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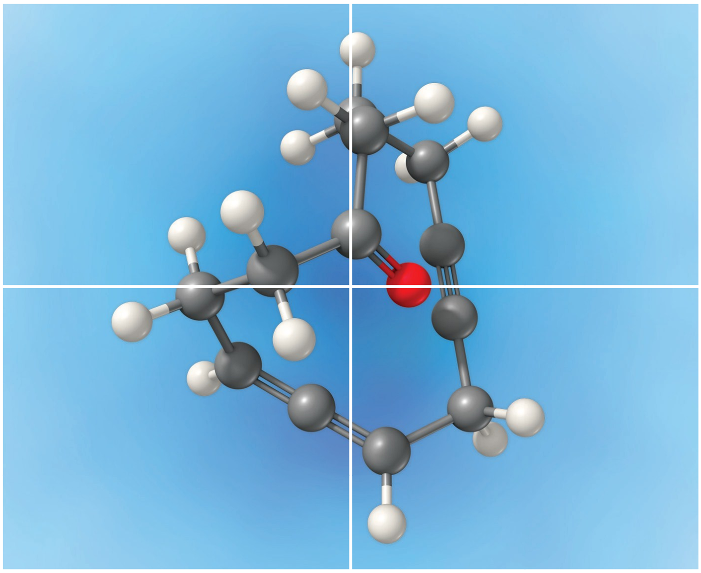

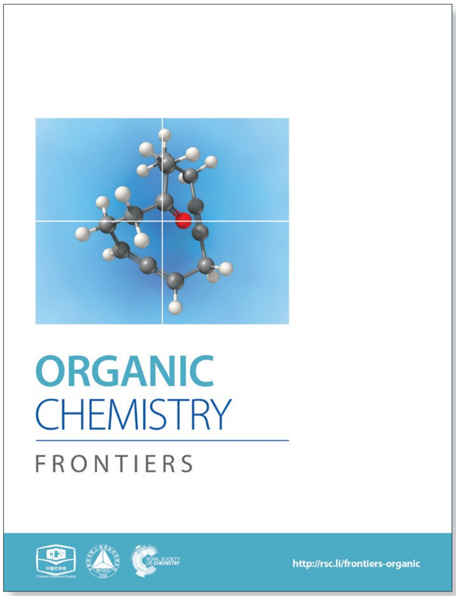

Journal Name

COMMUNICATION

Gold (I) catalyzed [1,3] O→C rearrangement of benzylvinyl ethers

Chandrababu Naidu Kona, Mahesh N. Patil and Chepuri V. Ramana,*

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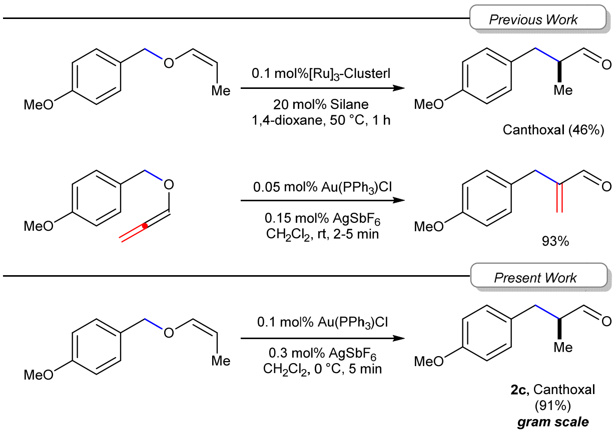
A simple procedure for the preparation of 3-(hetero)arylpropionaldehydes has been developed employing a gold-catalyzed [1,3] rearrangement of the vinyl ethers. Using this protocol, Canthoxal, an aromatic aldehyde used in perfumery, has been prepared on gram scale.

