

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.

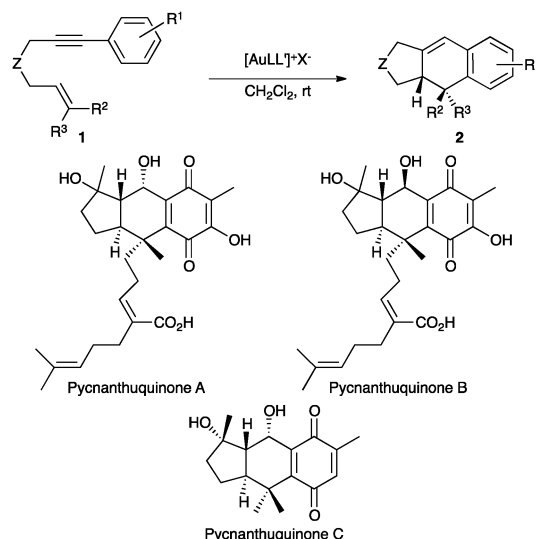
Introduction

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 alkoxy cyclization of 1,6-enynes with a cationic catalyst generated *in situ* from [(*R*)-Tol-BINAP(AuCl)₂] and AgSbF₆.¹⁶ Related enantioselective cyclizations of 1,6-enynes have been carried out more recently with chiral NHC–gold(i)¹⁷ and phosphine–gold¹⁸ 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



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

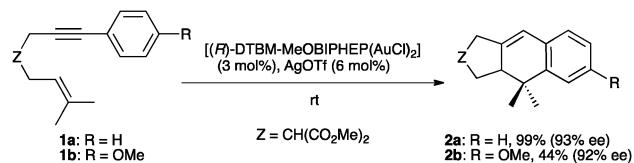
and AgOTf,²⁶ although in the case of **1b** the yield was significantly lower than that obtained with achiral catalysts²⁰ (Scheme 2).

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](SbF₆) (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-symmetry³³ 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.

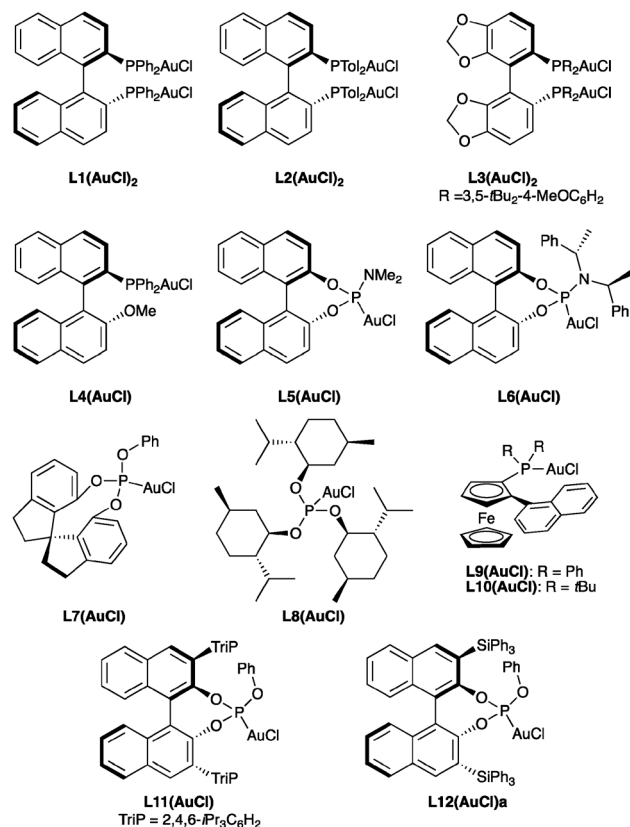


Fig. 1 Chiral gold(I) complexes of the cyclization of 1,6-enyne 1a.

