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Terpenoids |*Hot Paper*|

Competitive Gold-Promoted Meyer–Schuster and oxy-Cope Rearrangements of 3-Acyloxy-1,5-enynes: Selective Catalysis for the Synthesis of (+)-(*S*)-γ-Ionone and (−)-(2*S*,6*R*)-*cis*-γ-Irone

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Abstract: We report a simple, highly stereoselective synthesis of (+)-(*S*)-γ-ionone and (-)-(2*S*,6*R*)-*cis*-γ-irone, two characteristic and precious odorants; the latter compound is a constituent of the essential oil obtained from *iris* rhizomes. Of general interest in this approach are the photoisomerization of an *endo* trisubstituted cyclohexene double bond to an *exo* vinyl group and the installation of the enone side chain through a [(NHC)Au^{I}]-catalyzed Meyer–Schuster-like rearrangement. This required a careful investigation of the mechanism of the gold-catalyzed reaction and a judicious selection of reaction conditions. In fact, it was found that the Meyer–Schuster reaction may compete with the oxy-Cope rearrangement. Gold-based catalytic systems can promote either reaction selectively. In the present system, the mononuclear gold complex [Au(IPr)Cl], in combination with the silver salt $AgSbF_6$ in 100:1 butan-2-one/H_2O, proved to efficiently promote the Meyer–Schuster rearrangement of propargylic benzoates, whereas the digold catalyst [{Au(IPr)}$_2$(μ-OH)][BF_4] in anhydrous dichloromethane selectively promoted the oxy-Cope rearrangement of propargylic alcohols.

Introduction

Ionones and irones are C_{13} and C_{14} norterpenoids, respectively, which impart a powerful and pleasant violet-like scent to blooming violet flowers and the essential oil of *Iris* rhizomes, respectively.[1] Owing to their delicate odor palette, for centuries they have been used extensively as important raw materials for the production of many expensive fragrances, perfumes, and cosmetics.[2] Moreover, ionones have been employed as valuable building blocks for the preparation of more complex natural products.[3] Ionones and irones exist in nature as three different regioisomers (Figure 1), named α (**1**, **4**), β (**2**, **5**), and γ (**3**, **6**), depending on the position of the double bond. (−)-γ-Irone **8** occurs in different *Iris* species, for example in iris butter prepared from *I. germanica*;[4] in contrast, (+)-γ-ionone **7** seems to have a restricted distribution in nature.[5] Notably, the human nose is able to distinguish the odor of the five ionone and ten irone isomers, so that sensory evaluations were carried out and odor characters were established for single isomers, when they were obtained by enantioselective syntheses or chromatographic separations.[4–6]

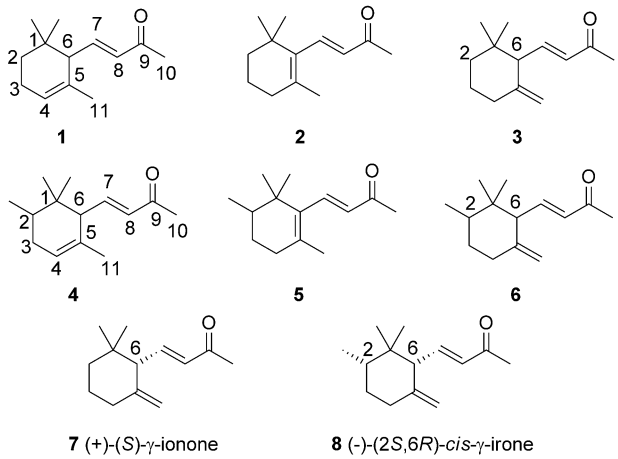

Figure 1. Ionone and irone regioisomers.

The (+)-(*S*)-γ-ionone **7** is the most powerful and pleasant of the ionone isomers for the floral, green, woody odor with a very natural violet tonality;[5] (−)-(2*S*,6*R*)-*cis*-γ-irone **8** (Figure 1) has a warm floral-woody odor tonality, with some fruity nuances, and its odor threshold by GC olfactometry was reported to be only 0.75 ng L^{-1}, significantly much lower than that of the (2*R*,6*S*)-enantiomer.[4]

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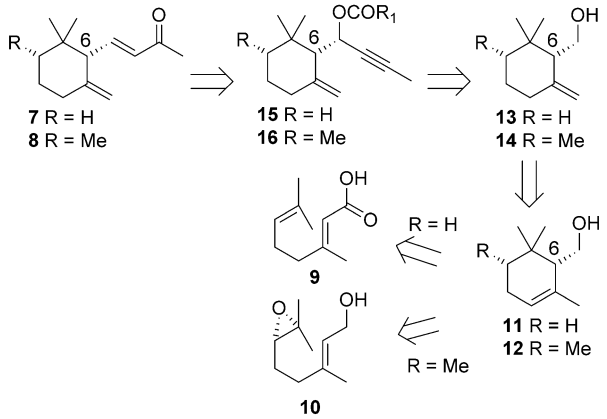
The syntheses of enantiopure γ-ionone enantiomers reported to date have mostly been based on long and tedious classical[7] or enzymatic resolution procedures.[5] Alternatively, the chiral information was encoded by a Sharpless asymmetric dihydroxylation of a geraniol derivative, containing a trimethylsilyl group to control the regioselective formation of an *exo* olefin intermediate in an elegant biomimetic cyclization.[8]

Equally challenging has been the synthesis of the γ-irone enantiomers. In a clever approach from the commercial product Irone Alpha, Fuganti and co-workers obtained the single stereoisomers of the three regioisomeric irones, including **8**. The process required, however, multiple lipase-mediated resolutions of racemic mixtures and separation of diastereomeric products.[4,6] Moreover, ex novo enantioselective synthesis of **8** required the invention of ingenious strategies for installing the thermodynamically disfavored *cis* relationship between H2 and H6, and enantioenriched starting materials were often difficult to obtain. These difficulties account for the limited number of enantioselective syntheses of irone **8** reported to date.[9]