The past decade has received significant attention over gold catalysis and many novel and efficient methodologies have been developed.[1] Generally, the gold complexes act as tunable soft π-acids.[2] In particular, the selective activation of alkynes[3a] and allenes[3b] by gold-complexes, followed by the subsequent inter and intramolecular nucleophilic additions and [3,3]-sigmatropic rearrangements (such as Claisen and Cope rearrangements), has received substantial attention.[3] Recently, we reported a gold (I) catalyzed [1,3] O→C rearrangement of the allenyl ethers leading to α-substituted acryl aldehydes.[4-6] We have proposed a mechanism that proceeds *via* the initial coordination of the Au-center with the oxygen of the allenyl ether resulting in elongation of the carbinol C–O bond and, if the pendant substituent of the oxygen is sufficiently elecrophilic, the cleavage of the carbinol C–O bond, leading to the formation of a contact-ion pair that subsequently undergoes the [1,3]-rearrangement.[6,7] Extending this concept, we were interested to explore the [1,3]-rearrangement reaction of vinyl ethers to understand the mechanism in general and especially in the context of the synthesis of the fragrance ingredient Canthoxal and related 3-arylpriopionaldehydes.[8] The generally adopted approaches for the synthesis of Canthoxal include mainly either Pd-based coupling of 4-haloaniosole or hydroformylation of the 4-allylanisole and subsequent functional group modifications.[9-11] Recently, Nagashima and co-workers revealed the [1,3] O→C rearrangement as a possible alternative while studying the Ru-catalyzed cationic polymerization of vinyl ethers, albeit, in moderate yield.[12]

To start in this direction, as a preliminary experiment, we have synthesized a set of three vinyl ethers of alkyl **1a**, benzyl **1b** and 4-methoxybenzyl **1c** groups from the corresponding allyl derivatives by treating with KO^{t}Bu in DMSO for 15 min.[13]

Figure 1. Selected [1,3] O→C rearrangements



All these vinyl ethers are screened for the initial optimization with Au(PPh$_3$)Cl alone and in combination with several silver salts like AgNTf$_2$, AgOTf, AgSbF$_6$, AgOAc and AgBF$_4$ in different concentrations from 1 mol% to 0.1 mol%. Several gold complexes are also screened for this purpose at different temperatures from 0 °C to rt [ESI]. After extensive optimization studies, 0.1 mol% Au(PPh$_3$)Cl in combination with 0.3 mol% AgsbF$_6$ has been identified as the catalyst of choice and only the rearrangement of 4-methoxybenzylvinyl ether **1c** to the corresponding α-metylated aldehyde **2c** was observed in 5 min at 0°C with 92% isolated yield. Whereas with the other two vinyl ethers having alkyl **1a** and benzyl **1b** groups, hydrolysis was the major event. This revealed that, analogous to allenyl ethers, the reaction progress with vinyl ethers was also significantly affected by the stability of the *in situ* generated benzylic carbocation and the basicity/coordinating ability of the counter anion.[6]

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune – 411 008 (India), E-mail: vr.chepuri@ncl.res.in

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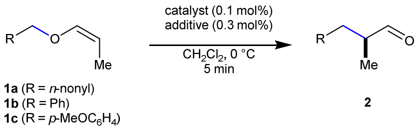
With the optimal catalytic conditions in hand, the scope of the rearrangement was investigated employing a wide range of vinyl ethers. With the 4-methoxybenzylvinyl ethers having the methyl **1d** and *n*-butyl **1e** substitution at the benzylic position delivered the corresponding aldehydes **2d**, **2e** in 87% and 86% respectively as 1:1 diastereomeric mixtures.

