The Meyer–Schuster Rearrangement of Ethoxyalkynyl Carbinols

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Abstract: The combination of electron-rich alkoxyacetylenes and cationic gold catalysts provides excellent reactivity for the Meyer–Schuster rearrangement under mild conditions. Optimization of the reaction conditions with respect to stereoselectivity and investigations into the scope and mechanism of the rearrangement of secondary ethoxyalkynyl carbinols (γ-ethoxy-substituted propargyl alcohols) to α,β-unsaturated esters are described.

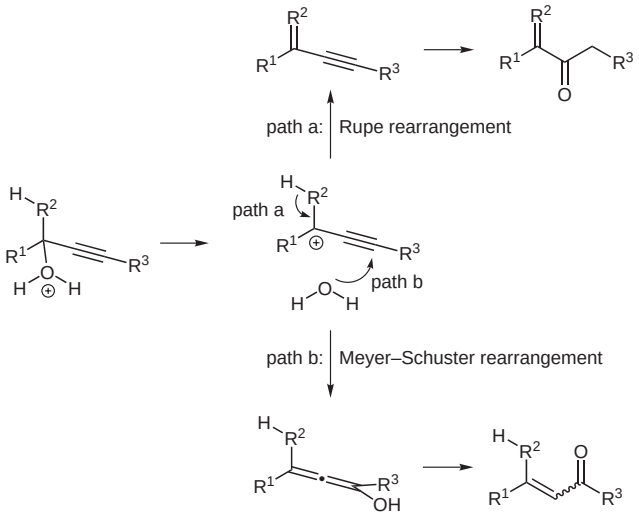
Key words: Meyer–Schuster, gold, alkoxyacetylene, propargyl alcohol, rearrangement

Propargyl alcohols are readily available, versatile tools in organic synthesis, providing access through different reaction pathways to alkenes, allenes, alkynes, ketones, etc.[1] For example, hydrometalation (*syn* or *anti*), substitution (at the α- or γ-centers), hydration, oxidation, hydrogenation, and deoxygenation all may be accomplished through selective activation of propargyl alcohol substrates. This study[2] focuses on using electron-rich alkoxyacetylenes to control selectivity so as to access the Meyer–Schuster rearrangement,[3] a formal 1,3-hydroxy migration followed by tautomerization.

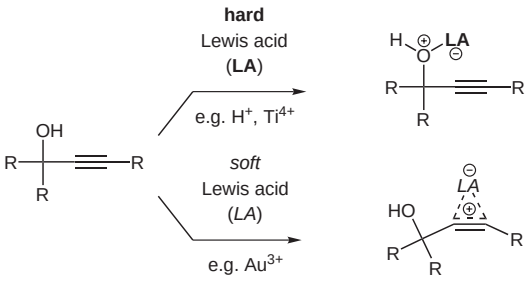
The Rupe and Meyer–Schuster rearrangements[3b] (Scheme 1) are not often used in chemical synthesis due to harsh conditions and poor selectivity. The Meyer–Schuster products (from path b) are especially rare because the dehydration that leads into the Rupe pathway (path a) generally takes precedence under traditional modes of activation that target the substrate through the alcohol moiety (i.e., acidic catalysts).

Coordination of the alkyne using soft, late-transition-metal Lewis acids,[4] including cationic gold catalysts,[5,6] provides a fundamentally different mechanism for activating propargyl alcohols (Scheme 2). 'Soft' activation of the alkyne is likely to be more tolerant of sensitive functionality than 'hard' activation of the oxygen atom and can provide complementary selectivities.

