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Gold-mediated synthesis of α-ionone

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ABSTRACT

A simple and convenient synthesis of α-ionone, an important component of flowers and fragrances, is reported. The key step in the formation of the α,β-unsaturated ketone moiety involves an NHC-Au^{I} catalyzed Meyer–Schuster-like rearrangement of readily prepared propargylic esters. The complex [{Au(IPr)}$_2$(μ-OH)][BF_4] proved to be the most efficient catalyst leading to α-ionone in 70% yield from a propargylic benzoate. This optimized procedure represents a valuable and attractive alternative to classical methods leading to α,β-unsaturated ketones, such as the Wittig or aldol reactions.

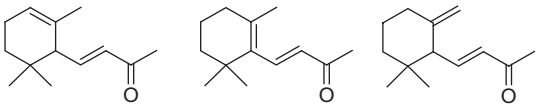
1. Introduction

α-Ionone (**1**) is a C_{13} norterpenoïd α,β-unsaturated ketone with remarkable olfactory properties.[1] It occurs in the headspace of different blooming flowers along with the other two regioisomers (**2**) and (**3**) (Fig. 1). α-Ionone (**1**) represents one of the most important fragrances used in the perfume industry for their distinctive fine violet and rose scents. In fact, it is of great economical value in the creation of violet and many other olfactory notes,[2] in addition to being an important building block in the synthesis of several natural products.[3]

In 1992, Fehr and Guntern[4] reported a synthesis of α-ionone starting from α-damascone in six-steps and 48% overall yield. In this synthesis, the tetrasubstituted cyclohexene ring and the α,β-unsaturated ketone are already present in the starting material. In 2002, Fuganti, Serra et al. summarized the main synthetic routes to α-ionone (as well as to a number of derivatives), including routes to single enantiomers and their corresponding olfactory properties.[5] All aforementioned syntheses were quite elaborate. In 2004, Vidari and co-workers reported a highly enantioselective synthesis of α-ionone **1**, which proceeded in 12-steps from a chiral building block prepared using the asymmetric Sharpless dihydroxylation reaction.[6]

α,β-Unsaturated carbonyl compounds are usually obtained by aldol or Knoevenagel-type condensation reactions[7] or by Wittig or Horner–Wadsworth–Emmons olefinations.[8] These reactions usually require strong basic conditions, which are often incompatible with various functional groups as well as with the integrity of stereogenic centers. Moreover, steric hindrance around the carbonyl group may severely jeopardize the addition of voluminous phosphor derivatives. For example, in our previous synthesis of **1**, the Horner–Wadsworth–Emmons olefination of aldehyde **5** afforded α-ionone very sluggishly, resulting in only 13% conversion after 17 h.[6] To circumvent the problem, we resourced to a Julia–Lythgoe olefination strategy which, however, lengthened the synthetic sequence significantly.[6] Therefore, a short and efficient synthesis of α-ionone **1** remained to be explored.

An alternative method to obtain α,β-unsaturated ketones, which is attracting increasing interest in the synthetic community, is the Meyer–Schuster (M.S.) rearrangement[9] of propargylic alcohols, and related propargylic esters. Strong protic or Lewis acids have mostly been used as promoters in the earliest versions of the M.S. reaction. The most recent procedures are based on a



α-ionone **1** β-ionone **2** γ-ionone **3**

Figure 1. Ionone regioisomers

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variety of catalytic organometallic species, to which Au^{I} or Au^{III} complexes have recently been added.[10]

In fact, gold derivatives often show high catalytic activity, improved selectivity compared to other methods, and are performed under mild reaction conditions.[11] Therefore, gold catalysis is receiving considerable attention in the field of natural product synthesis, where functional group compatibility and stereochemistry integrity are of paramount importance.[12]