We describe herein a straightforward approach to **7** and **8** from geranic acid **9** and (*S*)-epoxygeraniol **10**, respectively, which can easily be converted, in gram quantities, into enantioenriched building blocks **11**[3g] and **12**,[9d,10] respectively. Our common strategy to obtain both target compounds was based on two key reactions: the photoisomerization of the endocyclic (α) double bond to the exocyclic (γ) position (**11**→**13** and **12**→**14**, respectively),[11] and a [(NHC)Au^{I}]-promoted Meyer–Schuster rearrangement[12] of a suitable propargylic derivative (**15**→**7** and **16**→**8**, respectively; NHC = N-heterocyclic carbene; Scheme 1) to deliver the enone system. The olefin photoisomerization protocol[11] proved, indeed, to be much simpler than an alternative multistep route previously employed to move the α-double bond to the γ-position.[9d,11] Moreover, a recent synthesis of (*S*)-α-ionone (*S*)-**1**,[12e] suggested that the [(NHC)Au^{I}]-catalyzed[13] Meyer–Schuster-like rearrangement of a propargylic ester[12,14] in an aqueous medium is an attractive alternative to the classical Horner–Wadsworth–Emmons reaction to build the α,β-enone side-chain of **7**[8] and **8**.[9c,e] This new method, further preserving the stereochemical integrity at C6, exhibits other remarkable synthetic advantages, such as good atom economy, nontoxicity of the solvent, and the small amount of the catalyst employed.

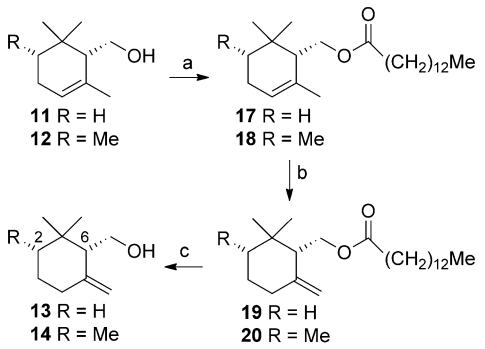


Scheme 1. Retrosynthesis of γ-ionone **7** and γ-irone **8**.

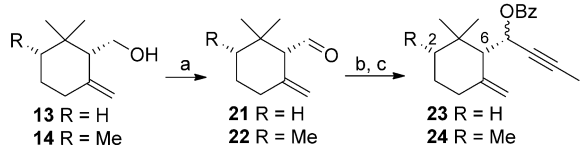
Results and Discussion

The common synthetic strategy to give compounds **7** and **8** was at first optimized in the synthesis of α-ionone and then extended to γ-irone. Due to the volatility of (*S*)-α-cyclogeraniol **11** (≥95% *ee*)[3g,10] and its acetate, optimized photoisomerization of the double bond to the γ-isomer **13** required implementation of a slightly modified Serra protocol.[11] Thus, alcohol **11**[3g,10] was at first converted to the corresponding myristate **17**, which was subsequently irradiated at 254 nm for 24 h in a degassed 4:1 *i*PrOH/xylene mixture (Scheme 2). To our delight, photoisomerization of **17** to the γ-isomer **19** occurred almost quantitatively (γ/α ≥ 98:2 by GC). Subsequently, myristate **19** was smoothly cleaved to give (*S*)-γ-cyclogeraniol **13** (≥95% *ee* by chiral GC)[8,11,15] in 97% yield. Following an identical procedure, alcohol **12** (≥99% *ee*),[9a,d] was converted in three steps to (2*S*,6*R*)-2-methyl-γ-cyclogeraniol **14** (≥99% *ee* by chiral HPLC)[9a,c,d] in 74% overall yield.

Subsequently, the two alcohols **13** and **14** were separately oxidized by stabilized 2-iodoxybenzoic acid (SIBX) in DMSO[16] to give the corresponding unstable aldehydes **21**[8] and **22**,[9c] respectively. One-pot addition of propynylmagnesium bromide to each aldehyde followed by benzoyl chloride, afforded benzoates **23** and **24**, respectively, in excellent overall yields (Scheme 3), as undetermined mixtures of diastereomers at the carbinol center.



Scheme 2. Synthesis of (*S*)-γ-cyclogeraniol **13** and (2*S*, 6*R*)-2-methyl-γ-cyclogeraniol **14**. Reagents and conditions: a) $Me(CH_2)_{12}CO_2H$, *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), RT, 6 h; 94% for **17**, 97% for **18**; b) *hν* (254 nm), 4:1 *i*PrOH/xylene, 24 h; 88% for **19**, 83% for **20**.; c) K_2CO_3, MeOH, RT, 6 h; 97% for **13**, 95% for **14**.

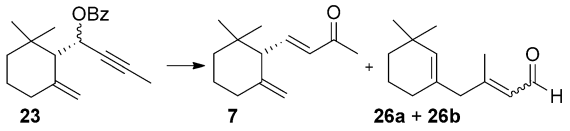


Scheme 3. Synthesis of benzoates **23** and **24**. a) SIBX, dry DMSO, RT, 2 h; b) Me–C≡CMgBr, dry THF, −78 °C to RT, 2 h; followed by c) BzCl, DMAP, dry THF, 0 °C to RT, 2 h; 68% overall yield of **23** from **13**; 64% of **24** from **14**.

Competitive gold-promoted Meyer–Schuster and oxy-Cope rearrangements of 3-acyloxy-1,5-enynes

Ester **23** was then subjected to the gold-mediated Meyer–Schuster-like rearrangement under the conditions that we optimized for the synthesis of α-ionone,[12e] namely, 2 mol% of the dinuclear gold complex [{Au(IPr)}$_2$(μ-OH)][BF$_4$] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) **25**,[17] in a mixture of butan-2-one-H_2O, 100:1, at 60 °C for 12 h.