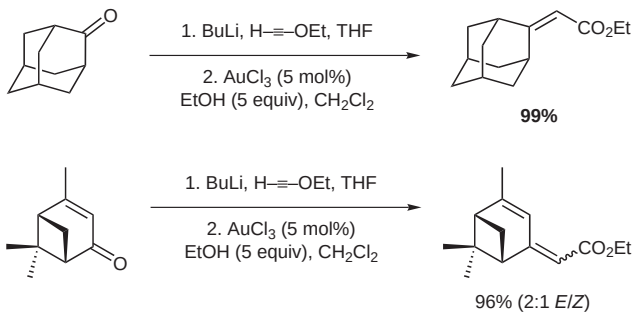
We recently reported on a two-step strategy for the HWE[7]-type olefination of hindered ketones:[2] (1) addition of ethoxyacetylide,[8] then (2) gold-catalyzed Meyer–Schuster rearrangement (Scheme 3). Alkyne addition to carbonyl groups is relatively insensitive to sterics, whereas the resulting congested tertiary ethoxyalkynyl carbinols are sterically and electronically primed for rearrangement.



Scheme 1 Competing Rupe and Meyer–Schuster pathways



Scheme 2 Complementary Lewis acid activation of propargyl alcohols



Scheme 3 Two-step olefination of hindered ketones[2]

Having identified this important two-stage tactical application, we focused our attention on step two, the Meyer–

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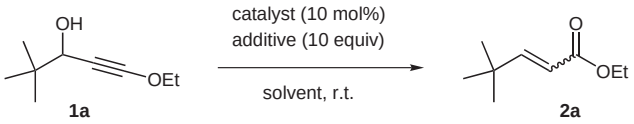
Schuster rearrangement.[9] In our earlier study, which featured highly reactive tertiary propargyl alcohol substrates, rearrangement occurred immediately upon addition of the gold catalyst. Main goals for this effort included (1) to increase the scope of the rearrangement, and (2) to identify, through rigorous experimentation, conditions that afford the enoate products stereoselectively.

Herein we report new reaction protocols and observations with respect to the rearrangement of secondary alcohol substrates (prepared by addition of lithium ethoxyacetylide to the corresponding aldehydes). In particular, our efforts focused on the rearrangement of secondary propargyl alcohols with simple alkyl substituents. These aliphatic substrates (e.g., **1a**, Equation 1) are less reactive towards the Meyer–Schuster reaction than tertiary propargyl alcohols, which ionize more easily. However, the dampened reactivity of secondary alcohols (and the steric distinction between the alkyl substituent and a hydrogen atom) provides greater control and the opportunity to enhance stereoselectivity in the formation of the α,β-unsaturated ester products **2**.

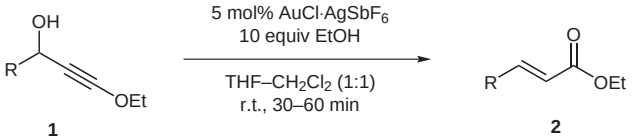


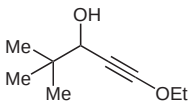
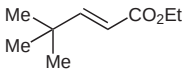
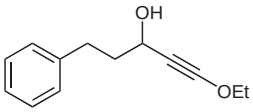
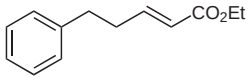
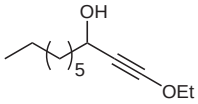
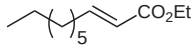
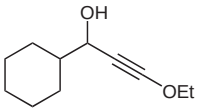
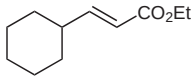
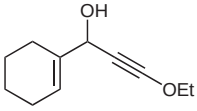
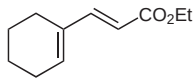
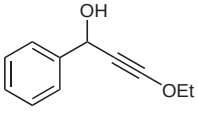
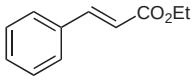
catalyst: **AuCl·AgSbF$_6$** > $AuCl_3$, AuCl, Ph_3P·AuCl >> $AgSbF_6$
additive: **EtOH** >> CF_3CH_2OH, AcOH, PhOH, morpholine, none
solvent: **THF–CH_2Cl_2** > THF, CH_2Cl_2, EtOH, H_2O

Equation 1 Qualitative screening for optimal conditions

Equation 1 summarizes observations from extensive qualitative experiments on the rearrangement of **1a** (derived from pivaldehyde) to **2a**. We examined three main

Table 1 Meyer–Schuster Reaction of Ethoxyalkynyl Carbinols[a]



