

Gold catalysed reactions with cyclopropenes†

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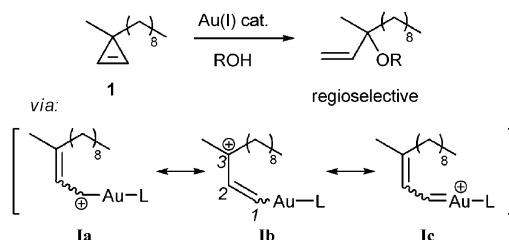
Gold(I) catalyses the ring-opening addition of cyclopropenes in a mild and regioselective manner.

Interest in organic transformations catalysed by Au(I) and Au(III) complexes has undergone a marked increase in recent years.¹ The majority of homogenous Au catalysed reactions draw on the superb Lewis acidity of gold for activation of alkynes.^{1d} More recently, gold carbenoid species have been proposed to exist transiently in a number of gold-catalysed reactions.^{1c,2} For example, gold carbenoid species are proposed to be generated from α -diazocarbonyl compounds,³ rearrangement of propargylic carboxylates⁴ and alkynyl sulfides,⁵ or intermolecular cyclopropanation of enynes.⁶ Although there have been many examples¹ of gold catalysed activation of alkynes, allenes and alkenes, there have been no reports to date on gold-catalysed reactions with highly strained cyclopropenes. Cyclopropenes display a diverse range of reactivities, thus presenting unique opportunities for organic synthesis.⁷ In this communication, we wish to report a novel and remarkably regioselective transformation of 3,3-disubstituted cyclopropenes catalysed by gold(I) (Scheme 1). We propose that gold(I) catalyses the ring opening of cyclopropenes to form intermediate gold vinyl carbenoid/cationic species (**I**), which can be trapped by nucleophiles. As far as the authors are aware, this constitutes the first report on gold-catalysed reactions with cyclopropenes.

The intermolecular gold(I) catalysed reaction of cyclopropene **1** with a range of alcohols is shown in Table 1. Entries 1–7 show that primary alcohols add exclusively and regioselectively at the C-3 position of the proposed intermediate **I** to produce the tertiary ether **2** rather than the primary ether **3** (arising from reaction at C-1) under mild conditions (20 °C, 1–2 h, without the need for dried or distilled solvents).⁸ In addition to simple primary alcohols MeOH and EtOH (Entries 1–3), allyl alcohol and benzyl alcohol (Entries 4 and 5) also smoothly undergo this regioselective addition on cyclopropene **1** to produce the corresponding allyl- and benzyl-protected tertiary allylic alcohols **2c** and **2d** in good yields (88% and 78%, respectively). The homoallylic alcohol 3-buten-1-ol and 2-phenylethanol also react smoothly to give the corresponding products **2e** and **2f** in good yields (88% and 77% respectively).

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Scheme 1 The regioselective gold(I) catalysed ring-opening addition of cyclopropene **1** to form *tert*-allylic ethers and the proposed intermediate **I**.

Secondary alcohol *i*-PrOH also successfully undergoes the regioselective ring-opening addition to cyclopropene **1** to produce the corresponding *sec*-alkyl *tert*-allylic ether **2g** in 70% yield (Entry 9). The regioselectivity is still excellent, though very slightly diminished with a 97 : 3 ratio of **2** : **3**, reflecting the more sterically hindered nature of the secondary alcohol.⁹ It is of interest to note that the employment of Gagosz's air-stable PPh₃AuNTf₂ catalyst¹⁰ (Entry 9) produces superior activity, regioselectivity and yield in this case compared to PPh₃AuOTf (formed *in situ* with PPh₃AuCl and AgOTf, Entry 8). Reaction of **1** with *t*-BuOH, however, provided only traces of the corresponding *tert*-alkyl *tert*-allylic ether **2h** with PPh₃AuNTf₂ as catalyst (Entry 10). The steric bulk of the tertiary alcohol is very likely to blame for the diminished activity as well as regioselectivity of the reaction.

Table 1 The regioselective gold(I) catalysed ring-opening addition of cyclopropene **1** with a variety of alcohols to form *tert*-allylic ethers

Entry ^a	ROH	Method	Yield of 2 ^b (%)	Product	Ratio 2/3 ^c
1	MeOH	B	86	2a	>99%
2	EtOH	A	64	2b	>99%
3	EtOH	B	83	2b	>99%
4	Allyl alcohol	B	88	2c	>99%
5	Benzyl alcohol	A	78	2d	>99%
6	HOCH ₂ CH ₂ CH=CH ₂	B	88	2e	>99%
7	HOCH ₂ CH ₂ Ph	B	77	2f	>99%
8	<i>i</i> -PrOH	A	N/A ^d	2g	2.5 : 1
9	<i>i</i> -PrOH	B	70	2g	97 : 3
10	<i>t</i> -BuOH	B	Traces	2h	N/A
11 ^e	H ₂ O	B	34	2i	>99%

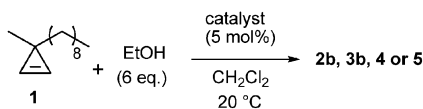
^a All reactions were carried out at 20 °C in CH₂Cl₂ for 1–2 h unless otherwise stated. ^b Isolated yield, unless otherwise stated. ^c Determined by ¹H NMR analysis of the crude mixture. ^d Reaction was allowed to stir for 4 days, after which ~50% conversion was observed to **2g** and **3g** (~30%), **4** and **5** (~20%). ^e 15 eq. of *t*-BuOH was added as a co-solvent and the reaction was allowed to stir for 24 h.