(*E*)-γ-ionone **7** was, indeed, formed in 48% yield. However, quite unexpectedly, it was accompanied by 16% of a mixture of *E* and *Z* dienals **26a** and **26b**, in a ratio of about 1:1 (Scheme 4). The chromatographically inseparable isomers **26a** and **b** were fully characterized by NMR spectroscopy after separation from **7** on a RP-18 column eluted with MeCN/H_2O (7:3). The overall yield and the ratio between **7** and **26a** and **b** did not change significantly by increasing the amount of H_2O in the solvent mixture, up to a ratio between butan-2-one and H_2O of 100:6. However, the reaction was much faster, going to completion in 6 h. Instead, the ratio between **7** and **26a** and **b** slightly increased to 4:1 when the reaction was performed in butan-2-one/5% aqueous $NaHCO_3$ (100:5). However, under stronger basic conditions, namely in butan-2-one/1 M aqueous NaOH (100/5), only extensive hydrolysis of the benzoate group was observed after heating at 60 °C for 48 h.[18]

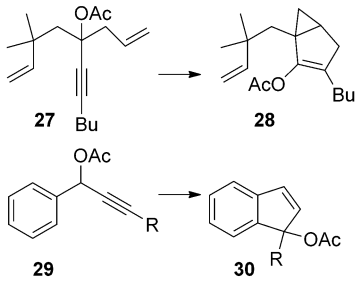


Scheme 4. Gold-promoted rearrangements of benzoate **23**. Reagents and conditions: [{Au(IPr)}$_2$(μ-OH)][BF$_4$] **25**, 100:1 butan-2-one/H_2O, 60 °C, 12 h.

Compounds **7** and **26a** and **b** appeared to derive from two different [3.3]-sigmatropic rearrangements of benzoate **23**. Actually, enone **7** corresponded to the expected product of the gold-promoted Meyer–Schuster rearrangement of propargylic esters,[12,14] while **26a** and **b** could be considered as the products of a formal gold-promoted oxy-Cope rearrangement[19] of a 3-acyloxy-1,5-enyne.[20]

The formation of structures such as **26a** and **b** was in striking contrast with previous findings on the [(NHC)Au^I]-assisted cycloisomerization of 1,5-enynes bearing a propargylic acyloxy group. Thus, [(NHC)AuCl]/AgBF$_4$ in dry DCM promoted the conversion of acetate **27** to the bicyclo[3.1.0]hexane derivative **28**,[21] whereas replacing the alkene moiety with an aryl ring, as in ester **29**, led to a substituted indene **30** (Scheme 5).[12b]

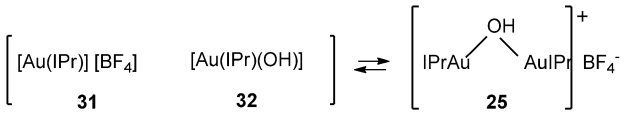
Although rather unexpected, our results confirmed previous findings for gold-catalyzed reactions, indicating that, in addition to the steric and electronic features of the substrate, the nature of the ligands on the gold center, as well as the counterion and the solvent, have a dramatic effect on the structures of products. In particular, the presence of H_2O in the solvent mixture appeared to play a crucial role in the rearrangement



Scheme 5. Examples of [(NHC)Au^I]-assisted cycloisomerization of 1,5-enynes bearing a propargylic acyloxy group. Reagents and conditions: [(IPr)AuCl]/AgBF$_4$, dry DCM, RT, 5 min.

of esters such as the benzoate **23**, in analogy with the gold-catalyzed reactions of other substrates.[12b]

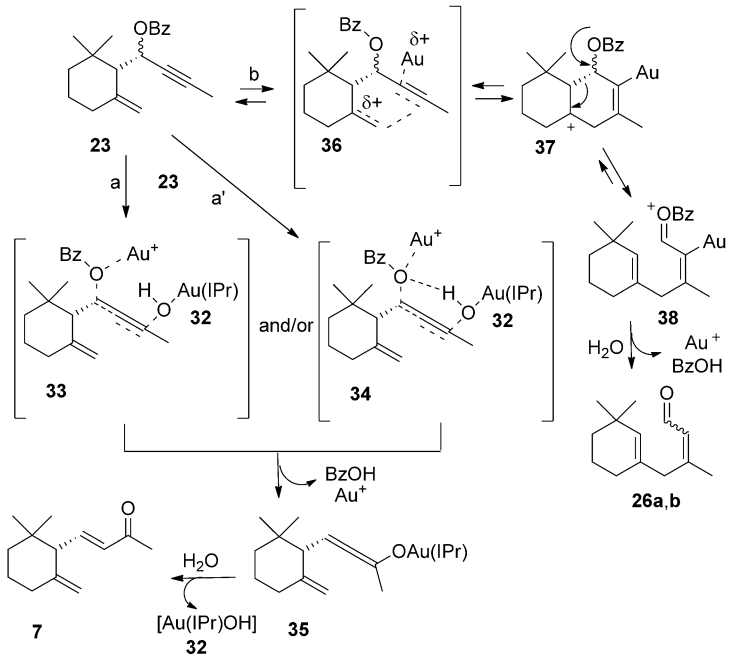
As far as the active catalytic gold species involved in the reaction of benzoate **23** was concerned, NMR data supported the hypothesis that in an aqueous medium the dinuclear gold complex **25**, further having a direct catalytic role, had the synthetically useful potential to deliver, simultaneously, the gold species [Au(IPr)][BF$_4$] **31** and [Au(IPr)(OH)] **32** (Scheme 6).[17a]



Scheme 6. Equilibrium between dinuclear and mononuclear gold complexes in an aqueous medium.

Remarkably, the former complex is an efficient cationic σ- and π-system-activating agent, whereas the mononuclear gold species **32** has the characteristics of a strong Brønsted base,[17d] Thus, a synergistic effect can result, leading to enhanced catalytic activity.