Table 1. Optimization of the catalytic conditions

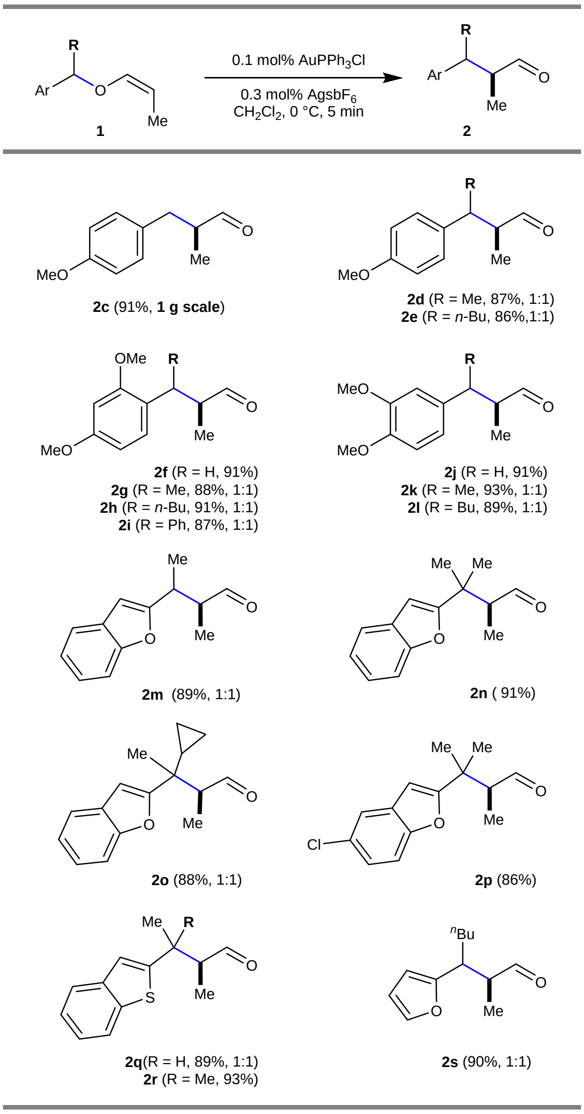


S.No.	Substrate	Catalyst	additive	Yield%
1-3	**1a** or **1b** or**1c**	Au(PPh$_3$)Cl	---	No reaction
4-5	**1a**or **1b**	Au(PPh$_3$)Cl	AgSbF$_6$	Hydrolysis
6	**1c**	Au(PPh$_3$)Cl	AgSbF$_6$	92
7-9	**1a** or **1b** or**1c**	---	AgSbF$_6$	**Hydrolysis**

A similar trend has been noticed in the case of 2,4-dimethoxy and 3,4-dimethoxybenzyl derived vinyl ethers **1f-1l** and procured the corresponding [1,3] O→C rearranged products **2f**–**2l** in excellent yield. Not only are the benzylvinyl ethers, some of the heteroarylmethylvinyl ethers are also facile for this rearrangement purpose. The rearrangement was successfully achieved by the benzofuran derived vinyl ethers **1m**–**1p** and afforded the α-substituted aldehydes **2m**–**2p** in good yield (86-91%). The vinyl ethers **1m**, **1o** afforded a 1:1 diastereomeric mixture of aldehydes **2m** (89%) and **2o** (88%). On the other hand, the vinyl ethers **1n**, **1p** gave the substituted C2-homologated benzofuran aldehydes **2n**, **2p** in 91% and 86% respectively. Gratifyingly, the benzothiophen derived vinyl ether **1q**, having the methyl- substitution at the benzylic position gave the 1:1 diastereomeric mixture of the rearranged product **2q** in 89% yield and **1r** with gem dimethyl substitution at the bezylic position delivered **2r** 93% yield. The rearrangement was quite clean with the furyl-derived vinyl ether **1s** and the C2-homologated aldehyde **2s** was obtained in 90% yield.

Coming to the mechanism, in case of the [1,3] O→C rearrangement of allenyl ethers, with the help of trapping experiments with *O*-nucleophiles, we have proposed a reaction path comprising an initial gold(I) complexation with the oxygen lone pair that results in the cleavage of the C–O bond with the simultaneous formation of a contact ion pair intermediate depending upon the stability of the benzylic cation.[14] If the resulting contact ion pair is sufficiently stable, the subsequent alkylation of the benzylic cation with gold enolate results in the formation of a new C–C bond with a net [1,3] O→C rearrangement of the allenyl ether unit.[6,15a] similar mechanism is apparent in the present case of vinyl ethers rearrangement (Figure 2).

