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Gold-catalysed cyclic ether formation from diols

Xiaolu Jiang, Emma K. London, David J. Morris, Guy J. Clarkson, Martin Wills *

Department of Chemistry, The University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK

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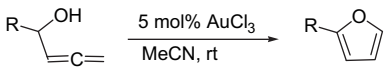
ABSTRACT

Gold(I) and (III) salts have been found to be highly effective at the catalysis of ether formation from alcohols. Intramolecular ether formation of a 1,5-diol was also achieved, with a stereoselectivity that indicates that an S_N1 mechanism predominates. In an attempt to form a seven-membered ring, a stable 14-membered dimer product was also formed. Attempts to control the diastereoselectivity of the reaction using a chiral anionic counterion did not give products with a high de.

1. Introduction

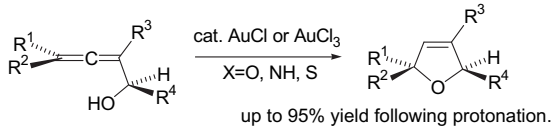
Gold salts and complexes can catalyse a variety of transformations, such as cycloadditions, isomerisations, hydroaminations or nucleophilic cyclisation of allenes.[1–5] Their soft, carbophilic Lewis acid character is capable of activating carbon–carbon double and triple bonds, leading to the formation of C–C, C–O, C–N and C–S bonds. In the specific arena of C–O bond formation reactions, Hashmi et al. described the use of gold(III)chloride in the cycloisomerisation of allenic alcohols to furans (Scheme 1).[2a]



Scheme 1. Gold(III) catalysed formation of furans from allenes.

Using chiral allenes as substrates, gold(I) or gold(III) chloride catalyse the *endo*-cycloisomerisation of **1** to the corresponding five-membered heterocycles with complete axis-to-centre chirality transfer (Scheme 2).[3,4] Gold salts catalyse the reaction by coordinating to an allenic double bond as a Lewis acid, resulting in increased electrophilicity of the terminal carbon atom.

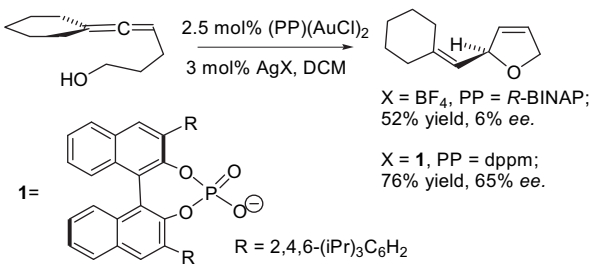
This axis-to-centre chirality transfer gold-catalysed *endo*-cycloisomerization was applied in the first enantioselective syntheses of the natural products β-carboline alkaloids (−)-isochrysotricine and (−)-isocyclocapitelline.[4] The cyclisation was



Scheme 2. Formation of 2,5-dihydrofurans by gold-catalysed cyclisation.

catalysed by as little as 0.05 mol % gold(III) chloride in THF, giving a key 2,5-dihydrofuran intermediate in a yield of 97% yield with a high level of stereochemical control (96% de, >98% ee).

It has also been found that high enantioselectivity may be achieved with the use of a chiral counterion in a gold-catalysed reaction. Toste et al.[5] carried out two sets of hydroalkoxylation reactions of an allene to test how chiral counterions mediate asymmetric gold reactions (Scheme 3); one catalysed by chiral phosphine-substituted gold catalysts $L(AuCl)_2$ and $AgBF_4$ and the other catalysed by $dppm(AuCl)_2$ and chiral silver phosphates AgX.



Scheme 3. Use of a chiral counterion in gold-catalysed reactions.

* Corresponding author. Tel.: +44 24 7652 3260; fax: +44 24 7652 4112; e-mail address: m.wills@warwick.ac.uk (M. Wills).