On this basis, we envisioned, as a working mechanistic hypothesis, different accessible pathways leading to enone **7** and aldehydes **26a** and **b** through competitive rearrangements of benzoate **23** (Scheme 7). A push–pull S_N2'-like mechanism (routes a and a′ in Scheme 7) could be involved in the formation of the Meyer–Schuster rearrangement product **7**. In accordance with this hypothesis, the nucleophilic hydroxyl–gold complex **32** would attack the distant carbon of the propargylic group of alkyne **23** with concomitant removal of the benzoate group to deliver the gold allenolate **35**. Moreover, coordination of the benzoate group to a cationic gold species, most likely complex **31**, appeared to be necessary to facilitate its expulsion and the entrance of the nucleophilic group, as shown in the TS **33**. In fact, the sole gold species **32** was shown to exhibit poor efficacy in enabling the Meyer–Schuster rearrangement of esters.[18] A double activation of the leaving group was also possible, in which not only the gold cation **31** but also the proton of the hydroxy group of the species **32**, intramolecularly transferred to the inner oxygen atom of the acyl group, would accelerate the release of the benzoate from the incipient allene system



Scheme 7. Proposed mechanism for the gold-catalyzed formation of the Meyer–Schuster and the oxy-Cope rearrangement products **7** and **26a**,**b**, respectively.

(TS **34**). To complete the catalytic cycle, water would finally add to intermediate **35** to deliver the enone **7** and regenerate [Au(IPr)(OH)] **32** (Scheme 7).[12b]

Alternative mechanisms for the Meyer–Schuster rearrangement involving the coordination of a cationic gold species to the triple bond of alkyne **23** appeared to be energetically less favored than the routes a and a′ (Scheme 7). In fact, Nolan, Maseras and co-workers calculated that, of the three possible complexes that a cationic NHC–gold species such as **31** can form with a propargylic ester such as the benzoate **23**, the most stable one involves the coordination of gold to the alcoholic oxygen atom of the ester and not to the triple bond, as might be expected.[12b]

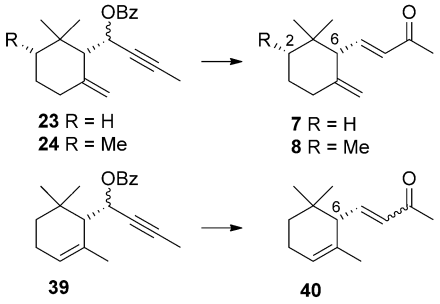
Enals **26a** and **b**, the minority products of the **25**-induced rearrangement of enyne **23**, possibly ensued from electrophilic activation of a cationic Au-coordinated triple bond (route b in Scheme 7), although such a gold complex was estimated to be less stable than the Au–benzoate one.[12b] In this context, considering the softer Lewis acid characteristics of the gold species occurring in the reaction medium (Scheme 6), the dinuclear gold complex **25** should play a more important activating effect on the triple bond than the mononuclear cation **31**. The resulting loss in electron density from the π-system of the triple bond would thus promote the nucleophilic 6-*endo*-dig-like addition of the *exo* double bond of enyne **23** to the more electrophilic end of the alkyne, affording the cyclocarbenium ion **37**. Subsequently, a Grob-type fragmentation in **37** would give rise to the more stable oxonium ion **38**, which would be rapidly cleaved by water to produce **26a** and **b** and regenerate the gold catalyst (route b in Scheme 7).

The overall process from benzoate **23** to **38** thus corresponds to a formal 1,5-enyne oxy-Cope rearrangement.[19] We have proposed a stepwise mechanism. However, at this stage of our studies, we cannot rule out a concerted process with exclusion of carbocation intermediates.

Selective Au catalysis for the Meyer–Schuster rearrangement of 3-benzoyloxy-1,5-enynes: Synthesis of (*S*)-γ-ionone, (2*S*,6*R*)-γ-irone, and (*S*)-α-ionone

A few key experiments nicely supported our proposed mechanism (Scheme 7). In a first instance, we changed the gold catalyst, using, instead of the complex **25**, the mononuclear gold complex [Au(IPr)Cl] in combination with the silver salt $AgSbF_6$. This catalyst has been shown to efficiently promote the Meyer–Schuster rearrangement of propargylic acetates in aqueous THF to afford the corresponding enones.[12b] After preliminary experiments in different solvents, benzoate **23** (0.1 M) was finally exposed to 2 mol% [Au(IPr)Cl] and 2 mol% $AgSbF_6$ in 100:1 butan-2-one/H_2O to deliver (*S*)-γ-ionone **7**[8] as the (*E*)-isomer, in 55% yield (Scheme 8).

To our delight, enals **26a** and **b** were not formed. Subsequently, by subjecting esters **24** and **39**[12e] to



Scheme 8. Meyer–Schuster rearrangement of benzoates **23**, **24**, and **39** to (*S*)-γ-ionone **7**, (2*S*,6*R*)-*cis*-γ-irone **8**, and (*S*)-α-ionone **40**, respectively. Reagents and conditions: **23**, **24**, or **39** (0.1 M), [(IPr)AuCl] (2 mol%), $AgSbF_6$ (2 mol%), 100:1 butan-2-one/H_2O, RT, 3 h, 60 °C, 3 h. Yields = 55% **7**; 65% **8**, 66% **40**.