Entry	Substrate	Product	Yield (%, *E*/*Z*)
1a[a] 1b[b]	 **1a**	 **2a**	91 (97:3) 93 (*E*)
2a[a] 2b[b]	 **1b**	 **2b**	80 (94:6) 82 (99:1)
3a[a] 3b[b]	 **1c**	 **2c**	91 (63:37) 90 (86:14)
4a[a] 4b[b]	 **1d**	 **2d**	75 (57:43) 78 (70:30)
5a[a] 5b[b]	 **1e**	 **2e**	72 (40:60) 70 (40:60)
6a[a] 6b[b] 6c[c]	 **1f**	 **2f**	90 (47:53) 92 (91:9) 90 (53:47)

[a] Solutions of $AgSbF_6$ (5 mol%) and AuCl (5 mol%)[13] in 1:1 THF–CH_2Cl_2 added sequentially to ethoxyalkynyl carbinol (**1**, 1.0 equiv) and EtOH (10 equiv) in 1:1 THF–CH_2Cl_2. No camphorsulfonic acid (CSA) was included unless otherwise inidcated.
[b] 1.0 Equiv CSA.
[c] Reaction conducted in 2-butanone instead of 1:1 THF–CH_2Cl_2.[14]

variables: gold catalyst, additive, and solvent. Among the protic additives, which are envisioned to assist in the formal 1,3-hydroxy migration, ethanol was significantly more effective than other agents tested. Reactions conducted in a mixed system of THF and CH_2Cl_2 were most efficient (qualitatively) and selective for the *E*-alkene isomer (quantitatively). Finally, only minor differences were observed among the various gold catalysts; all of the cationic gold catalysts that we screened were more or less effective. Silver(I) hexafluoroantimonate ($AgSbF_6$) showed little activity on its own, but when employed in conjunction with the gold catalysts it exerted a positive effect on the *E*/*Z*-selectivity of the reaction.

Further experimentation indicated that a catalyst loading of 5 mol% was optimal. We observed no significant effects of activated silica gel on these small-scale reactions.[10] Addition of camphorsulfonic acid (CSA) accelerated the reaction, whereas an acid scavenger [2,6-di-(*tert*-butyl)-4-methylpyridine, DTBMP] inhibited the reaction. These results, along with earlier experiments,[11] indicate that exchangeable protons play an important supporting role in the gold-catalyzed rearrangement.

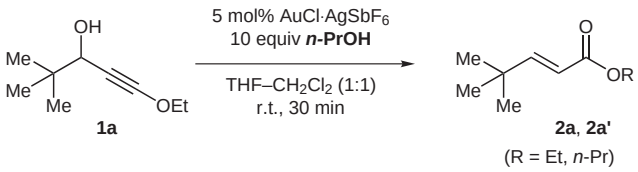
We tested the rearrangement protocol on a series of representative secondary alcohol substrates (**1a**–**f**, Table 1).[12] Neopentyl alcohol (**1a**) gave rise to nonenolizable enoate **2a** with nearly complete stereoselectivity (entry 1a). Alkyl-substituted alcohols **1b**–**d** afforded enoates **2b**–**d** (entries 2a–4a) to the complete exclusion of dehydration products (cf. path a of Scheme 1).

Inclusion of camphorsulfonic acid (CSA) in the reaction mixture improved the stereoselectivity of most reactions (entries 1b–6b, cf. 6a vs. 6b); however, in this protocol the substrates must tolerate more acidic conditions.

Sequential addition of the silver and gold precatalysts in solution to the reaction mixture provided optimal stereoselectivity and reproducibility.[15] Premixing the gold and silver salts gave poorer results with respect to selectivity, as did addition of the precatalysts as solids. Reactions were typically conducted under an inert atmosphere of argon using anhydrous THF and CH_2Cl_2, but similar results were obtained in 'open-flask' reactions using reagent-grade solvents. The small amount of water present in reagent-grade ethanol does not interfere with (and may facilitate) the reaction.

