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Gold compounds as efficient co-catalysts in palladium-catalysed alkynylation

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Abstract

A series of inorganic and organometallic compounds of gold [AuCl(tht)], [Au(C_6F_5)(tht)] and Na[$AuCl_4$] (tht = tetrahydrothiophene) are shown to efficiently co-catalyze the Sonogashira-type cross-coupling reaction of phenylacetylene with aryl halides in THF solution. [AuCl(tppts)] (tppts = trisodium salt of tris(*m*-sulfonatophenyl)phosphine) co-catalyzes the same reaction in biphasic aqueous systems. Gold compounds are thus revealed as efficient transmetalation catalysts to palladium.

Keywords: Palladium-catalysed alkynylation; Gold compounds; Homogeneous catalysis

1. Introduction

The use of gold in homogeneous catalysis has received increased attention recently [1]. Previously considered catalytically inactive for use in organic synthesis, a range of organic transformations has now been reported that are efficiently catalyzed by gold [2]. Examples are the reaction of amines [3], alcohols and water with alkynes [4], propargylic amine synthesis [5], benzannulation [6] and phenol syntheses [7]. These particular procedures exploit the ability of gold compounds to catalytically activate alkynes, and this ability to activate alkynes towards inter- and intra-molecular reaction with various functional groups has proved a versatile synthetic tool for convenient access to complex structures [8]. They benefit from a low catalyst concentration and, in some cases, high activity in aqueous solution [4c,5] or using green methodologies [2c].

An extensively used synthetic method involving catalytic alkyne activation is the Sonogashira cross-coupling reaction [9]. First presented in 1975 [10] it has become a widespread method for the construction of organic compounds bearing alkyne groups with diverse applications in organic synthesis, including the preparation of natural products [11]. The classic experimental procedure involves [$PdCl_2(PPh_3)_2$] as a Pd(0) precursor and CuI as a co-catalyst in a solution containing an amine base. The CuI is required to activate the alkyne, and transmetalation occurs from the alkynylcopper intermediate formed in solution to the organopalladium(II) centre, previously formed by oxidative addition of the Pd(0) catalyst to the organic halide. Subsequent reductive elimination releases the cross-coupled alkyne derivative. This is a widely assumed mechanism but has not been rigorously established [9,11]. Intensive research efforts have developed many variations of this reaction to address the unsuitability of the original experimental conditions in some situations. For example, the use of bulky, electron rich phosphine ligands have been used to increase yields of relatively unreactive aryl bromides [12]. Some alternatives to the CuI co-catalyst have been developed to overcome the problem of competitive homocoupling to the diyne [13]. For example, stoichiometric amounts of Ag_2O or tetrabutylammonium salts may be used in place of CuI [14] and judicious Pd catalyst or experimental design may preclude the need for a CuI co-catalyst (i.e. a direct Heck alkynylation) [15] or any metal catalyst at all [16]. Pd catalysed alkynylation may also take place with alkynyl derivatives of the type RM (where R is the alkynyl group and M is, amongst others, Zn, Mg, or Sn) [9,17].

The necessity for a stoichiometric amount of alkynyl metal starting material in these methods makes the development of a

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new co-catalyst as an alternative to CuI desirable. We have thus initiated studies to provide further details on the activation of alkynes by gold in terms of its ability to transmetalate alkynes to palladium when present in catalytic quantities. The gold compounds [AuCl(tht)], [AuCl(tppts)], [AuCl(PPh_3)], [Au(C_6F_5)(tht)] and Na[$AuCl_4$] were used as co-catalysts in Sonogashira-type cross-coupling reactions (tht = tetrahydrothiophene, tppts = trisodium salt of tris(*m*-sulfonatophenyl)phosphine).

2. Results and discussion

The first cross-couplings of phenylacetylene were performed in THF utilising NH(*i*-Pr)$_2$ as a base. The results are presented in Table 1.

Na[$AuCl_4$] and [AuCl(tht)] are shown to be efficient co-catalysts. It is observed that full conversion may be obtained for aryl iodides at room temperature (Table 1; entries 1, 2, 6 and 7) and activated aryl bromides (Table 1; entries 4, 5 and 9) at reflux (66 °C) in 14 h for coupling reactions with phenylacetylene. Non-activated aryl bromides (Table 1; entries 3 and 8) proceed in poor yield due to the lower reactivity of the Pd(0) catalyst to the aryl bromide electrophile. Identical experiments with *n*-hexyne in place of phenylacetylene also gave poor yields (<10%), showing that the gold co-catalysts used are much more efficient in activating aryl alkynes than alkyl alkynes. NH(*i*-Pr)$_2$ was found to be the most efficient amine base, with NH(Et)$_2$ giving substantially reduced conversions under the same conditions in the same reaction time (less than 30%).

