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Modular chiral gold(I) phosphite complexes†

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Chiral gold(I) phosphite complexes are readily prepared modularly from 3,3'-bis(triphenylsilyl)-1,1'-bi-2-naphthol. These chiral gold(I) phosphite complexes are very reactive precatalysts for the [4+2] cycloaddition of aryl-substituted 1,6-enynes with enantiomeric ratios ranging from 86 : 14 up to 94 : 6.

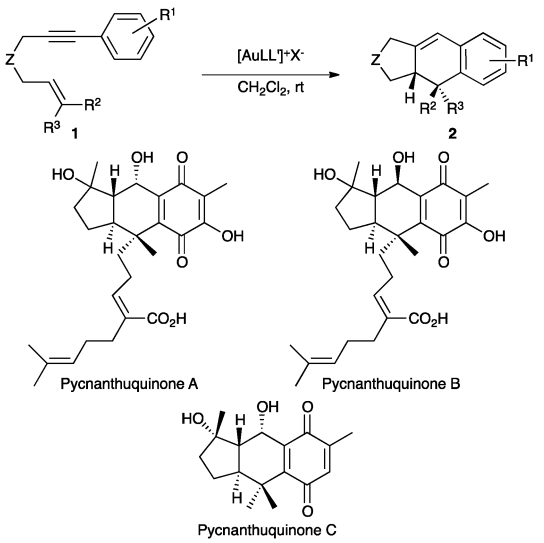
Introduction

Homogeneous gold catalysis provides efficient solutions for the construction of complex carbon skeletons under mild conditions.[1–4] Much of the progress in the enantioselective C–C multiple bond activation catalysed by gold has been achieved in the last few years in intramolecular reactions.[5–15] However, wide-scope enantioselective gold-catalysed transformations are still relatively scarce.

In 2005 we reported the first gold(I)-catalysed enantioselective alkoxycyclization of 1,6-enynes with a cationic catalyst generated *in situ* from [(*R*)-Tol-BINAP(AuCl)$_2$] and $AgSbF_6$.[16] Related enantioselective cyclizations of 1,6-enynes have been carried out more recently with chiral NHC–gold(I)[17] and phosphine–gold[18] complexes, or using platinum catalysts.[19]

We have developed a general gold(I)-catalysed cycloisomerization of substrates **1** by formal [4+2] cycloaddition of arylalkynes with alkenes to form stereospecific cycloadducts **2**,[20] with the core structure of pycnanthuquinones (Scheme 1).[21–23]

As part of a program on the development of general strategies for the synthesis of these terpenoid quinones, we examined an alternative pathway based on the gold-catalysed cyclization of benzyl-substituted 1,5-enynes.[24] In parallel, we also studied the enantioselective cycloaddition of aryl-substituted 1,6-enynes **1** using a variety of gold(I) catalysts with chiral phosphine ligands. Whereas we obtained modest enantioselectivities in most cases,[25] the group of Genêt and Michelet reported good results in the cyclization of two substrates **1a–b** in the presence of a gold(I) catalyst generated *in situ* from DTBM-MeOBIPHEP and AgOTf,[26] although in the case of **1b** the yield was significantly lower than that obtained with achiral catalysts[20] (Scheme 2).



Scheme 1 Gold(I)-catalyzed [4+2] cycloaddition of 1,6-enynes **1** and the structures of pycnanthuquinones A–C.

In an effort at developing general and practical methods for the screening of a large variety of chiral ligands in gold-catalysed reactions, we recently reported a procedure that allows performing enantioselective processes from catalysts prepared *in situ* from a cationic complex [Au(tmbn)$_2$](SbF$_6$) (tmbn = 2,4,6-trimethoxybenzonitrile) and the corresponding chiral ligand.[27] As an alternative, we prepared a series of complexes bearing chiral phosphite ligands based on the BINOL motive using a relatively simple, modular approach from a commercially available 1,1'-bi-2-naphthol. We focused on phosphite ligands over phosphines because of their lower sensitivity to air and other oxidizing agents,[28] and because phosphite gold(I) complexes are the most reactive catalysts for