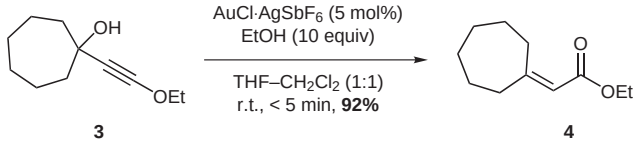
Scheme 4 shows one reasonable mechanistic sequence for the Meyer–Schuster reaction (**1** → **2**). Coordination between the ethoxyalkyne and the cationic gold catalyst promotes γ-substitution to generate a 1,1-diethoxyallene. The immediate expulsion of water (**I** → **II**) accounts for the lack of β-hydroxy ester byproducts, which stands in contrast to acidic hydrolysis of ethoxyalkynyl carbinols.[11a,c] The gold catalyst may or may not promote the subsequent reincorporation of water to produce **III**; this step (**II** → **III**) determines the stereochemistry of the eventual product.[16] Rapid collapse of intermediate **III** yields enoate **2**.

The mechanism outlined in Scheme 4 implies that the external alcohol incorporates into the enoate ester product to a partial (but not statistical) degree, based on competitive collapse of tetrahedral intermediate **III**.[17] Alcohol **1a** was subjected to the rearrangement conditions using *n*-propanol as the external alcohol promoter (Equation 2) under the assumption that *n*-propanol and ethanol would be expelled from the tetrahedral intermediate at similar rates. The corresponding α,β-unsaturated ethyl and *n*-propyl esters (**2a** and **2a′**) were obtained in an approximately 1:1 ratio,[18] which is consistent with our mechanistic hypothesis.

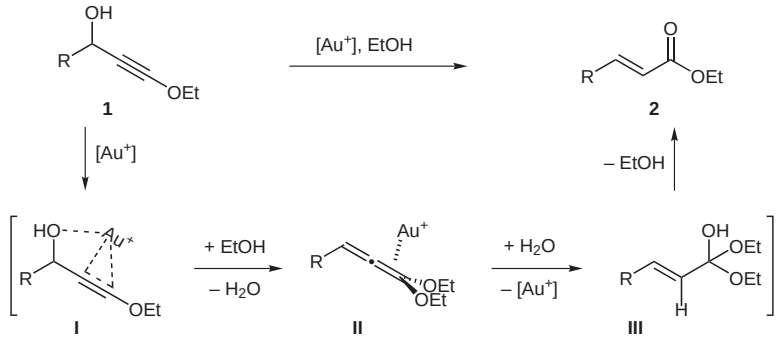


Equation 2 Partial incorporation (ca. 50%) of external alcohol additive is consistent with postulated dialkoxyallene intermediate (**II**)

Finally, the experiment illustrated in Equation 3 demonstrates the applicability of these conditions to the synthesis of α,β-unsaturated esters from tertiary alcohols (**3** → **4**).[12]



Equation 3 Facile rearrangement of a tertiary ethoxyalkynyl carbinol



Scheme 4 Hypothesis on the Meyer–Schuster reaction pathway

In summary, α,β-unsaturated esters were prepared from ethoxyalkynyl carbinols using cationic gold catalysts. Substitution on the alcohol substrate, including aryl, alkyl, and vinyl groups, is well tolerated, with aliphatic substituents providing the highest stereoselectivity. Neither Rupe-type elimination products (from loss of water) nor β-hydroxy ester products (from addition of water) were observed. Mechanistic observations and important factors that influence the stereochemical course of the reaction are reported.