It was not necessary to use argon purged distilled solvents or purified starting materials for these reactions. Quantitative conversions were obtained by using reagent grade materials as received, though a blanket of argon was kept over the reaction mixtures during the reaction. Isolated yields of 95% or over were obtained for all compounds where full conversion was observed by NMR. Interestingly, the formation of the coupled product and other derivatives are observed without the use of co-catalyst in a low extension (<5%), being the gold complexes [AuCl(tht)] and Na[$AuCl_4$] totally inactive without the presence of palladium complex [$PdCl_2(PPh_3)_2$].

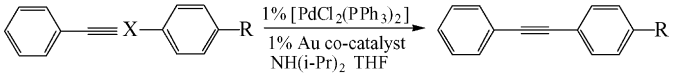
We assume the inactivity of [AuCl(PPh_3)] (Table 1, entry 10) is due to its high stability under the experimental conditions, making it a poor pre-catalyst. [AuCl(tht)] can easily lose its tht ligand and this may occur to form the active catalyst in solution. The mode of action of the Na[$AuCl_4$] pre-catalyst is unknown, and further mechanistic studies and collection of catalytic results is necessary to shed light on the mechanism of alkyne activation. The high reactivity of both Au(I) and Au(III) is frequently observed in homogeneous gold chemistry, and although mechanistic details are sometimes proposed it is assumed that Au(III) compounds are pre-catalysts, though theoretical studies indicate that Au(I) and Au(III) catalysts feature similar overall reaction barriers [18].

An examination of entries 3 and 8 in Table 1 for the cross-coupling of bromobenzene with phenylacetylene suggests that [AuCl(tht)] is a more effective catalyst than Na[$AuCl_4$] under the same conditions. We thus followed the reaction of three gold co-catalysts and CuI to completion to see which complex gave full conversion to the cross-coupled product in the shortest time (Table 2).

CuI (Table 2, entry 1) is shown to be the catalyst with the best turn over rate, giving full conversion under the conditions employed in just 30 min. [AuCl(tht)] is the most active gold catalyst studied, and direct comparison with [Au(C_6F_5)(tht)] shows that the substitution of the chloro ligand by the organometallic C_6F_5 fragment decreases the activity, with over twice as long required to fully convert the starting materials to the cross-coupled product. Although the gold complexes are slower they maintain the advantage that the formation of diyne products is totally avoided, and we did not observe any formation of diyne products even when using reagent grade solvents that were purged with air prior to reaction.

The observation that some catalytic processes of gold are effective in water [4c,5] and our recent contributions on the preparation of gold(I), (II) and (III) complexes soluble in water

Table 1
Experimental conditions and conversions for cross-coupling reactions with phenylacetylene[a]



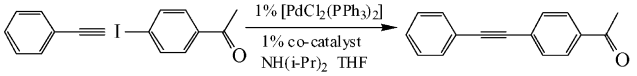
	R	X	Au co-catalyst	Conditions	Conversion (%)[b]
1	H	I	Na[$AuCl_4$]	14 h, r.t.[c]	100
2	COMe	I	Na[$AuCl_4$]	14 h, r.t.[c]	100
3	H	Br	Na[$AuCl_4$]	14 h, reflux	<5
4	COMe	Br	Na[$AuCl_4$]	14 h, reflux	100
5	CHO	Br	Na[$AuCl_4$]	14 h, reflux	100
6	H	I	[AuCl(tht)]	14 h, r.t.[c]	100
7	COMe	I	[AuCl(tht)]	14 h, r.t.[c]	100
8	H	Br	[AuCl(tht)]	14 h, reflux	26
9	COMe	Br	[AuCl(tht)]	14 h, reflux	100
10	COMe	I	[AuCl(PPh_3)]	14 h, r.t.	<1

[a] Experimental conditions: phenylacetylene (0.75 mmol), aryl halide (0.5 mmol), NH(*i*-Pr)$_2$ (0.75 mmol), [$PdCl_2(PPh_3)_2$] (0.005 mmol), Au co-catalyst (0.005 mmol), THF 1 mL.

[b] Determined by NMR in $CDCl_3$ after removal of THF. The complete absence of aryl halide starting material peaks is interpreted as 100% conversion. All NMR spectra were clean showing no major impurities.

[c] Full conversion could also be obtained by 4 h reflux (66 °C).