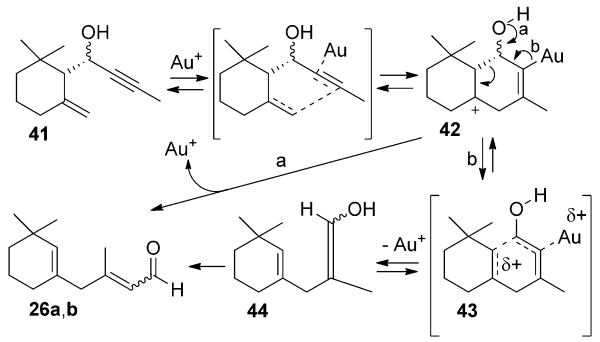
the same reaction conditions, (2*S*,6*R*)-γ-irone **8**[7] and (*S*)-α-ionone **40**[12e] were produced in good yields (Scheme 8). Notably, no products derived from an oxy-Cope-like rearrangement were detected in these experiments. However, whereas **7** and **8** were stereochemically homogeneous, **40** was a mixture of *E* and *Z* stereoisomers. At present, we do not have a clear explanation for this different diastereoselecivity. GC and HPLC analyses indicated 95% *ee* for **7** and ≥99% *ee* for **8**.

The selective Meyer–Schuster rearrangement promoted by the gold-catalyst [Au(IPr)Cl]/$AbSbF_6$, with suppression of the oxy-Cope rearrangement further supported our hypothesis that the dinuclear gold species **25** played a key role in catalyzing the conversion of propargylic benzoate **23** to enals **26a** and **b**.

Selective Au catalysis for the oxy-Cope rearrangement of 3-hydroxy-1,5-enynes

In another series of experiments, propargylic alcohol **41**, readily obtained by addition of propynylmagnesium bromide to aldehyde **21**, was exposed to 2 mol% of $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ **25** in dry DCM. Indeed, water appeared to play a crucial role in different steps of the Meyer–Schuster rearrangement promoted by the gold complex **25**, mainly by producing the catalytically active nucleophilic species **32** (routes a and a′ in Scheme 7). By excluding water from the reaction mixture, we thus expected to increase the Lewis acid character of the gold complex and to force the gold-catalyzed transformations of alcohol **41** selectively towards the oxy-Cope rearrangement products **26a** and **b**.

Upon exposure of alcohol **41** to catalyst **25** in anhydrous DCM, the two isomeric *E* and *Z* aldehydes **26a** and **26b** were smoothly formed in combined 99% yield in less than 30 min at room temperature. Notably, the Meyer–Schuster rearrangement product, namely enone **7**, was not detected (Scheme 9).



Scheme 9. Oxy-Cope rearrangement of propargylic alcohol **41**. Reagents and conditions: **41** (0.1 M), **25** (2 mol%), dry DCM, RT, 30 min. Yield = 99%.

The proposed mechanism for the formation of aldehydes **26a** and **b** under these conditions (Scheme 9) closely resembles route b in Scheme 7. Thus, gold coordination to the triple bond would induce electrophilic addition of the exocyclic double bond to give the bicyclic carbocation **42**. Grob-type fragmentation of this intermediate (Scheme 9, route a) would then afford aldehydes **26a** and **b** and regenerate the gold catalyst. This rearrangement is more likely initiated by deprotonation of the hydroxy group (Scheme 9, route a) than by gold detachment from the cyclohexene double bond (Scheme 9, route b) to give allenol **44**. In the latter case, ring fragmentation would proceed through a high-energy cyclic TS containing an incipient allene system (TS **43** in Scheme 9).

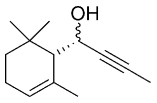
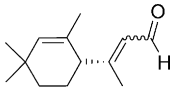
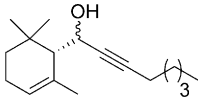
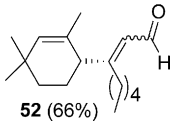
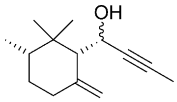
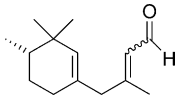
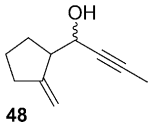
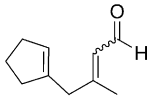
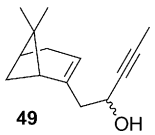
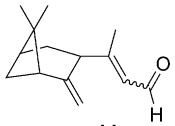
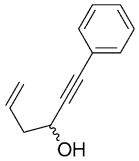
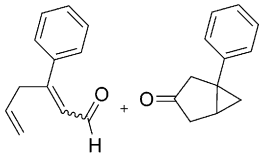
The oxy-Cope reaction has found widespread use in organic synthesis[19] and dienals such as **26a** and **b** are versatile electrophilic reagents. This prompted us to extend the reaction conditions optimized for the rearrangement of alcohol **41** to other secondary propargylic alcohols, to find the limits and applicability of our gold-mediated procedure in synthetic organic chemistry.

To this end, each of the model 3-hydroxy-1,5-enynes **45**–**50** (0.1 M in anhydrous DCM) was treated with 2 mol% of **25** (Table 1). All reactions proceeded smoothly at room temperature, reaching completion in ca. 30 min, with the exception of the reaction of alcohol **49**, that required 4 h.

The compounds formed by the oxy-Cope rearrangement were the main isolated products, whereas the Meyer–Schuster rearrangement product (< 10%) was formed only in the reaction of bicyclic alcohol **49**.

As expected on the basis of the proposed mechanism (Scheme 9), yields of the isolated rearrangement products ranged from good to excellent for substrates **45**–**49**. In contrast, the monosubstituted olefin **50** gave **56** in low yield, accompanied by the bicyclo[3.1.0]hexane derivative **57**. According to the proposed reaction mechanism (Scheme 9), these results nicely reflect the higher stability of tertiary carbocation intermediates arising from substrates **45**–**49**, rather than the secondary analogue resulting from enyne **50**. Moreover, the slightly lower yields of the oxy-Cope rerrangement products

Table 1. Gold catalyzed oxy-Cope rearrangement of propargylic alcohols.[a,b]

Starting compound	Product (yield)[c]
 **45**[22]	 **51** (65%)
 **46**	 **52** (66%)
 **47**	 **53**[d] (79%)
 **48**	 **54** (70%)
 **49**	 **55** (66%)[e]
 **50**[23]	 **56**[24] (30%) **57** (15%)

[a] Reaction conditions: Propargylic alcohol (0.1 M), $[[(IPr)Au]_2(\mu\text{-}OH)][BF_4]$ **25** (2 mol%), dry DCM, RT, 30 min; [b] alcohols **45** and **50** were known compounds, whereas **46**–**49** were prepared by the addition of 1-propynylmagnesium bromide to aldehydes; [c] yields refer to isolated product; [d] ≥ 95% *E*-stereoisomer; [e] the reaction went to completion in 4 h.

