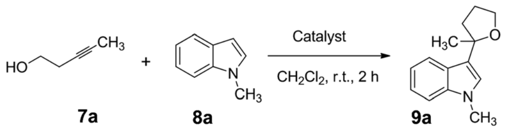


Fig. 3 (a) Substrate scope of propargylamine synthesis catalyzed by **1**. (b) Modification of D-raffinose aldehyde *via* three-component coupling reaction.

Table 2 Screening of catalysts for synthesis of alkylated indoles[a]



Entry	Catalyst (mol%)	Isolated yield[b] (%)
1	**1** (2.5) + $AgBF_4$ (5)	80
2	**2** (2.5) + $AgBF_4$ (5)	47
3	**1** (2.5) + $Zn(OTf)_2$ (5)	76
4	**1** (2.5) + $Yb(OTf)_3$ (5)	39
5	**1** (5)	13[c]
6	**2** (5)	0
7	$AgBF_4$ (5)	10[c]
8	$Zn(OTf)_2$ (5)	0
9	$Yb(OTf)_3$ (5)	0

[a] Reaction conditions: **7a** (0.24 mmol) and **8a** (0.2 mmol) in CH_2Cl_2 (2 mL). [b] Isolated yield. [c] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

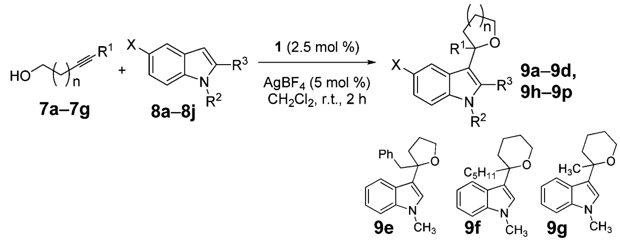
Using **1** (2.5 mol%) with $AgBF_4$ (5 mol%), alkynyl alcohol **7a** reacted with indole **8a** to give alkylated indole **9a** in 80% isolated yield at room temperature in 2 h (entry 1). The reaction using complex **2** (2.5 mol%) with $AgBF_4$ (5 mol%) gave 47% isolated yield (entry 2). Combination of **1** with $Zn(OTf)_2$ or $Yb(OTf)_3$ could also catalyze the reaction to afford 76% and 39% isolated yields, respectively (entries 3 and 4). In the control experiments (entries 5–9), poor yields (10–13%) or no product formation were found when only a single metal catalyst was used. Catalyst screening using various metal salts was also conducted (see ESI†). These findings indicate that appropriate combination of dual metal catalysts[15] is a feasible approach to render stable bis-cyclometallated gold(III) complexes as efficient catalysts in organic transformation reactions.

The substrate scope of the dual metal catalysis for indole alkylation was demonstrated by using alkynyl alcohols of different chain lengths **7a–7g** and indoles with different substituents **8a–8j** to afford alkylated indoles **9a–9p** with up to 94% isolated yields (Table 3). The reactivity and regioselectivity of the present reaction were found to be consistent with literature reports.[14,16]

An important advantage of using gold(III) complexes over simple gold(III) salts is the recyclability in catalysis. The recyclability experiments of catalyst **1** in propargylamine synthesis were conducted (Table 4). Catalyst **1** could be repeatedly used for 7 cycles leading to 638 product turnovers in total. However, the conversion when using $KAuCl_4$ decreased significantly leading to only 29% conversion in the 7th cycle. These findings clearly indicate the recyclability of catalyst **1**.

Next, we set out to examine the recyclability of catalyst **1** in the dual catalysis of indole alkylation (Table 5). Catalyst **1** could be repeatedly used for 11 cycles to give 73–88% conversions with addition of $AgBF_4$ at the 6th and 11th cycles. At the end of the 10th cycle, complex **1** was found to remain intact by ESI-MS analysis of the reaction mixture. These results suggest that catalyst **1** is stable under the reaction conditions and could be reused with further addition of $AgBF_4$. Yet, the recyclability experiments conducted using

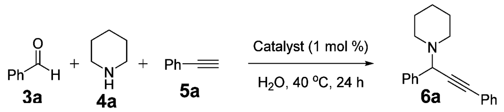
Table 3 Gold(III) complex-silver catalyzed cyclization–addition reactions of alkynyl alcohols **7a–7g** and substituted indoles **8a–8j**[a]