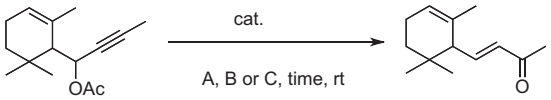
In 2009, Vidari and co-workers reported a M.S. rearrangement involving propargylic alcohols mediated by a rhenium(V)-oxo complex, initially applied to the synthesis of several α,β-unsaturated ketones, including α-ionone **1**.[10] In addition to its intrinsic importance, this substrate was selected for its particular electronic and steric hindrance features, and for the absence of any aromatic system conjugated to the α,β-unsaturated moiety, which could function as the driving force behind the M.S. rearrangement. *However, when we repeated the same reaction of* **4a** *to* **1** *with other batches of the rhenium catalyst, prepared from rhenium sources different from the original one, we were unable to reproduce the high yields of the Meyer–Schuster rearrangement previously observed with* **4a**.[10] *At present, we do not have any rationale for these contradictory results, which need further investigation.* Thus, we believe that **1** still represents an ideal substrate to evaluate the efficiency of catalytic methods leading to the construction of the enone system. Zhang and co-workers first observed the formation of enones from the rearrangement of propargylic acetates catalyzed by phosphine Au^{I} complexes.[13] Later, Nolan and co-workers reported a study on the same reaction with several model substrates, efficiently catalyzed by different NHC-Au^{I} (NHC = *N*-heterocyclic carbene) complexes in an aqueous medium.[14] The course of the reaction was affected by different factors that include in particular the nature of the substrate and of the ligand. The reaction mechanism involved the formation of an intermediate gold-allenolate, eventually collapsing to an α,β-unsaturated ketone.[15]

Therefore, we envisaged the NHC-Au^{I} catalyzed route to enones from propargylic esters as a simple alternative approach to α-ionone **1** (Scheme 1). Moreover, we were attracted by a few remarkable features of the present method that nicely agree with the principles of *Green chemistry*, such as the non-toxicity of the solvent and metal ligands and the small amount of the catalyst employed.

Propargylic ester **4b**[16] was easily obtained from aldehyde **5**, which was prepared in only three steps from acyclic geranic acid **6**, as reported in the literature.[3g,10]

Initial Au^{I} catalyst optimization experiments (Table 1) made use of propargylic acetate **4b** (R′ = Me), which is the ester-type substrate most frequently encountered in this transformation. The reactions were performed in three different solvents (A = acetone; B = MeOH/H_2O 10:1; C = 2-butanone/H_2O 100:1) in which Au^{I} catalysts have shown the highest efficacy in previous studies.[13,14,17] As for the NHC-Au^{I} catalysts, our attention focused on a selection of (IPr)Au^{I} complexes,[18] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) both of mononuclear and dinuclear types[18b] (Table 1). The digold complexes are generated by Brønsted acid activation of [Au(OH)(IPr)]. Thus, several well-defined (IPr)Au^{I} complexes or catalytic systems containing different cationic gold(I) species were readily prepared by adding 0, 0.5, 1, and 1.5 equiv of a Brønsted acid to [Au(OH)(IPr)] (Table 1). All experiments were carried out at room temperature and monitored by GC until complete consumption of the starting material **4b**. Results are summarized in Table 1.