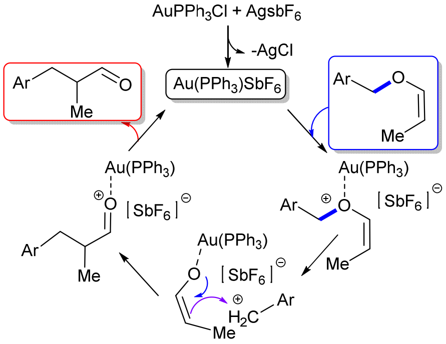
Scheme 1. Substrate scope for the gold(I) catalyzed [1,3] O→C rearrangement[a)]

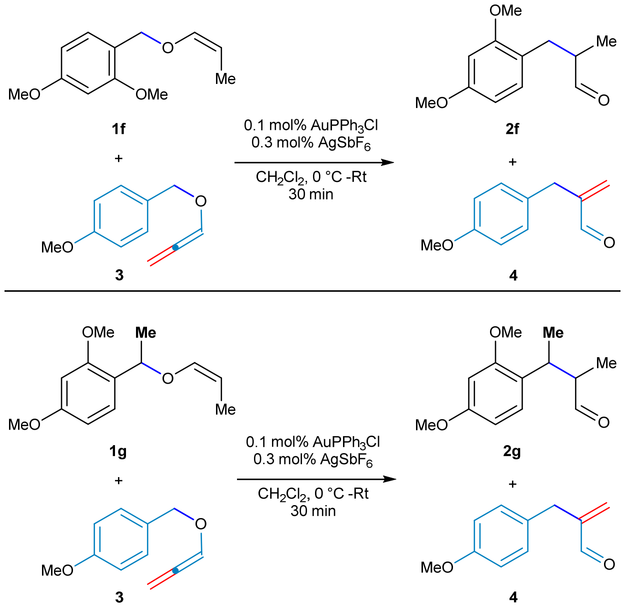


[a)] Crude vinyl ethers resulting from KO^{t}Bu mediated olefin-migration of the corresponding allyl ethers have been used directly for the [1,3]-rearrangement. Selected vinyl ethers were purified and characterized (see ESI).

At this point, in search of conclusive proof for the nature of the contact ion-pair intermediate [either tight contact ion-pair or dispersed in the solvent media] involved in the rearrangement, the following two crossover experiments have been conducted. An equimolar mixture of 4-methoxybenzylallenyl ether **3** and vinyl ethers **1f** or **1g** were subjected for the gold-catalyzed rearrangement at 0° C for 30 min (Scheme 2). In general, the rearrangement of allenyl ether **3** was facile even with 0.05 mol% catalyst (half of what vinyl ethers need). On the other hand, the hydrolysis of vinyl ethers **1f**/**1g** and the stability of the resulting counter cations are better than that of the PMB group present in the allenyl ether **3**. Hence, if the 1,3-rearrangement of these substrates is proceeding *via* a solvent-dispersed contact ion-pair, the scrambling of these counter cations is expected and thus, a mixture with 4 products is expected. Whereas, if the reaction proceeds through a tight-contact pair, only two separate products are expected without any scrambling. In case of the reaction employing a mixture of 4-methoxybenzylallenyl ether **3** and vinyl ethers **1f**, only the rearranged products **4** and **2f** were noticed in the LCMS analysis. A similar trend has been noticed in case of the LCMS analysis of the second cross-over experiment employing a 1:1 mixture of **4** and **2g**. Thus, these experiments provided a clear evidence for the involvement of a tight contact ion-pair intermediate in these gold-catalyzed [1,3]-O→C rearrangements and thus ruled out an operative ion-pairing effect.

Figure 2: plausible mechanistic pathway for the gold(I)-catalyzed [1,3] O→C rearrangement





Scheme 2: Crossover experiments for the mechanistic support

Conclusions

In conclusion, gold(I) catalyzed [1,3] O→C rearrangement of benzylvinyl ethers has been developed as a practical method for the preparation of 2-methyl-3-(hetero)arylpropionaldehydes. The rearrangement is facile with the substrates having the benzylic aryl ring substituted with +M groups. The crossover experiments between vinyl- and allenyl ethers provided an indirect evidence for the involvement of a tight contact ion-pair intermediate in the reaction path. As an off-shoot, a gram-scale process was established for the synthesis of fragrance ingredient Canthoxal.

Acknowledgements

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