Entry	*n*	R^1	R^2	R^3	X	Product	Isolated yield (%)
1	1	CH_3	CH_3	H	H	**9a**	80
2	1	C_2H_5	CH_3	H	H	**9b**	74
3	1	C_3H_7	CH_3	H	H	**9c**	78
4	1	Ph	CH_3	H	H	**9d**	75
5	2	Ph	CH_3	H	H	**9e**	74[b]
6	3	C_4H_9	CH_3	H	H	**9f**	84[c]
7	3	H	CH_3	H	H	**9g**	94[c]
8	1	CH_3	CH_3	H	Br	**9h**	80
9	1	CH_3	CH_3	H	OMe	**9i**	80
10	1	CH_3	CH_3	H	NO_2	**9j**	67[d]
11	1	CH_3	CH_3	CH_3	H	**9k**	40
12	1	CH_3	H	H	H	**9l**	75
13	1	CH_3	H	H	Br	**9m**	71[e]
14	1	CH_3	H	H	OMe	**9n**	53
15	1	CH_3	H	H	NO_2	**9o**	70[d]
16	1	CH_3	H	CH_3	H	**9p**	58

[a] Reaction conditions: **7a–7g** (0.24 mmol) and **8a–8j** (0.2 mmol) in CH_2Cl_2 (2 mL). [b] 5-Exo-dig cyclized product was formed. [c] 6-Exo-dig cyclized products were formed. [d] 16 h. [e] 4 h.

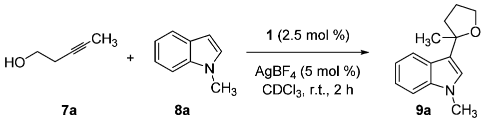
Table 4 Recyclability experiments of **1** and $KAuCl_4$ in three-component reaction[a]



Cycle	1	2	3	4	5	6	7
Conversion[b] (%) by **1**	99	97	93	85	89	86	89
Conversion[b] (%) by $KAuCl_4$	99	94	82	65	51	38	29

[a] Reaction conditions: **3a** (1 mmol), **4a** (1.1 mmol) and **5a** (1.5 mmol) in H_2O (1 mL). [b] Determined by ^1H NMR.

Table 5 Recyclability experiment of "**1** + $AgBF_4$" in the reaction of **7a** and **8a** at room temperature in $CDCl_3$[a]



Cycle	1	2	3	4	5	6[c]	7	8	9	10	11[c]
Conversion[b] (%)	85	81	81	78	73	88	87	85	81	74	83

[a] Reaction conditions: **7a** (0.24 mmol) and **8a** (0.2 mmol) in $CDCl_3$ (2 mL). [b] Determined by ^1H NMR. [c] Additional $AgBF_4$ (5 mol%) was added.

$KAuCl_4$ or "$KAuCl_4$ + $AgBF_4$" as catalysts gave no product in the 2nd cycle.

In conclusion, we have developed two novel strategies rendering stable bis-cyclometallated gold(III) complexes as efficient catalysts in organic synthesis by (1) ligand design and (2) dual catalysis.

We are thankful for the financial support from the Hong Kong Research Grants Council (PolyU 5031/11p) and The Hong Kong Polytechnic University (SEG PolyU01). We also thank Prof. Chun-Yu Ho of South University of Science & Technology of China for his comments on the bis-cyclometallated gold(III) complexes.

Notes and references

1 (*a*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (*b*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395; (*c*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (*d*) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev.*, 2011, **111**, 1657.

2 Reviews: (*a*) N. Krause and C. Winter, *Chem. Rev.*, 2011, **111**, 1994; Selected examples: (*b*) G. Dyker, E. Muth, A. S. K. Hashmi and L. Ding, *Adv. Synth. Catal.*, 2003, **345**, 1247; (*c*) G. Dyker, D. Hildebrandt, J. H. Liu and K. Merz, *Angew. Chem., Int. Ed.*, 2003, **42**, 4399; (*d*) Z. Shi and C. He, *J. Am. Chem. Soc.*, 2004, **126**, 13596; (*e*) M. Georgy, V. Boucard and J. M. Campagne, *J. Am. Chem. Soc.*, 2005, **127**, 14180; (*f*) D. A. Engel and G. B. Dudley, *Org. Lett.*, 2006, **8**, 4027.

3 Reviews: (*a*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (*b*) H. Schmidbaur and A. Schier, *Arabian J. Sci. Eng.*, 2012, **37**, 1187; Selected examples: (*c*) A. S. K. Hashmi, M. C. Blanco, D. Fischer and J. W. Bats, *Eur. J. Org. Chem.*, 2006, 1387; (*d*) D. Aguilar, M. Contel, R. Navarro and E. P. Urriolabeitia, *Organometallics*, 2007, **26**, 4604; (*e*) D. Aguilar, M. Contel, R. Navarro, T. Soler and E. P. Urriolabeitia, *J. Organomet. Chem.*, 2009, **694**, 486.