Table 1
Optimization of the catalytic system for the synthesis of α-ionone **1**



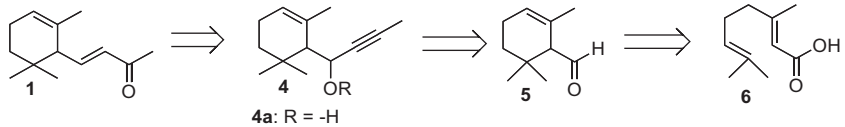
4b **1**

A = acetone
B = MeOH/H_2O 10:1
C = 2-butanone/H_2O 100:1

Entry	Cat. (mol %)	Solvent	Time (h)	Yield[a] (%)
1		A	96[b]	0
2	HBF_4 (6)	B	96[b]	0
3		C	96[b]	0
4		A	96[b]	0
5	[Au(IPr)(OH)] (4)	B	96[b]	40
6		C	96[b]	0
7		A	0.75	31
8	**[{Au(IPr)}$_2$(μ-OH)][BF$_4$] (2)**	**B**	**18**	**52**
9		C	30	33
10		A	0.75	30
11	[{Au(IPr)}$_2$(μ-OH)][NTf_2] (2)	B	24	49
12		C	30	36
13		A	0.75	31
14	[Au(IPr)(CH_3CN)][BF_4] (4)	B	24	38
15		C	30	44
16		A	0.75	29
17	[Au(IPr)][NTf_2] (4)	B	24	44
18		C	30	44
19	[Au(IPr)(OH)] (4)	A	0.75	40
20	+ aq. HBF_4 (6)	B	1	51
21		C	5	51
22	[Au(IPr)(OH)] (4)	A	5	37
23	+ $HNTf_2$ (6)	B	5	48
24		C	5	45

[a] Isolated yield.
[b] 24 h at rt and 72 h at 60 °C.

In control experiments, Brønsted acid alone did not lead to any conversion of **4b,** which was recovered unchanged (Table 1, entries 1–3). Noteworthy, in good agreement with previous work by Nolan,[18b] a catalytic amount of [Au(IPr)(OH)] promoted the conversion of **4b** to **1** only if the solvent was a mixture of MeOH/H_2O (10/1) (Table 1, entry 5), where [Au(OH)(IPr)] was observed to be in equilibrium with a dinuclear species of type [{Au(IPr)}$_2$(μ-OH)][X].[18b] All cationic Au^{I} complexes showed good catalytic activity for the conversion of porpargylic acetate **4b**, affording the expected α-ionone **1** in 29–52% isolated yield (Table 1, entries 7–24). In acetone (Table 1, entries 7, 10, 13, 16, and 19) the reaction of **4b** took place in only 45 min, while in the other two solvents B and C the conversion was much slower. On the other hand, in all the three solvents, especially in acetone, considerable amounts of unidentified by-products were formed. On the contrary, in MeOH/H_2O (10:1) or 2-butanone/H_2O (100:1), in spite of longer reaction times



4a: R = -H
4b: R = -(CO)R'

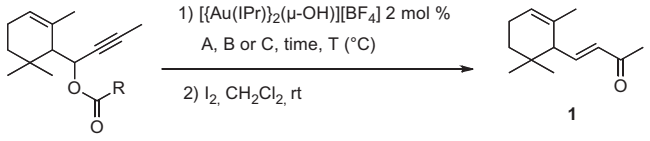
Scheme 1. Retrosynthesis of α-ionone.

(1–30 h), yields of α-ionone **1** were constantly higher (33–52%) than in acetone. The use of NTf_2 as a counter anion,[19], which is an inner sphere counter anion and well-known to improve selectivity, gave results comparable to BF_4. Finally, the best yield of α-ionone **1** was obtained with $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ (2 mol %) as the catalyst, in a mixture of MeOH/H_2O (10:1) as the solvent (Table 1, entry 8).

Subsequently, to improve the chemoselectivity of the reaction, we turned our attention to the R substituent of the propargylic ester **4** (Scheme 1). Propargylic benzoate **4c**, *p*-methoxybenzoate **4d**, and *p*-chlorobenzoate **4e** were investigated in order to evaluate the electronic effects of the acyl R group on the nucleophilicity of the carbonyl group that was anticipated to play a key role in the reaction mechanism (see below). The reactions were conducted in the three different solvents A–C at 60 °C and monitored by GC until consumption of the starting material. $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ was selected as the best catalyst on the basis of the optimization results discussed above. In all reactions, a mixture of (*Z*)- and (*E*)-α-ionone **1** was obtained which, after solvent exchange to CH_2Cl_2, was equilibrated with I_2 to the sole (*E*)-diastereomer.[20] Results are presented in Table 2.