51 and **52** compared to **26** and **53**–**54**, likely depended on the higher molecular steric strain required by overlapping the alkyne π-electrons with an *endo* double bond than with an *exo* olefin.

In striking contrast, but according to our expectations, in analogy with esters **23**, **24**, and **39**, benzoates of alcohols **46**, **49**, and **50** gave the corresponding products of the Meyer–Schuster rearrangement upon exposure to [Au(IPr)Cl] and 2 mol% $AgSbF_6$ in 100:1 butan-2-one/H_2O (data not included). Notably, in the absence of the gold catalyst **25**, no rearrangement occurred, even upon heating a propargylic alcohol in dry DCM at 35 °C for a few hours. This result confirmed the catalytic effects of this unique gold complex.

Conclusion

In summary, we have described a novel and highly enantioselective synthesis of naturally occurring (*S*)-γ-ionone **7** and (2*S*,6*R*)-γ-irone **8**, which are characteristic and valuable components of expensive perfumes and fragrances. These efficient syntheses started from easily accessible, almost enantiopure, starting materials and were based on the photoisomerization of an endocyclic cyclohexene olefin to an *exo* double bond, followed by a gold-catalyzed Meyer–Schuster rearrangement of a propargylic benzoate to deliver the characteristic enone side-chain. The latter procedure proved to be an efficient eco-friendly alternative to the classical Wittig-type olefination methodology used in previous syntheses of these compounds. In the course of these studies, we examined the competition of the gold-assisted Meyer–Schuster rearrangement of 3-acyloxy-1,5-enynes with the oxy-Cope rearrangement. Under controlled conditions, highly divergent reaction pathways can be implemented. Specifically, upon exposure of 3-benzoyloxy-1,5-enynes to the mononuclear gold complex [Au(IPr)Cl]/$AbSbF_6$ in 100:1 butan-2-one/H_2O, only the products of the Meyer–Schuster rearrangement were obtained, whereas the digold catalyst [{Au(IPr)}$_2$(μ-OH)][BF_4] **25** in anhydrous DCM catalyzed the selective oxy-Cope rearrangement of the corresponding 3-hydroxy-1,5-enynes. With 1,5-enynes incorporating a double bond *endo* or *exo* to a ring, the oxy-Cope rearrangement proceeded rapidly under very mild conditions, affording α,β,δ,ε-dienals in yields ranging from good to excellent.

We think that this methodology will add to the great array of remarkable gold-catalyzed reactions discovered in the last decade, furnishing organic chemists with another useful tool for accomplishing directed syntheses. Moreover, our results have clearly proven the different reaction mechanisms triggered by the various gold-based catalytic systems and the importance of a judicious selection of the gold species for selective synthesis.

Experimental Section

Photoisomerization of the double bond: General procedure

(*S*)-(2,2-dimethyl-6-methylenecyclohexyl)methyl tetradecanoate (**19**): A solution of α-ester **17** (309 mg, 0.84 mmol, 1.0 equiv) in a degassed 4:1 *i*PrOH/xylene solvent mixture (6.8 mL/1.7 mL) in a sealed quartz vessel was irradiated in a Rayonet photochemical reactor equipped with four 254 nm high-pressure Hg lamps. The reaction was monitored by GC-MS and the irradiation was interrupted after 24 h, when the starting compound was completely consumed. The reaction mixture was then concentrated under reduced pressure and the residue was purified by chromatography on a column (150 mm × 30 mm) of silica gel (15 g). Elution with 98:2 hexane/Et_2O afforded γ-ester **19** (273 mg, yield = 88%) as a yellow oil. $[\alpha]_D^{20} = -1.6$ ($c = 0.84$, CH_2Cl_2); TLC (SiO_2): $R_f = 0.33$ (hexane/Et_2O, 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.85 (br s, 1H), 4.60 (br s, 1H), 4.30–4.15 (m, 2H), 2.25 (t, $J = 7.5$ Hz, 2H), 2.23–2.20 (m, 2H), 2.18–2.02 (m, 1H), 1.64–1.55 (m, 4H), 1.42–1.23 (m, 22H), 0.99 (s, 3H), 0.90–0.87 (overlapped s + t, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 173.9 (s), 147.1 (s), 109.7 (t), 62.6 (t), 52.2 (d), 37.8 (t), 34.4 (t), 34.3 (s), 33.3 (t), 31.9 (t), 29.6 (t), 29.6 (t), 29.4 (t), 29,3 (t), 29.2 (t), 29.1 (t), 28.7 (q), 25.1 (q), 25.0 (t), 23.4 (t), 22.7 (t), 14.1 (q); IR (neat product): $\tilde{\nu} = 2925$, 2854, 1737, 1466, 1170, 891 cm^{-1}; HRMS: calcd for $C_{24}H_{44}O_2$ 364.3341; found 364.3345.

The γ/α ratio (≥ 98:2) was determined by GC analysis on a capillary HP5 column (30 m, 0.25 mm i.d., 0.25 μm f.t.); carrier gas = He, flow = 1 mL min^{-1}; injector temperature = 250 °C; detector: MS; temperature program: 80 °C (1 min), then 10 °C min^{-1} to 280 °C (5 min); t_R of α-ester **17** = 19.67 min; t_R of γ-ester **19** = 19.80 min.