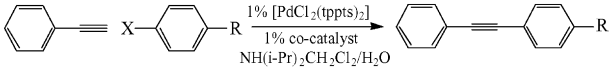
Table 2
Time taken to reach full conversion for different co-catalysts[a]



	Co-catalyst	Time (min.)
1	CuI	30
2	[AuCl(tht)]	350
3	Na[$AuCl_4$]	580
4	[Au(C_6F_5)(tht)]	790

[a] Experimental conditions: 4-iodoacetophenone (0.5 mmol), phenylacetylene (0.75 mmol), NH(*i*-Pr)$_2$ (0.75 mmol), [$PdCl_2(PPh_3)_2$] (0.005 mmol), co-catalyst (0.005 mmol), THF 1 mL, room temperature. Small samples were taken from the reaction mixture during the course of the reaction and analysed by NMR for conversion until no 4-iodoacetophenone starting material was observed.

Table 3
Experimental conditions and conversions for coupling reactions with phenylacetylene in a biphasic system



	X	R	Co-catalyst	Conditions	Conversion (%)
1	I	$COCH_3$	CuI	14 h, r.t.	31
2	I	$COCH_3$	None	14 h, r.t.	59[a]
3	I	H	$Na[AuCl_4]$	14 h, r.t.	19
4	I	$COCH_3$	$Na[AuCl_4]$	14 h, r.t.	24
5	I	$COCH_3$	[AuCl(tppts)]	14 h, r.t.	100
6	I	H	[AuCl(tppts)]	14 h, r.t.	100
7	Br	H	[AuCl(tppts)]	14 h, r.t.	<5
8	Br	$COCH_3$	[AuCl(tppts)]	14 h, r.t.	<5

[a] Significant amounts of various impurities observed in the aromatic region of the ^1H NMR.

[19], led us to test the compatibility of the processes in aqueous systems. $[PdCl_2(PPh_3)_2]$ was substituted for the water soluble $[PdCl_2(tppts)_2]$ [20]. Table 3 summarises the results and shows CuI and $Na[AuCl_4]$ to give poor yields in biphasic CH_2Cl_2/H_2O systems under the conditions employed. However, the $[PdCl_2(tppts)_2]$/[AuCl(tppts)] catalyst system achieves quantitative conversion for cross-coupling of the aryl iodides with phenylacetylene (Table 3; entries 5 and 6). The aryl bromides were not reactive enough to give a significant amount of product, a situation that could not be improved on heating. Interestingly, a moderate yield of the coupled product is observed without the use of co-catalyst, indicating that the biphasic system employed is somewhat favourable to direct Heck-alkynylation. However, the addition of the gold catalyst allows the reaction to proceed in quantitative yield and much cleaner, without the impurities observed in the products of the co-catalyst free system. The use of a biphasic system also faciliates the recovery of the precious metal catalysts.

The activity of [AuCl(tppts)] in the aqueous biphasic system is in contrast with the inactivity of $[AuCl(PPh_3)]$ in THF (entry 10, Table 1). We presume that the water plays a vital role in the catalytic cycle in that it promotes the generation of an active catalyst by a mechanism not available in the pure organic solvent.

3. Conclusion

In conclusion, we have presented preliminary studies on the ability of gold compounds to act as transmetalation agents to Palladium when present in catalytic quantities. Although reaction times are slightly longer than with CuI in THF, the use of the gold co-catalysts present the advantage of cleaner reactions, avoiding coupling products, and permits the use of technical grade solvents without previous purification or air exclusion. The compounds presented are efficient and practical co-catalysts for Sonogashira-type coupling of aryl iodides in THF and H_2O/CH_2Cl_2 biphasic systems and for activated aryl bromides in THF. The ability of the water soluble gold complex, [AuCl(tppts)], to remain active in aqueous solution is particularly pleasing. Continuing studies on the effect of structure–activity relationships of gold catalysts and attempts to elucidate mechanistic detail will allow us to further the usefulness of gold in organic synthesis, and permit the evaluation of its further potential as a transmetalating agent in catalytic quantities.

4. Experimental

Reagent grade chemicals were used for all catalytic reactions. A blanket of Argon was kept over the solutions during the course of the reaction. ^1H and $^{31}P\{^1H\}$ NMR spectra were recorded on a 400 MHz Bruker Avance spectrometer. Chemical shifts are quoted relative to external TMS (^1H) and 85% H_3PO_4 (^{31}P); coupling constants are reported in Hertz at room temperature. Mass spectra were obtained with a VG Autospec mass spectrometer operating in electron impact (EI) mode and liquid secondary ion mass spectrometry (LSIMS) mode using NBA as matrix. Elemental compositions were analysed with a Perkin-Elmer 2400B.