Interestingly, independently from the starting benzoate, the highest yields of α-ionone **1** were obtained in the 2-butanone/H_2O (100/1) solvent mixture (Table 2, entries 3, 6, and 9). In stark contrast, the reaction led to the formation of a large quantity of by-products in acetone. This was expected on the basis of the results observed for the rearrangement of acetate **4b** (Table 2, entries 1, 4, and 7). Either an-electron donating (Table 2, entries 4–6) or an electron-withdrawing substituent (Table 2, entries 7–9) at the *para* position of the benzoate ring caused no improvement of the reaction chemoselectivity. Finally, the best reaction conditions were obtained with the unsubstituted propargylic benzoate **4c** in the presence of $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ (2 mol %), in a mixture of 2-butanone/H_2O (100:1) at 60 °C for 12 h, affording (*E*)-α-ionone **1** in reproducible 70% isolated yield (Table 2, entry 3).

Table 2
Optimization of the ester for the α-ionone **1** synthesis

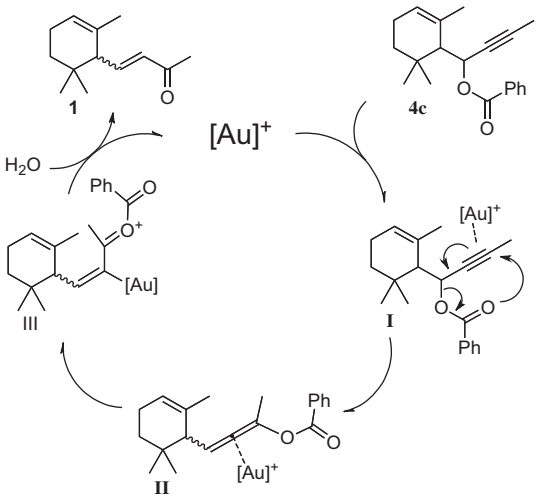


R = Ph **4c**, *p*-methoxyphenyl **4d**, *p*-chlorophenyl **4e**

A = acetone
B = MeOH/H_2O 10:1
C = 2-butanone/H_2O 100:1

Entry	Ester	Solvent	Time (h)	*T* (°C)	Yield[a] (%)
1	**4c**	A	14[b]	60	22
2	**4c**	B	14[b]	60	43
3	**4c**	**C**	**14**[b]	**60**	**70**
4	**4d**	A	14[b]	60	38
5	**4d**	B	14[b]	60	43
6	**4d**	C	14[b]	60	52
7	**4e**	A	48[c]	60	30[d]
8	**4e**	B	24	rt	25
9	**4e**	C	48	60	42[e]

[a] Isolated yield.
[b] Reaction afforded a mixture of (*E*)- and (*Z*)-α-ionone at 60 °C in 12 h. Subsequently, the solvent was removed; CH_2Cl_2 and two crystals of I_2 were added, to isomerize the entire mixture to (*E*)-α-ionone.
[c] 24 h at rt + 24 h at 60 °C.
[d] Only 70% starting material was converted.
[e] Only 85% starting material was converted.



Scheme 2. Proposed mechanism for the formation of α-ionone **1** from propargylic ester **4c**.

Based on our recent work on Au-catalyzed allene synthesis,[21] and the previous work of Zhang on α-iodo-α,β-unsaturated ketone synthesis,[17] we propose the mechanism shown in Scheme 2 for the conversion of **4c** into **1**. Initially, activation of the acetylenic π-system by coordinated Au^I induces migration of the benzoate group to give the allenic ester **II**. The latter, after activation of the π-system of the allenyl framework by the gold center, evolves to the metallated intermediate **III**, which then collapses to the enone moiety of α-ionone **1** by proton-Au exchange and hydrolysis of the ester.

In conclusion, we have developed a convenient and efficient synthesis of the valuable (*E*)-α-ionone **1** through a NHC-Au^I catalyzed Meyer–Schuster-like rearrangement of readily prepared propargylic esters. Under optimized conditions, only 2 mol % of the dimeric species $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ were required to promote the smooth conversion of the unsubstituted benzoate **4**c to **1** in 2-butanone/H_2O (100/1). This synthesis of enone **1** represents the most straightforward approach to the important perfume ingredient α-ionone, readily proceeding in only seven-steps from cyclogeranic acid **6**, which is available on multigram scale.