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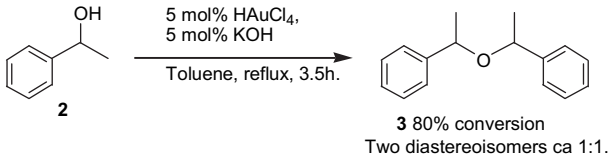
The hydroalkoxylation catalysed by chiral counterions[6] was more enantioselective (65% ee in DCM, up to 97% ee in benzene).

In this paper, we describe the use of gold catalysts for the cyclisation of diols under mild conditions.

2. Results and discussion

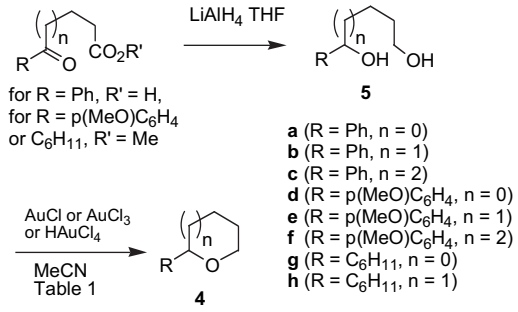
During the course of our ongoing studies on alcohol dehydrogenation,[7] we screened a series of organometallic complexes for the oxidation of 1-phenylethanol **2** to acetophenone. In the case of gold salts, including AuCl and $AuCl_3$, a new product was observed. This was identified from its characteristic methine proton quartet resonances in the ^{1}H NMR spectrum, as the known ether **3**,[8] formed as a diastereoisomeric mixture by the condensation of two molecules of the alcohol (Scheme 4). Some studies into this reaction permitted its optimisation to give a product in 80% conversion (5 mol % $HAuCl_4$, 5 mol % KOH, toluene, reflux, 3.5 h). A survey of the literature revealed that this condensation has been reported to be promoted by a Pd(II)/AgOTf catalyst,[8a] and TfOH.[8b] The closely related intramolecular cyclisation of 1,5-dihydroxy-1,5-diphenylpentane[9] has also been achieved using a range of acids,[9a] and $PtCl_2/AgSbF_6$.[9b] However we were aware of no similar reaction catalysed by a gold salt. Since this represented a potentially mild alternative to some relatively strong acids, we elected to study this reaction in more detail.



Scheme 4. Gold-catalysed formation of an ether from 1-phenylethanol.

We investigated the potential of the gold-catalysed method to form cyclic ethers **4** from diols **5**. Initially, diols **5a**–**h** were prepared, in each case from the reduction of a ketoacid or ester (Scheme 5).[10] The ester substrates were prepared by addition of a Grignard reagent to the precursor acid chloride in the presence of a copper salt,[11] whilst the ketoacid precursors were commercially available. Cyclisation of **5a**–**c** bearing phenyl groups was first conducted using 5 mol % of the three gold catalysts; chloroauric acid ($HAuCl_4$), gold(I) chloride (AuCl) and gold(III) chloride ($AuCl_3$), at 40 °C for 20 h. Of these, only the five-membered ring precursor **5a**, in the presence of $HAuCl_4$, was cyclised in any significant yield; 63%, whilst all other combinations gave only 0–4% conversion. At the higher temperature of 80 °C, further reagent/catalyst combinations were successfully cyclised (Table 1). In each case, $HAuCl_4$ was the most active catalyst, followed by $AuCl_3$, whilst as expected the rate of cyclisation was higher for the smallest ring product, and slowest for the largest of the series. The seven-membered product **4c** was formed in very low conversion and was accompanied by a second product, which could not be fully characterised but may be a dimer similar to that formed in the cyclisation of **5f** (see below).

Using the more electron-rich substrates **5d**–**f**, all the cyclisations, with each gold catalyst, were completed, at 40 °C within 1 h (5% catalyst initially used).[12] Further studies revealed that the catalyst loading could be reduced to 0.5 mol % and the temperature to 25 °C, for full cyclisations to be observed within reasonable reaction times (Table 1). Following these reactions using ^{1}H NMR spectroscopy revealed complete cyclisations in times as short as 6.5 min. The time-conversion graphs for the AuCl catalysts indicated the operation of an induction period (Fig. 1), which may be suggestive of the slow formation of an active catalytic species, or some form of autocatalysis.