Selective Meyer–Schuster rearrangement: General procedure

(*S*,*E*)-4-(2,2-dimethyl-6-methylenecyclohexyl)but-3-en-2-one [(*S*)-γ-ionone (**7**)]: [Au(IPr)Cl] (3.4 mg, 5.4×10^{-3} mmol, 0.02 equiv) and $AgSbF_6$ (1.9 mg, 5.4×10^{-3} mmol, 0.02 equiv) were added to a solution of **23** (81 mg, 0.27 mmol, 1.0 equiv) in 100:1 butan-2-one/H_2O (2.7 mL/0.027 mL). The mixture was stirred at RT for 3 h and then warmed at 60 °C for 3 h. The solvent was then removed under reduced pressure ($p > 80$ mmHg). The residue, comprising only the *E*-isomer, was purified by chromatography on a column (150 mm × 15 mm) of silica gel (8 g). Elution with 98:2 pentane/Et_2O afforded (*E*,*S*)-γ-ionone **7** (29 mg, yield = 55%) as a pale yellow oil. ^{1}H NMR and ^{13}C NMR data of compound **7** are identical to those reported in the literature.[8]

Selective Oxy-Cope rearrangement. General procedure

(*E*)- and (*Z*)-4-(3,3-dimethylcyclohex-1-en-1-yl)-3-methylbut-2-enal (**26a** and **b**): [{Au(IPr)}$_2$(μ-OH)][BF_4] **25** (6.8 mg, 5.0×10^{-3} mmol, 0.02 equiv) was added to a solution of propargylic alcohol **41** (51 mg, 0.26 mmol, 1.0 equiv) in dry CH_2Cl_2 (2.6 mL). After stirring at RT for 30 min, the solvent was removed under reduced pressure ($p > 80$ mmHg). The residue was purified by chromatography on a column (150 mm × 15 mm) of silica gel (5 g). Elution with 98:2 pentane/Et_2O afforded a 2:1 mixture of inseparable (*E*)- and (*Z*)-aldehydes **26a** and **26b** (50 mg, combined yield = 99%). TLC (SiO_2): $R_f = 0.29$ (pentane/Et_2O, 98:2); ^{1}H NMR (300 MHz; CD_2Cl_2): δ (ppm) = 10.00 (d, $J = 7.9$ Hz, 0.5H); 9.98 (d, $J = 8.1$ Hz, 1H), 5.97 (d, $J = 8.2$ Hz, 1H), 5.94 (d, $J = 8.1$ Hz, 1H); 5.36 (br s, 0.5H), 5.29 (br s, 1H); 3.21 (s, 2H), 2.83 (s, 1H); 2.12 (s, 1.5H), 1.93 (s, 3H); 1.82–1.87 (m, 3H); 1.64–1.69 (m, 3H); 1.40–1.44 (m, 3H); 1.01 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ (ppm) = 191.8 (d), 191.5 (d), 163.1 (s), 162.8 (s), 136.9 (d), 136.1 (d), 132.4 (s), 132.1 (s), 130.1 (d), 129.0 (d), 50.0 (t), 41.4 (t), 37.7 (t), 32.6 (s), 30.4 (q), 30.3 (q), 29.0 (t), 28.8 (t), 25.2 (q), 20.6 (t), 17.5 (q); IR (neat product): $\tilde{\nu} = 3480$, 2950, 2932, 2855, 1673, 1456, 1170 cm^{-1}; HRMS: calcd for $C_{13}H_{20}O$ 192.1514; found 192.1518.

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Keywords: fragrances · gold · homogeneous catalysis · sigmatropic rearrangement · terpenoids

[1] a) G. Ohloff, *Scent and Fragrances: The Fascination of Odors and Their Chemical Perspectives*, Springer-Verlag, Berlin, **1994**; b) *The Chemistry of Fragrances* (Eds.: D. H. Pybus, C. S. Sell), The Royal Society of Chemistry, Cambridge, **1999**; c) A. Tschirsch in *Handbuch der Pharmakognosie*, C. H. Tauchnitz Verlag, Leipzig, **1917**; d) L. Jaenicke, F. J. Marner, *Pure Appl. Chem.* **1990**, *62*, 1365 – 1368.

[2] a) K. Bauer, D. Garbe, H. Surburg, *Common Fragrance and Flavor Materials*, 4th ed., Wiley-VCH, Weinheim, Germany, **2001**; b) D. Pybus in *The Chemistry of Fragrances* (Eds.: D. H. Pybus, C. S. Sell), The Royal Society of Chemistry, Cambridge, **1999**, p. 14; c) G. Ohloff, W. Pickenhagen, P. Kraft, *Scent and Chemistry: The Molecular World of Odors*, Wiley-VCH, Weinheim, **2012**, p. 214.

[3] Selected examples: a) G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633 – 7703; b) R. Buchecker, R. Egli, H. Regel-Wild, C. Tscharner, C. H. Eugster, G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1973**, *56*, 2548 – 2563; c) P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, E. Polo, D. Simoni, *J. Chem. Soc. Chem. Commun.* **1986**, 757 – 758; d) P. Uebelhart, A. Baumeler, A. Haag, R. Prewo, J. H. Bieri, C. H. Eugster, *Helv. Chim. Acta* **1986**, *69*, 816 – 834; e) M. I. Colombo, J. Zinczuk, E. A. Ruveda, *Tetrahedron* **1992**, *48*, 963 – 1037; f) Y. Wang, J. Lugtenburg, *Eur. J. Org. Chem.* **2004**, 3497 – 3510; g) M. Luparia, P. Boschetti, F. Piccinini, A. Porta, G. Zanoni, G. Vidari, *Chem. Biodiversity* **2008**, *5*, 1045 – 1057.

[4] E. Brenna, C. Fuganti, S. Serra, *C. R. Chim.* **2003**, *6*, 529 – 546, and references therein; b) E. Brenna, C. Fuganti, S. Serra, *Tetrahedron: Asymmetry* **2003**, *14*, 1 – 42, and references therein.