We anticipate that this NHC-Au^I catalyzed variant of the Meyer–Schuster-like rearrangement will find audience among organic chemists devoted to the synthesis of complex natural products or synthetic molecules, where the α,β-unsaturated ketone moiety frequently occurs. In fact, we believe that our optimized procedure is a valuable and attractive alternative to classical methods leading to enone systems, such as the Wittig or aldol reactions.

2. Experimental section

2.1. Benzoate 4c

Pyridine (0.18 ml, 2.23 mmol) was added to a solution of alcohol **4a** (75 mg, 0.39 mmol) in dry CH_2Cl_2 (4 ml). Subsequently, benzoyl chloride (0.085 ml, 0.73 mmol), followed by catalytic amount of DMAP, were slowly added at 0 °C. After 1 h of stirring at rt, the reaction mixture was quenched by the addition of saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were washed with H_2O, saturated aqueous solution of $CuSO_4$, dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O 97:3) to give the pure benzoate **4c** (77.2 mg, 73%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 3H), 1.12 (s, 3H), 1.74–1.82 (m, 2H), 1.85 (s, 3H), 1.86 (s, 3H), 2.01 (m, 1H), 2.01–2.07 (m, 2H), 5.64 (m, 1H), 5.70 (t, 1H),

7.47 (m, 2H), 7.57–7.60 (m, 1H), 8.05–8.07 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.8 (q), 22.9 (t), 24.2 (q), 27.3 (q), 28.5 (q), 32.1 (t), 32.5 (s), 53.7 (d), 63.6 (d), 77.6 (s), 82.8 (s), 124.5 (d), 128.4 (d), 129.8 (d), 130.4 (s), 131.1 (s), 133.0 (d), 165.5 (s) ppm. HRMS (ES^+): calcd for $C_{20}H_{24}O_2Na$: 319.1674. Found: 319.1677.

2.2. Au^I-catalyzed rearrangement of 4c: α-ionone (1)

In a screw cap vial, [{Au(IPr)}$_2$(μ-OH)][BF_4] (6.3 mg, 4.9×10^{-3} mmol) was added to a solution of propargylic benzoate **4c** (73 mg, 0.25 mmol) in a mixture of butanone/water (2.5 ml + 25 μl), then the reaction mixture was stirred at 60 °C for 12 h. The solvent was removed at reduced pressure and CH_2Cl_2 (2.5 ml), followed by two crystals of I_2 were added. After 2 h of stirring at rt, the reaction mixture was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$, then the aqueous layer was extracted with CH_2Cl_2 (3×20 ml), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O 98:2) to give pure (*E*)-α-ionone **1**, identical with a commercial authentic sample (33 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.94 (s, 3H), 1.19–1.29 (m, 1H), 1.47 (ddd, J = 13.3, 8.3, 8.1 Hz, 1H), 1.58 (q, J = 1.7 Hz, 3H), 2.0–2.10 (m, 2H), 2.26 (s, 3H), 2.30 (d, J = 9.2 Hz, 1H), 5.48–5.55 (m, 1H), 6.06 (d, J = 16.0 Hz, 1H), 6.63 (dd, J = 16.0, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (q), 23.0 (t), 26.7 (q), 26.9 (q), 27.8 (q), 31.1 (t), 32.5 (s), 54.2 (d), 122.6 (d), 131.9 (s), 132.3 (d), 149.1 (d), 198.6 (s); HRMS calcd for $C_{13}H_{20}O$: 192.15142. Found: 192.15145.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.010.

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16. We are well aware that, in principle, the direct Meyer–Schuster rearrangement of propargylic alcohol **4a** could yield the expected enone **1**; however, under our conditions, a complex mixture was obtained, containing also an unidentified product, which is under investigation in our laboratories. For a recent application of the Meyer–Schuster rearrangement to the synthesis of natural products, see: Ramón, R. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665–3668.
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