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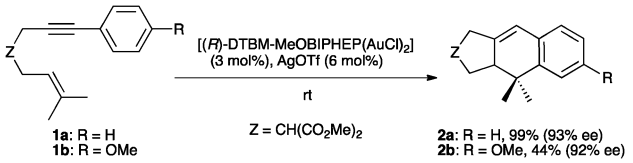
† Electronic supplementary information (ESI) available: Experimental results and NMR data. CCDC 933751 (**L11(AuCl)**), 933752 (**L12(AuCl)a**), 933753 (**L9(AuCl)**), 933754 (**L10(AuCl)**), 933756 (**L8(AuCl)**), 933757 (**L12(AuCl)e**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cy00250k



Scheme 2 Enantioselective gold(I)-catalysed [4+2] cycloaddition of 1,6-enynes **1a**–**b**.

the activation of alkynes.[29,30] Herein we report our efforts towards the development of chiral BINOL-derived phosphite gold(I) complexes. Chiral BINOL-derived phosphites have been used as building blocks for synthesis of chiral palladacycles, bis(phosphite) and mixed phosphite–phosphinite PCP-palladium pincer complexes.[31,32] Monodentate phosphite gold(I) complexes with C_3-symmetry[33] and chiral gold phosphoramidite-based catalysts have also been used in a number of gold-catalysed reactions.[10–12,34]

Results and discussion

We initially examined the gold(I)-catalysed cyclization of enyne **1a** to form adduct **2a** using a wide range of complexes as precatalysts (Fig. 1). The structures of complexes **L8(AuCl)** (Fig. 2), **L9(AuCl)**, **L10(AuCl)** (Fig. 3), **L11(AuCl)** (Fig. 4), and **L12(AuCl)a** (Fig. 5) and **L12(AuCl)e** were determined using X-ray diffraction.

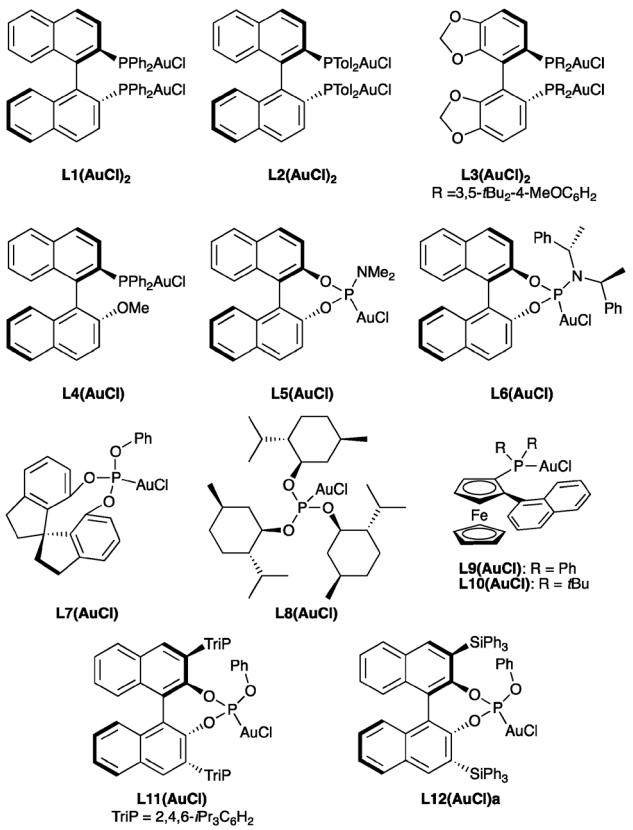


Fig. 1 Chiral gold(I) complexes of the cyclization of 1,6-enyne **1a**.

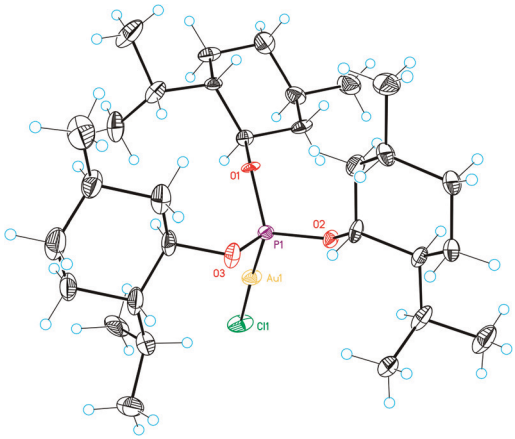


Fig. 2 X-Ray crystal structure of gold complex **L8(AuCl)**. ORTEP plot (50% thermal ellipsoids).