[5] a) C. Fuganti, S. Serra, A. Zenoni, *Helv. Chim. Acta* **2000**, *83*, 2761 – 2768; b) E. Brenna, C. Fuganti, S. Serra, P. Kraft *Eur. J. Org. Chem.* **2002**, 967 – 978.

[6] E. Brenna, C. Fuganti, S. Serra, *Chem. Soc. Rev.* **2008**, *37*, 2443 – 2451, and references therein.

[7] a) C. H. Eugster, R. Buchecker, C. Tscharner, G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1969**, *52*, 1729 – 1731; b) T. Oritani, K. Yamashita, *Agric. Biol. Chem.* **1987**, *51*, 1271 – 1275.

[8] S. Beszant, E. Giannini, G. Zanoni, G. Vidari, *Tetrahedron: Asymmetry* **2002**, *13*, 1245 – 1255.

[9] a) C. Chapuis, R. Brauchli, *Helv. Chim. Acta* **1993**, *76*, 2070 – 2088; b) T. Inoue, H. Kiyota, T. Oritani, *Tetrahedron: Asymmetry* **2000**, *11*, 3807 – 3818; c) S. Beszant, E. Giannini, G. Zanoni, G. Vidari, *Eur. J. Org. Chem.* **2003**, 3958 – 3968; d) S. Bugoni, D. Boccato, A. Porta, G. Zanoni, G. Vidari, *Chem. Eur. J.* **2015**, *21*, 791 – 799. Formal synthesis: e) G. Laval, G. Audran, J.-M. Galano, H. Monti, *J. Org. Chem.* **2000**, *65*, 3551 – 3554.

[10] M. Bovolenta, F. Castronovo, A. Vadalà, G. Zanoni, G. Vidari, *J. Org. Chem.* **2004**, *69*, 8959 – 8962.

[11] S. Serra, F. G. Gatti, C. Fuganti, *Tetrahedron: Asymmetry* **2009**, *20*, 1319 – 1329.

[12] a) M. Yu, G. Li, S. Wang, L. Zhang, *Adv. Synth. Catal.* **2007**, *349*, 871 – 875; b) N. Marion, P. Carlqvist, R. Gealageas, P. de Frémont, F. Maseras, S. P. Nolan, *Chem. Eur. J.* **2007**, *13*, 6437 – 6451; c) R. S. Ramón, N. Marion, S. P. Nolan, *Tetrahedron* **2009**, *65*, 1767 – 1773; d) D. A. Engel, G. B. Dudley, *Org. Biomol. Chem.* **2009**, *7*, 4149 – 4158; e) V. Merlini, S. Gaillard, A. Porta, G. Zanoni, G. Vidari, S. P. Nolan, *Tetrahedron Lett.* **2011**, *52*, 1124 – 1127.

[13] S. P. Nolan, *Acc. Chem. Res.* **2011**, *44*, 91 – 100.

[14] a) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750 – 2752; *Angew. Chem.* **2007**, *119*, 2806 – 2809; b) X.-Z. Shu, D. Shu, C. M. Schienebecka, W. Weiping Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698 – 7711; c) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, DOI: 10.1021/cr500691k.

[15] a) C. Fehr, J. Galindo, *Helv. Chim. Acta* **1995**, *78*, 539 – 552; b) H. Tanimoto, T. Oritani, *Tetrahedron* **1997**, *53*, 3527 – 3536.

[16] A. Ozanne, L. Pouységu, D. Depernet, B. Francois, S. Quideau, *Org. Lett.* **2003**, *5*, 2903 – 2906.

[17] a) S. Gaillard, J. Bosson, R. S. Ramón, P. Nun, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2010**, *16*, 13729 – 13740; b) R. S. Ramón, S. Gaillard, A. Poater, L. Cavallo, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2011**, *17*, 1238 – 1246; c) A. Gómez-Suárez, S. P. Nolan, *Angew. Chem. Int. Ed.* **2012**, *51*, 8156 – 8159; *Angew. Chem.* **2012**, *124*, 8278 – 8281; d) Y. Oonishi, A. Gómez-Suárez, A. R. Martin, S. P. Nolan, *Angew. Chem. Int. Ed.* **2013**, *52*, 9767 – 9770; *Angew. Chem.* **2013**, *125*, 9949 – 9953.

[18] It must be noted that, under strong basic conditions, $[\{Au(IPr)\}_2(\mu\text{-OH})][BF_4]$ is largely converted into [Au(IPr)(OH)], which shows low catalytic activity in the Meyer – Schuster rearrangement. See reference [17a] and S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 2742 – 2744.

[19] a) R. Lutz, *Chem. Rev.* **1984**, *84*, 205 – 247; b) L. Paquette, *Tetrahedron* **1994**, *50*, 4071.

[20] To our knowledge, only two examples of a similar rearrangement promoted by a Au^I catalyst, albeit in the presence of a Ag^I salt, have been reported so far for 5-en-1-yn-3-ols; however, the reaction has not been further investigated. See: a) F. Gagosz, *Org. Lett.* **2005**, *7*, 4129 – 4132; b) C. Fehr, I. Magpantay, J. Arpagaus, X. Marquet, M. Vuagnoux, *Angew. Chem. Int. Ed.* **2009**, *48*, 7221 – 7223; *Angew. Chem.* **2009**, *121*, 7357 – 7359.

[21] N. Marion, P. de Frémont, G. Lemière, E. D. Stevens, L. Fensterbank, M. Malacria, S. P. Nolan, *Chem. Commun.* **2006**, 2048 – 2050.

[22] K. Mori, M. Amaike, M. Itou, *Tetrahedron* **1993**, *49*, 1871 – 1878.

[23] V. Mamane, T. Gress, H. Krause, A. Furstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654 – 8655.

[24] T. Mitzel, J. Wzorek, A. Troutman, K. Allegue, *J. Org. Chem.* **2007**, *72*, 3042 – 3052.

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