Scheme 5. Preparation and intramolecular gold-catalysed cyclisation of 1,5-diols.

Table 1
Cyclisations of diols **5a**–**h** to cyclic ethers **4a**–**h** using Au(III) and Au(I) salts as catalysts

Substrate	Catalyst	Loading (%)	T/°C[a]	t/h[a]	Conv (%)[a]
5a	$HAuCl_4$	5	40 (80)	20 (20)	63 (100)
5a	AuCl	5	40 (80)	20 (20)	1 (13)
5a	$AuCl_3$	5	40 (80)	20 (20)	4 (28)
5b	$HAuCl_4$	5	40 (80)	20 (20)	0 (54)
5b	AuCl	5	40 (80)	20 (20)	0 (8)
5b	$AuCl_3$	5	40 (80)	20 (20)	0 (26)
5c	$HAuCl_4$	5	40 (80)	20 (20)	0 (11)[b]
5c	AuCl	5	40 (80)	20 (20)	0 (7)[b]
5c	$AuCl_3$	5	40 (80)	20 (20)	0 (15)[b]
5d	$HAuCl_4$	5 (0.5)	40 (25)	<1 (0.25)	100 (100)
5d	AuCl	5 (0.5)	40 (25)	<1 (0.25)	100 (100)
5d	$AuCl_3$	5 (0.5)	40 (25)	<1 (0.1)	100 (100)
5e	$HAuCl_4$	5 (0.5)	40 (25)	<1 (0.2)	100 (100)
5e	AuCl	5 (0.5)	40 (25)	<1 (1)	100 (100)
5e	$AuCl_3$	5 (0.5)	40	<1	100
5f	$HAuCl_4$	0.5	25	0.2	>95[c,d]
5f	AuCl	0.5	25	3.5	>95[c]
5f	$AuCl_3$	0.5	25	0.2	>95[c]
5g	$HAuCl_4$	5	80	20	100
5g	AuCl	5	80	20	19
5g	$AuCl_3$	5	80	20	47
5h	$HAuCl_4$	5	80	20	12[e]
5h	AuCl	5	80	20	3[e]
5h	$AuCl_3$	5	80	20	8[e]

Solvent=MeCN, [diol]=0.2 M. No cyclisation was observed in the absence of catalyst.
[a] Numbers in parenthesis represent a second data point.
[b] A second product was observed, which may be a cyclic dimer.
[c] A dimer, **4fD**, was also formed in this reaction in the following ratios of **4f**/**4fD**; $HAuCl_4$; 4:1, AuCl; 1:2, $AuCl_3$; 3:1.
[d] Cyclisation in $CDCl_3$ under the same conditions resulted in the formation of **4f** accompanied by <10% **4fD**.
[e] Product is tentatively assigned due to low conversions.

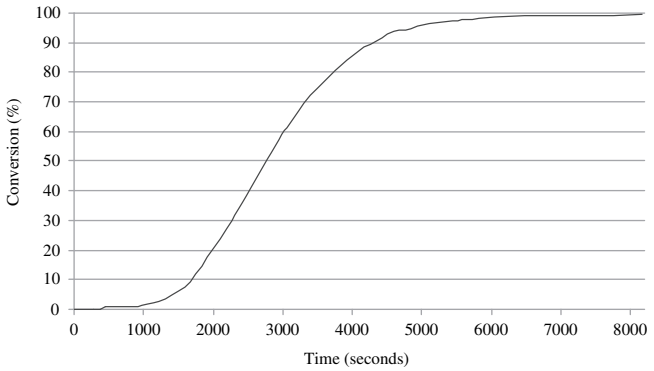


Fig. 1. Conversion versus time for the cyclisation of **5d** by AuCl (0.5 mol % AuCl, 25 °C).

The formation of **4f** was accompanied by the formation of a second product, which precipitated from the reaction and when AuCl was used, was the major product. This was isolated and fully characterised, including by X-ray crystallography (Fig. 2; CCDC