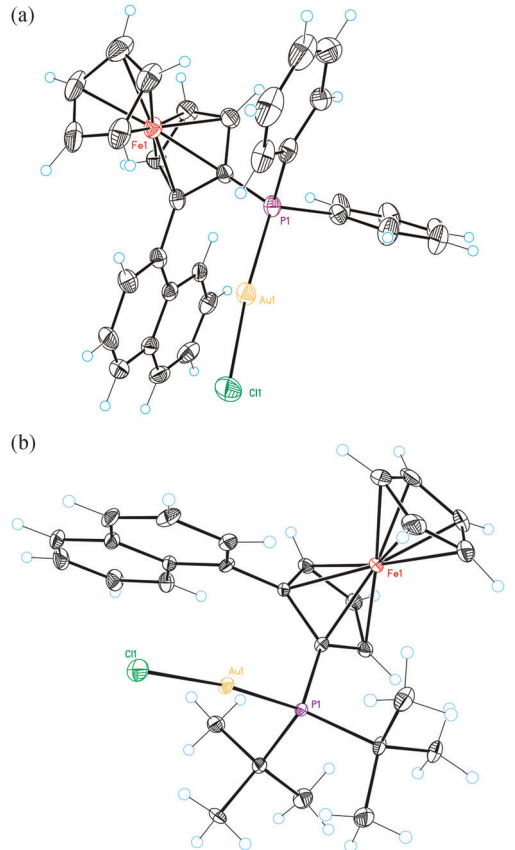


Fig. 3 X-Ray crystal structures of ferrocenylphosphine gold complexes (a) **L9(AuCl)** and (b) **L10(AuCl)**. ORTEP plot (50% thermal ellipsoids).

The cycloadditions were performed either at room temperature (condition A) or under microwave heating (condition B) (Table 1). Diphosphine–digold complexes **L1(AuCl)$_2$**, **L2(AuCl)$_2$**, and **L3(AuCl)$_2$** were investigated first (Table 1, entries 1–9). Cycloadduct **2a** was obtained in all cases in good to excellent yield but only with low to moderate enantioselectivities. The best results with these diphosphine–digold complexes (56% ee) were obtained with **L2(AuCl)$_2$** in

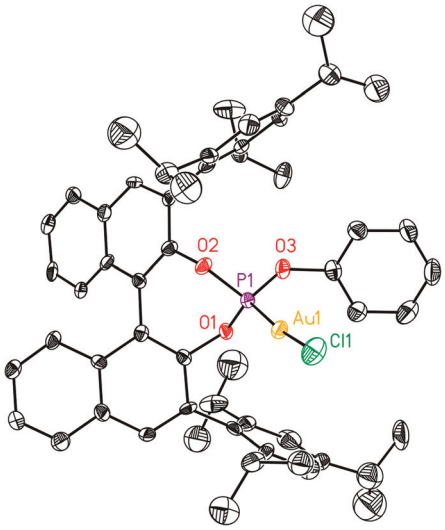


Fig. 4 X-Ray crystal structure of gold complexes **L11(AuCl)** and **L10(AuCl)**. ORTEP plot (50% thermal ellipsoids). Hydrogens are omitted for clarity.