Even water can successfully act as a nucleophile to produce the corresponding tertiary alcohol **2i**, albeit in low conversion and yield (34%, Entry 11).¹¹ Upon repeating the reaction shown in Entry 3 with a reduced Au(I) catalyst loading (1 mol%), complete conversion to **2b** (>99% regioselectivity) is still observed within 1.5 h. Indeed, reactions with primary alcohol nucleophiles such as EtOH (Entry 3) are facile and often complete in <10 min (see ESI†).

In an effort to ascertain whether the reaction is truly gold-catalysed, we carried out some control reactions (Table 2). The gold(I) catalyst PPh₃AuOTf is formed *in situ* from PPh₃AuCl and the hygroscopic AgOTf, resulting in the possibility of there being slight traces of TfOH present during the reaction (64% **2b**, Entry 1).¹² Reaction with the air stable PPh₃AuNTf₂, which does not require any hygroscopic co-catalyst, produces an even better yield of the product **2b** (83%, Entry 2). The control reaction employing 5 mol% of TfOH as catalyst results in no reaction, suggesting that traces of acid are not catalytically active (Entry 3). Reaction with Ag(OTf) as catalyst is also greatly inferior to gold(I), resulting in incomplete consumption of the starting material, along with a complex mixture of products (Entry 4). We also wanted to ascertain if (Rh(OAc)₂)₂, which is believed to ring-open related cyclopropenes to form the corresponding rhodium carbenoid intermediates, could also catalyse this reaction.¹³ In stark contrast to Au(I), employment of (Rh(OAc)₂)₂ as catalyst, produces a mixture of **4** and **5**, along with traces of both **2b** and **3c**. Interestingly, employment of Au(III) instead of Au(I) as catalyst also completely changes the outcome of the reaction, with the aldehydes **4** and **5** being the major products (Entry 6). This difference in reactivity further exemplifies the differences between Au(I) and Au(III) catalysts.^{14,15}

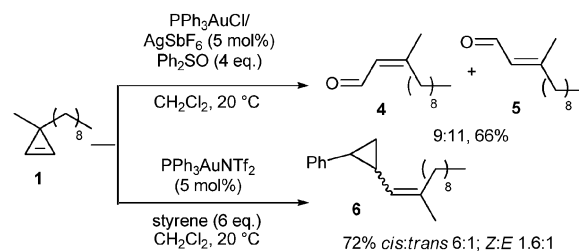
The remarkable regioselectivity with gold(I) is rather surprising, since these species (*vide infra*) usually involve attack at the C-1 position next to gold, rather than at C-3.¹⁶ We propose that the intermediate **I** can have its positive charge delocalised

Table 2 Transition metal-catalysed reaction of **1** with EtOH



Entry	Catalyst	t/h	Result
1	PPh ₃ AuCl/AgOTf	1.5 ^a	64% 2b ^b
2	PPh ₃ AuNTf ₂	1.5	83% 2b ^b
3	HOTf	24	No reaction ^c
4	AgOTf	24	7 : 4 ratio of 1 : 2b along with traces of 3b , 4 and 5 and other unidentified by-products ^c
5	(Rh(OAc) ₂) ₂	24	Major products: 4 and 5 (with traces of 2b and 3b and other unidentified by-products) ^c
6	AuCl ₃	24	Complex mixture of products: 4 and 5 (with traces of 2b and 3b and other unidentified by-products) ^c

^a No change in yield or selectivity is observed if the reaction is allowed to stir for 24 h. ^b Isolated yield; **3b**, **4** and **5** were not detected by ¹H NMR analysis of the crude mixture. ^c By ¹H NMR analysis of the crude mixture.

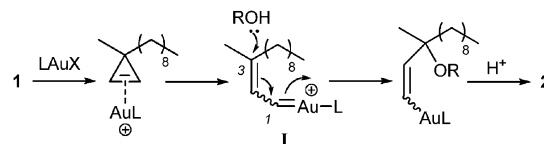


Scheme 2 Gold(I) catalysed ring-opening oxidation and ring-opening cyclopropanation of **1**.