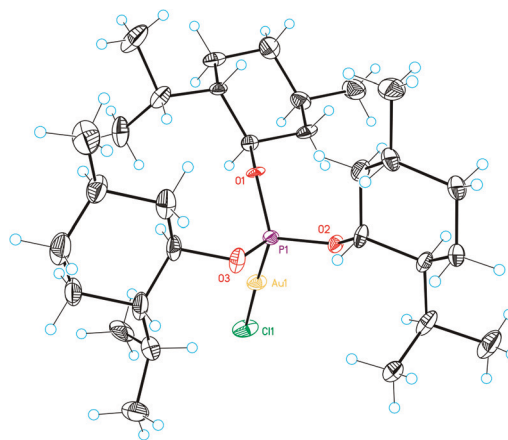


Fig. 2 X-Ray crystal structure of gold complex L8(AuCl). ORTEP plot (50% thermal ellipsoids).

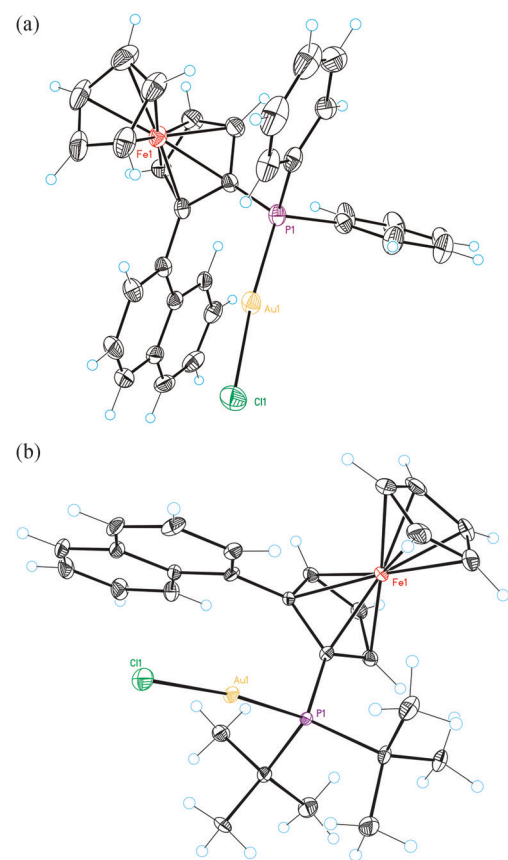


Fig. 3 X-Ray crystal structures of ferrocenylphosphine gold complexes (a) L9(AuCl) and (b) L10(AuCl). ORTEP plot (50% thermal ellipsoids).

The cycloadditions were performed either at room temperature (condition A) or under microwave heating (condition B) (Table 1). Diphosphine-gold 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-gold complexes (56% ee) were obtained with L2(AuCl)₂ in



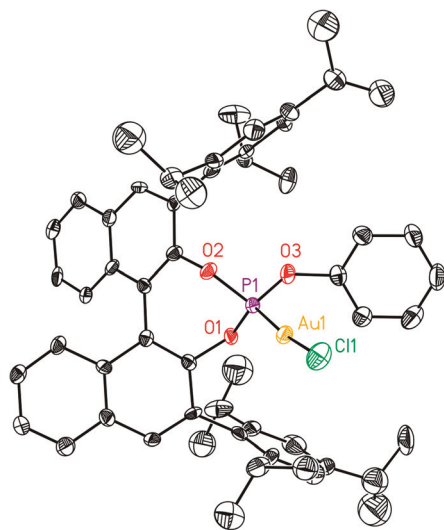


Fig. 4 X-Ray crystal structure of gold complexes **L11(AuCl)** and **L10(AuCl)**. ORTEP plot (50% thermal ellipsoids). Hydrogens are omitted for clarity.