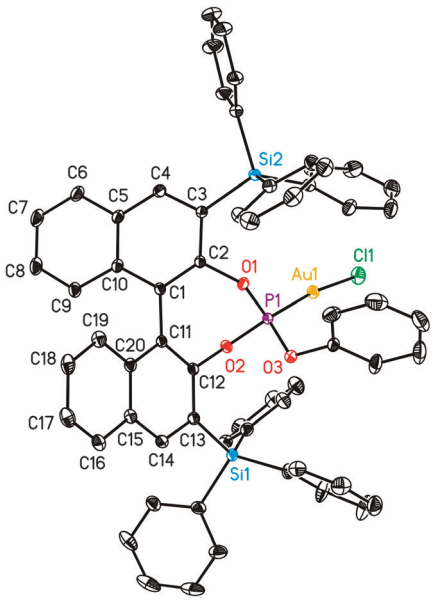


Fig. 5 X-Ray crystal structure of gold complex **L12(AuCl)a**. ORTEP plot (50% thermal ellipsoids). Hydrogens are omitted for clarity.

$CHCl_3$ using $AgPF_6$ under both conditions A and B (Table 1, entries 7 and 8). Using a 1 : 1 ratio of the digold complex to silver salt, under conditions in which the monocationic species are presumably formed, low enantioselectivities were observed. Biaryl gold–phosphine complex **L4(AuCl)** with the (*R*)-MOP ligand gave low enantiomeric excesses (Table 1, entries 11–13). BINOL-derived phosphoramidite complexes **L5(AuCl)** and **L6(AuCl)** also led to **2a** in excellent yield but very poor enantioselectivities (Table 1, entries 14–19). Whereas reactions of complexes **L7(AuCl)**–**L11(AuCl)** led to poor to moderate enantioselectivities (Table 1, entries 20–27), results with phosphite gold complex **L12(AuCl)** were more promising (Table 1, entries 28 and 29). Although the

Table 1 Enantioselective gold(I)-catalysed [4+2] cyclization of 1,6-enyne **1a** to form **2a** with complexes of Fig. 1[a]

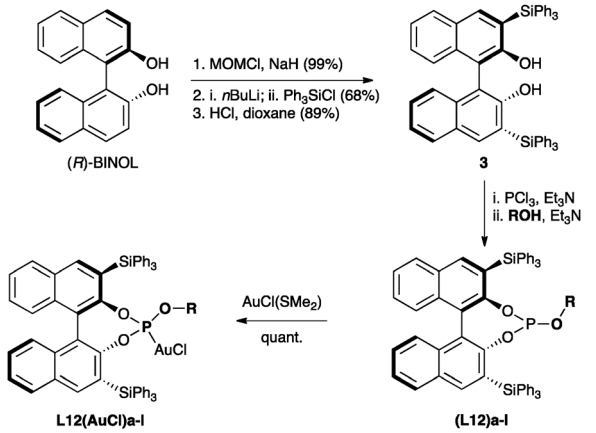
Entry	Au complex	AgX	Conditions	Time	Yield (%)	ee (%)
1	**L1(AuCl)$_2$**	$AgSbF_6$	A	24 h	71	24
2	**L1(AuCl)$_2$**	$AgSbF_6$	B	18 min	92	7
3	**L1(AuCl)$_2$**	$AgPF_6$	A	24 h	81	31
4	**L1(AuCl)$_2$**	$AgPF_6$	B	18 min	90	39
5	**L2(AuCl)$_2$**	$AgSbF_6$	A	30 h	90	25
6	**L2(AuCl)$_2$**	$AgSbF_6$	A[b]	18 min	80	38
7	**L2(AuCl)$_2$**	$AgPF_6$	A[b]	24 h	89	56
8	**L2(AuCl)$_2$**	$AgPF_6$	B[b]	15 min	89	56
9	**L3(AuCl)$_2$**	$AgBF_4$	A	16 h	91	25
10	**L4(AuCl)**	$AgSbF_6$	A	78 h	56	18
11	**L4(AuCl)**	$AgSbF_6$	B	18 min	78	20
12	**L4(AuCl)**	$AgPF_6$	A	78 h	67	23
13	**L4(AuCl)**	$AgPF_6$	B	18 min	84	25
14	**L5(AuCl)**	$AgSbF_6$	A	24 h	91	8
15	**L5(AuCl)**	$AgSbF_6$	B	18 min	95	12
16	**L5(AuCl)**	$AgPF_6$	A	24 h	88	9
17	**L5(AuCl)**	$AgPF_6$	B	18 min	94	14
18	**L6(AuCl)**	$AgSbF_6$	B	18 min	95	5
19	**L6(AuCl)**	$AgPF_6$	B	18 min	94	4
20	**L7(AuCl)**	$AgSbF_6$	A	12 h	92	26
21	**L8(AuCl)**	$AgSbF_6$	A	2 h	98	<1
22	**L9(AuCl)**	$AgSbF_6$	A	24 h	>99[c]	35
23	**L9(AuCl)**	OTf	A[d]	24 h	>99[c]	46
24	**L9(AuCl)**	NTf_2	A[d]	24 h	60[c]	50
25	**L10(AuCl)**	$AgSbF_6$	A[e]	24 h	>99[c]	50
26	**L10(AuCl)**	$AgSbF_6$	A[d]	24 h	>99[c]	39
27	**L11(AuCl)**	$AgSbF_6$	A	12 h	92	26
28	**L12(AuCl)**	$AgSbF_6$	A	12 h	99	57
29	**L12(AuCl)**	$AgBF_4$	A	16 h	90	57