4 Reviews: (*a*) N. D. Shapiro and F. D. Toste, *Synlett*, 2010, 675; (*b*) F. D. Toste, *Synlett*, 2012, 46; Selected examples: (*c*) P. Mauleón, R. M. Zeldin, A. Z. González and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 6348; (*d*) W. Wang, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.*, 2012, **134**, 5697; (*e*) M. C. B. Jaimes, C. R. N. Böhling, J. M. Serrano-Becerra and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2013, **52**, 7963, DOI: 10.1002/anie.201210351.

5 (*a*) A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph and E. Kurpejović, *Angew. Chem., Int. Ed.*, 2004, **43**, 6545; (*b*) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfle, W. Frey and J. W. Bats, *Angew. Chem., Int. Ed.*, 2005, **44**, 2798; (*c*) N. Debono, M. Iglesias and F. Sánchez, *Adv. Synth. Catal.*, 2007, **349**, 2470; (*d*) A. S. K. Hashmi, M. Rudolph, H. U. Siehl, M. Tanaka, J. W. Bats and W. Frey, *Chem.–Eur. J.*, 2008, **14**, 3703; (*e*) N. D. Shapiro, Y. Shi and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 11654; (*f*) Y. Zhang, B. Feng and C. Zhu, *Org. Biomol. Chem.*, 2012, **10**, 9137; (*g*) J. A. O'Neill, G. M. Rosair and A.-L. Lee, *Catal. Sci. Technol.*, 2012, **2**, 1818.

6 (*a*) V. K.-Y. Lo, Y.-G. Liu, M.-K. Wong and C.-M. Che, *Org. Lett.*, 2006, **8**, 1529; (*b*) V. K.-Y. Lo, M.-K. Wong and C.-M. Che, *Org. Lett.*, 2008, **10**, 517; (*c*) M.-Z. Wang, M.-K. Wong and C.-M. Che, *Chem.–Eur. J.*, 2008, **14**, 8353.

7 W. Henderson, *Adv. Organomet. Chem.*, 2006, **54**, 207.

8 (*a*) V. K.-Y. Lo, K. K.-Y. Kung, M.-K. Wong and C.-M. Che, *J. Organomet. Chem.*, 2009, **694**, 583; (*b*) K. K.-Y. Kung, G.-L. Li, L. Zou, H.-C. Chong, Y.-C. Leung, K.-H. Wong, V. K.-Y. Lo, C.-M. Che and M.-K. Wong, *Org. Biomol. Chem.*, 2012, **10**, 925; (*c*) K. K.-Y. Kung, V. K.-Y. Lo, H.-M. Ko, G.-L. Li, P.-Y. Chan, K.-C. Leung, Z. Zhou, M.-Z. Wang, C.-M. Che and M.-K. Wong, *Adv. Synth. Catal.*, 2013, **355**, 2055, DOI: 10.1002/adsc.201300005.

9 H.-L. Kwong, H.-L. Yeung, C.-T. Yeung, W.-S. Lee, C.-S. Lee and W.-L. Wong, *Coord. Chem. Rev.*, 2007, **251**, 2188.

10 (*a*) P. A. Bonnardel, R. V. Parish and R. G. Pritchard, *J. Chem. Soc., Dalton Trans.*, 1996, 3185; (*b*) D. Fan, C.-T. Yang, J. D. Ranford, P. F. Lee and J. J. Vittal, *Dalton Trans.*, 2003, 2680; (*c*) K. J. Kilpin, W. Henderson and B. K. Nicholson, *Inorg. Chim. Acta*, 2009, **362**, 3669.

11 C. Wei and C.-J. Li, *J. Am. Chem. Soc.*, 2003, **125**, 9584.

12 D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012.

13 C. Ferrer, C. H. Amijs and A. M. Echavarren, *Chem.–Eur. J.*, 2007, **13**, 1358.

14 S. Bhuvaneswari, M. Jeganmohan and C.-H. Cheng, *Chem.–Eur. J.*, 2007, **13**, 8285.

15 (*a*) A. S. K. Hashmi, *Chem.–Eur. J.*, 2013, **19**, 1058; (*b*) Y.-Z. Wang, L.-Z. Liu and L.-M. Zhang, *Chem. Sci.*, 2013, **4**, 739.

16 A. Zanardi, J. A. Mata and E. Peris, *Chem.–Eur. J.*, 2010, **16**, 13109.