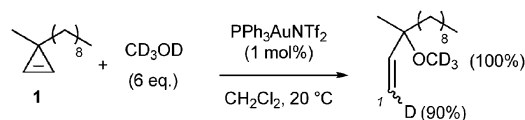
across C-1, C-3 and Au (**1a** ↔ **1b** ↔ **1c**, Scheme 1).¹⁷ The regioselectivity of the reaction with nucleophiles, however, is highly dependent on the identity of the nucleophile. When the nucleophilic oxidant Ph₂SO is employed,^{4b} exclusive attack at C-1 occurs, producing the *Z* and *E* isomers **4** and **5** in 66% yield (Scheme 2). In addition, **1** can also undergo intermolecular olefin cyclopropanation with styrene to form the cyclopropane **6**, albeit in low stereoselectivity (Scheme 2). The success of these reactions lends some support for the carbenoid nature of intermediate **I**.^{4a,b}

Our proposed mechanism for the regioselective gold(I) catalysed ring-opening addition of cyclopropene **1** with alcohols is shown in Scheme 3. Activation of the strained cyclopropene double bond by gold(I) results in ring-opening to produce the proposed intermediate **I** (only one resonance structure shown). Attack of the alcohol at the C-3 position followed by protodemetalation thus furnishes the *tert*-allylic ether **2**. In order to probe the validity of our proposed mechanism, the reaction was carried out with CD₃OD as the nucleophilic alcohol (Scheme 4). Deuterium is indeed incorporated at the C-1 position (90%), lending support to our proposed mechanism.

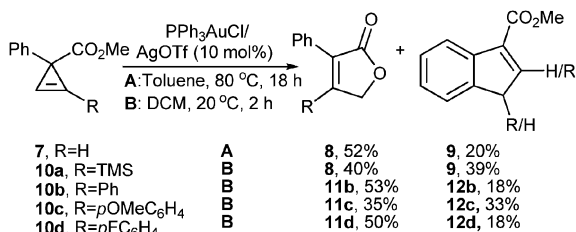
The reason for this intriguing switch of regioselectivity from C-1 to C-3 when alcohol nucleophiles are employed is currently unclear and will be the subject of future investigation in our laboratory. However, it is interesting to note that an excess of alcohol is necessary to ensure good regioselectivity. When the reaction in Entry 2, Table 2 is repeated with only 1.5 eq. (instead of 6 eq.) of EtOH, the regioselectivity is diminished: a 4 : 1 ratio of **2b** : **3b** is observed. However, when the reaction is carried out with 1 eq. of EtOH and 5 eq. of *t*-BuOH, as an additive, the regioselectivity is retained (>99% **2b**, 64% yield). The presence of the unreactive *t*-BuOH as a



Scheme 3 Proposed mechanism for the regioselective gold(I)-catalysed ring-opening addition of **1** with alcohols.



Scheme 4 The regioselective gold(I) catalysed ring-opening addition of **1** with CD₃OD.



Scheme 5 Gold(I) catalysed rearrangement of cyclopropenes **7** and **10a–d**.

protic co-solvent, seems to enhance the regioselectivity of the reaction. Thus the alcohol nucleophile need not be in excess, as long as *t*-BuOH is present as an additive.

Finally, we varied the cyclopropene by replacing the two alkyl substituents in **1** with carbonyl and phenyl substituents to ascertain if *intramolecular* attack of the proposed vinyl cationic/carbenoid intermediate could occur under gold(I) catalysis. Indeed, cyclopropene **7** rearranges to the furanone **8** (52%), with indene **9** (20%) formed as the major by-product.¹⁸ Furanone **8** can be envisaged to result from the *C-1* intramolecular attack of the ester carbonyl oxygen moiety followed by hydrolysis, whereas the indene **9** results from intramolecular attack of the Ph substituent, thus further supporting our proposed vinyl carbenoid/cationic intermediate.¹⁹ Several substituted cyclopropenes **10a–d** also undergo gold(I)-catalysed rearrangements to the corresponding furanones and a mixture of regioisomeric indenenes under milder conditions (Scheme 5).¹⁸ Upon subjecting cyclopropene **7** to 15 eq. of EtOH under Au(I) catalysis, the intramolecular rearrangement to **8** and **9** still predominates (52% and 19%, respectively) with only traces of intermolecular addition products being observed. When substituted cyclopropene **10c** is used, however, the intermolecular addition of EtOH becomes competitive with the intramolecular rearrangement (~1 : 1, see ESI† for further details).

In summary, we have described the first examples of gold-catalysed ring-opening addition of cyclopropenes. The reaction of alkyl-disubstituted cyclopropene **1** with a series of alcohols is mild and highly regioselective, yielding the corresponding *tert*-allylic ethers. Gold(I) catalysts were found to be unique and superior in terms of reactivity and regioselectivity. Upon introduction of ester and Ph substituents on the cyclopropene (**7**, **10**), gold(I) catalysed rearrangement to furanones and indenenes is observed. Further exploration of the scope, reactivity and utility of the gold vinyl carbenoid/cation intermediates formed from cyclopropenes, as well as further investigations into the mechanism of the process is under way and will be reported in a full article in due course.

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- See ESI† for full mechanistic proposal and further details.