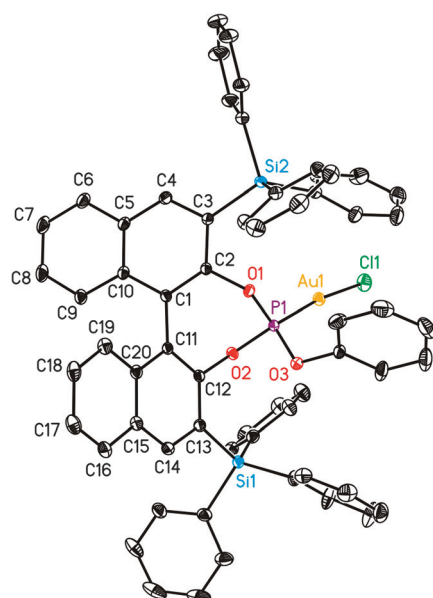


Fig. 5 X-Ray crystal structure of gold complex **L12(AuCl)a**. ORTEP plot (50% thermal ellipsoids). Hydrogens are omitted for clarity.

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

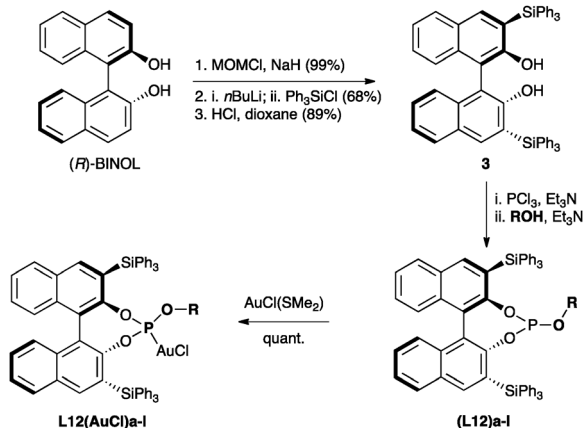
^a Au complex (2.5 mol%) and AgX (2.5 or 5 mol% for mono and digold complexes, respectively). Conditions A: 23 °C, CH_2Cl_2 . Conditions B: microwave heating at 80 °C, CH_2Cl_2 . ^b Reaction in CHCl_3 . ^c Conversion determined using ^1H NMR. ^d Reaction in benzene. ^e Reaction at –20 °C.

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 (**L12a**)–**n** with different OR groups can be easily carried out using known methods^{31,32} from commercially available (*R*)-BINOL³⁶ by known procedures via 3,3'-bis(triphenylsilyl)-1,1'-bi-2-naphthol (**3**) (Scheme 3),³⁷ which is also commercially available. Ligands (**L12a**)–**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 $[\text{AuCl}(\text{SMe}_2)]$.





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

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	2a (95)	88
2	1b	<i>p</i> -MeO	–20	30	2b (85)	86
3	1c	<i>p</i> -Me	–20	15	2c (98)	87
4	1d	<i>o</i> -Me	–20	30	2d (70)	79
5	1e	<i>p</i> -O ₂ N	0	15	2e (80)	73

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*-NO₂ group at the phenyl ring gave cycloadduct **1d** in 80% yield and 73% ee at 0 °C (Table 3, entry 5).

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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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	<i>m</i> -Tol	72
3	L12(AuCl)c	<i>p</i> -Tol	80
4 ^b	L12(AuCl)c	<i>p</i> -Tol	83
5	L12(AuCl)d	4- <i>t</i> BuC ₆ H ₄	82
6 ^c	L12(AuCl)d	4- <i>t</i> BuC ₆ H ₄	88
7	L12(AuCl)e	4-MeOC ₆ H ₄	60
8	L12(AuCl)f	2,4-Me ₂ C ₆ H ₃	74
9	L12(AuCl)g	3,5-Me ₂ C ₆ H ₃	81
10	L12(AuCl)h	2,4,6-Cl ₃ C ₆ H 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- <i>t</i> Bu ₂ C ₆ H ₃ CH 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.

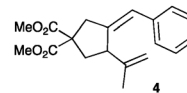


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