[a] Au complex (2.5 mol%) and AgX (2.5 or 5 mol% for mono and digold complexes, respectively). Conditions A: 23 °C, CH_2Cl_2. Conditions B: microwave heating at 80 °C, CH_2Cl_2. [b] Reaction in $CHCl_3$. [c] Conversion determined using ^1H NMR. [d] Reaction in benzene. [e] Reaction at −20 °C.

enantiomeric excess was only marginally better than that obtained with **L2(AuCl)$_2$**, phosphite gold complex **L12(AuCl)** was a significantly more reactive catalyst, leading to **2a** in nearly quantitative yield in 12 h reaction time (*vs.* 24 h required with **L2(AuCl)$_2$**).

Overall, the structures of Au(I) complexes **L11(AuCl)** and **L12(AuCl)a** in the solid state are similar (Fig. 4 and 5), although the Au–P–OPh angle in **L12(AuCl)a** (102.90°) is significantly more acute than that of **L11(AuCl)** (114.98°). Complex **L12(AuCl)a** shows a cone-shaped binding pocket surrounding with a closest distance of 3.304 Å between the gold centre and a phenyl ring of one of the $SiPh_3$ groups, which is within the range (3.0–3.2 Å) observed in gold(I) complexes in bulky biaryl Buchwald phosphines.[35] This weak Au(I)–arene interaction is not present in complex **L11(AuCl)**.

The preparation of a series of phosphite ligands **(L12)a–n** with different OR groups can be easily carried out using known methods[31,32] from commercially available (*R*)-BINOL[36] by known procedures *via* 3,3'-bis(triphenylsilyl)-1,1'-bi-2-naphthol (**3**) (Scheme 3),[37] which is also commercially available. Ligands **(L12)a–n** were routinely purified by chromatography on silica gel under an inert atmosphere and the corresponding gold(I) complexes **L12(AuCl)a–n** were prepared in quantitative yields by reaction with [AuCl(SMe_2)].



Scheme 3 Synthesis of gold(I) phosphite complexes **L12(AuCl)a–l** from **3** and alcohols or phenols.

We assayed the catalytic activity of gold(I) complexes **L12(AuCl)a–l** (5 mol%) by mixing with $AgSbF_6$ (5 mol%) at 0 °C in CH_2Cl_2, followed by addition of substrate **1a** and slowly warming the reaction mixture to 23 °C over 2 h (Table 2).

Under these conditions, **L12(AuCl)a** led to **2a** in 70% ee (Table 2, entry 1). The enantioselectivity was raised further by using phosphite ligands **L12** derived from *p*-alkylsubstituted phenols (Table 2, entries 3–6). The best result (88% ee) was achieved with **L12(AuCl)d** derived from the *tert*-butylphenol group when the reaction was performed at −20 °C (Table 2, entry 6).[38] Satisfactory results were also obtained with **L12(AuCl)g** and **L12(AuCl)k** (Table 2, entries 9 and 13).