[AuCl(tht)] [21], $[Au(C_6F_5)(tht)]$ [21] and $[PdCl_2(tppts)_2]$ [20] were synthesised as previously described and their characterisation data was in line with that reported in the above named references. A sample of TPPTS was kindly provided by European Oxo GmbH. All other reagents and solvents were obtained from commercial sources and used as received.

4.1. Synthesis of [AuCl(tppts)]

[AuCl(tht)] (120 mg, 0.37 mmol) was added to a solution of TPPTS (210 mg, 0.37 mmol) in MeOH (15 mL) and stirred for 50 min. The solution was filtered through celite to remove insoluble impurities and then ether (80 mL) was added to give a white solid that was collected, washed with chloroform, ether then dried under high vacuum. Yield 272 mg, 92%.

NMR (D_2O, 400 MHz); ^1H: 7.94–8.06 (m, 6H, *H*2, *H*4), 7.63–7.76 (m, 6H, *H*6, *H*5) ppm. $^{31}P\{^1H\}$ NMR (D_2O, 162 MHz): 33.46 (s) ppm. ^{13}C NMR (CD_3OD): 130.00 (d, $^1J_{P-C}$ = 61.5 Hz, 3C, C*ipso*), 130.96 (d, $^2J_{P-C}$ = 11.7 Hz, 3C, C*o*), 131.07 (d, $^4J_{P-C}$ = 2.2 Hz, 3C, C*p*), 132.62 (d, $^2J_{P-C}$ = 16.8 Hz, 3C, C*o*), 136.54 (d, $^3J_{P-C}$ = 12.4 Hz, 3C, C*m*), 147.96 (d, $^3J_{P-C}$ = 12.4 Hz, 3C, C*m*-SO_3Na). LSIMS: 800 $[M]^+$; microanalysis; found: C, 26.86; H, 1.98; S 11.90%. Calc. for [AuCl(tppts)]·1/2H_2O $C_{18}H_{12}O_9ClPS_3AuNa_3$·1/2$H_2O$ (808.85)%, C, 26.70; H, 1.62; S, 11.86.

4.2. Preparative reactions

Product NMR details are as follows:

1-(4-Phenylethynyl-phenyl)-ethanone: ^1H NMR ($CDCl_3$); 7.94 (2H, d), 7.61 (2H, d), 7.57–7.52 (2H, m), 7.38–7.35 (3H, m), 2.62 (3H, s).
1-(4-Phenylethynyl-phenyl)-ethanal: ^1H NMR ($CDCl_3$); 10.03 (1H, s), 7.88 (2H, d), 7.68 (2H, d), 7.56–7.54 (2H, m), 7.39–7.36 (3H, m).
Diphenylacetylene: ^1H NMR ($CDCl_3$); 7.59–7.54 (4H, m), 7.38–7.34 (6H, m).

4.2.1. Reactions in THF were performed and worked up as outlined in the representative synthesis

4-Iodoacetophenone (369 mg, 1.5 mmol), phenylacetylene (0.248 mL, 2.25 mmol), and NH(*i*-Pr)$_2$ (0.33 mL, 2.25 mmol) were stirred in THF (3 mL) under argon. [$PdCl_2(PPh_3)_2$] (10.5 mg, 0.015 mmol) was added and the mixture stirred for 10 min before the addition of $NaAuCl_4 \cdot 2H_2O$ (6.0 mg, 0.015 mmol). The mixture was stirred at room temperature for 14 h then added to aqueous hydrochloric acid (10 mL, 1 M). Extraction to dichloromethane and purification on an alumina column (CH_2Cl_2) gave pure 1-(4-phenylethynyl-phenyl)-ethanone (313 mg, 95%).

4.2.2. Typical example of a biphasic preparative procedure

4-Iodoactephenone (123 mg, 0.5 mmol), phenylacetylene (0.083 mL, 0.75 mmol), NH(*i*-Pr) (0.11 mL, 0.75 mmol) were stirred in a mixture of CH_2Cl_2 (1 mL) and H_2O (1 mL). [$PdCl_2$(tppts)$_2$] (6.6 mg, 0.005 mmol) was added followed by [AuCl(tppts)] (4.0 mg, 0.005 mmol). The mixture was stirred for 14 h under a blanket of argon. An extra 3 mL CH_2Cl_2 was added to the mixture and the organic phase was loaded onto an alumina column. Elution with CH_2Cl_2 gave the pure product, 1-(4-phenylethynyl-phenyl)-ethanone (see NMR above). Isolated yield 106 mg, 96%. Microanalysis: found C, 87.45%; H, 5.27%. Calculated for $C_{16}H_{12}O$; C, 87.29%; H, 5.49%.

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