The reactions with the best catalyst **L12(AuCl)d** were slower (16–24 h) in 1,2-dichloroethane, ethyl ether, or acetone as solvent (63–82% ee), whereas no reaction was observed in toluene or 1,4-dioxane after 1–2 days. On the other hand, changing the silver salt from $AgSbF_6$ to AgOTf or $AgNTf_2$ did not significantly affect the reactivity and enantioselectivity, while slightly lower enantiomeric excesses were obtained with $AgPF_6$.[39]

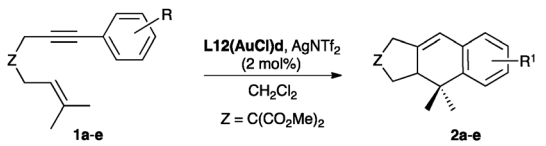
Finally, the optimized phosphite gold(I) catalyst **L12(AuCl)d** was applied for the cyclization of 1,6-enynes **1a–e** using 2 mol% catalyst loadings (Table 3). Substrate **1b** with a *p*-OMe group gave the corresponding cycloadduct **2b** in good yield and enantioselectivity, although a longer reaction time was required (Table 3, entry 2). Good enantioselectivity was also obtained with enyne **2c** bearing a *p*-Me group (Table 3, entry 3). Sterically more demanding substrate **1d** could also be cyclized in 70% yield and 79% ee (Table 3, entry 4). Finally, cyclization of **2e** with a strong electron-withdrawing *p*-NO_2 group at the phenyl ring gave cycloadduct **1d** in 80% yield and 73% ee at 0 °C (Table 3, entry 5).

Table 2 Enantioselective gold(I)-catalysed [4+2] cyclization of 1,6-enyne **1a** to form **2a** with complexes **L12(AuCl)a–n**[a]

Entry	Au complex	R	ee (%)
1	**L12(AuCl)a**	Ph	70
2	**L12(AuCl)b**	*m*-Tol	72
3	**L12(AuCl)c**	*p*-Tol	80
4[b]	**L12(AuCl)c**	*p*-Tol	83
5	**L12(AuCl)d**	4-*t*BuC_6H_4	82
6[c]	**L12(AuCl)d**	4-*t*BuC_6H_4	88
7	**L12(AuCl)e**	4-MeOC_6H_4	60
8	**L12(AuCl)f**	2,4-$Me_2C_6H_3$	74
9	**L12(AuCl)g**	3,5-$Me_2C_6H_3$	81
10	**L12(AuCl)h**	2,4,6-$Cl_3C_6H_2$	46
11	**L12(AuCl)i**	2-Napht	70
12	**L12(AuCl)j**	Me	5
13[d]	**L12(AuCl)k**	$PhCH_2$	81
14[e]	**L12(AuCl)l**	3,5-*t*$Bu_2C_6H_3CH_2$	74

[a] Au complex (5 mol%) and $AgSbF_6$ (5 mol%), 0 to 23 °C, 2 h, CH_2Cl_2. [b] Reaction at −20 °C for 4 h. [c] Reaction at −20 °C for 16 h. [d] Reaction at −25 °C for 36 h. [e] Reaction at 0 °C for 7 h.

Table 3 Gold(I)-catalysed [4+2] cycloaddition of 1,6-enynes **1a–n** with catalyst **L12(AuCl)d**



Entry	Enyne	R	*T* (°C)	Time (h)	Product (yield, %)	ee (%)
1	**1a**	H	−20	18	95	88
2	**1b**	*p*-MeO	−20	30	85	86
3	**1c**	*p*-Me	−20	15	98	87
4	**1d**	*o*-Me	−20	30	70	79
5	**1e**	*p*-O_2N	0	15	80	73

Conclusions

We have developed a series of chiral phosphite gold(I) complexes **L12(AuCl)a–n** that are easily prepared in a modular manner from BINOL. Cyclization of aryl-substituted 1,6-enynes with these complexes in the presence of a silver salt occurs with enantiomeric ratios ranging from 86 : 14 up to 94 : 6. It is also important to note that these chiral catalysts rival in reactivity with the most active catalysts for the cyclization of this more challenging class of compounds bearing a disubstituted alkyne.

Acknowledgements

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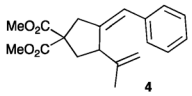

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39 See ESI† for details.