The mild, efficient, and convenient reaction conditions should find use in chemical synthesis. This work illustrates the potential role of activated, electron-rich alkyne substrates in the rapidly emerging field of catalysis using soft, late-transition-metal cations.[19]

Typical Procedure for the Addition of Ethoxyacetylene of Aldehydes: 1-Ethoxy-3-*tert*-butyl-1-propyn-3-ol (1a)

To a THF solution (5 mL) of ethyl ethynyl ether (0.4 g, ca. 40% by weight in hexane, ca. 5.7 mmol) was added *n*-BuLi (2.5 M in hexane, 1.4 mL, 3.4 mmol) dropwise over 5 min at –78 °C under argon atmosphere. The solution was allowed to warm to 0 °C over 1 h and held at 0 °C for an additional 30 min, then recooled to –78 °C. Pivaldehyde (0.28 mL, 3.2 mmol) was added in one portion dropwise. The solution was allowed to warm to r.t. over 1 h and held at r.t. for an additional 3 h. A sat. aq NH_4Cl solution was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with H_2O, sat. aq $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered, and concentrated. The residue was purified using silica gel column chromatography (EtOAc–hexane) to give 1-ethoxy-3-*tert*-butyl-1-propyn-3-ol (**1a**) as a light yellow oil; yield 0.48 g (97%).

Typical Procedure for the Gold-Catalyzed Meyer–Schuster Rearrangement of Ethoxyalkynyl Carbinols: Ethyl 4,4-Dimethylpent-2-enoate (2a)

A mixture of AuCl (7.4 mg, 0.032 mmol) in 1:1 CH_2Cl_2–THF (5 mL) was prepared and allowed to stir for 20 min to give a homogeneous solution with an insoluble residue. A separate 25 mL round-bottomed flask under argon was charged with **1a** (100 mg, 0.64 mmol), EtOH (95%, 0.36 mL, 6.4 mmol) and a solution of $AgSbF_6$ (11 mg, 0.032 mmol) in 1:1 CH_2Cl_2–THF (5 mL). The mixture of AuCl in 1:1 CH_2Cl_2–THF (5 mL) was then added dropwise. After 40 min, the reaction mixture was filtered through a plug of SiO_2 with the aid of 1:7 Et_2O–hexane. The filtrate was concentrated and purified using silica gel column chromatography (Et_2O–hexane, 1:50) to give ethyl 4,4-dimethylpent-2-enoate (**2a**); yield 0.091 g (91%, 97:3 *E*/*Z* ratio).

Typical Procedure for the Gold-Catalyzed Meyer–Schuster Rearrangement of Ethoxyalkynyl Carbinols in the Presence of Camphorsulfonic Acid (CSA)

A mixture of AuCl (7.4 mg, 0.032 mmol) in 1:1 CH_2Cl_2–THF (5 mL) was prepared and allowed to stir for 20 min to give a homogeneous solution with an insoluble residue. A separate 25 mL round-bottomed flask under argon was charged with **1a** (100 mg, 0.64 mmol), EtOH (95%, 0.36 mL, 6.4 mmol), CSA (0.15 g, 0.64 mmol) and a solution of $AgSbF_6$ (11 mg, 0.032 mmol) in 1:1 CH_2Cl_2–THF (5 mL). The mixture of AuCl in 1:1 CH_2Cl_2–THF (5 mL) was then added dropwise. After 40 min, the reaction mixture was filtered through a plug of SiO_2 with the aid of 1:7 Et_2O–hexane. The filtrate was concentrated and purified using silica gel column chromatography (Et_2O–hexane, 1:50) to give ethyl (*E*)-4,4-dimethylpent-2-enoate (**2a**); yield 0.093 g (93%).

Acknowledgment

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(8) Ethoxyacetylene was purchased from Sigma-Aldrich as a 40% solution in hexane and used as received.

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(11) Protic acids in the absence of gold are significantly less effective (ref. 2). Examples of the protic-acid-catalyzed Meyer–Schuster rearrangement of ethoxyalkynyl carbinols: (a) Welch, S. C.; Hagan, C. P.; White, D. H.; Fleming, W. P.; Trotter, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 549. (b) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1983**, *105*, 3252. (c) Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, *53*, 7139.

(12) Satisfactory characterization data (^{1}H NMR, ^{13}C NMR, IR, HRMS) were obtained for all compounds. Yields refer to at least 50 mg of material isolated in >95% purity.

(13) An insoluble residue, which has no apparent impact on the course of the reaction, was observed in the solutions of AuCl (Aldrich, 99.9%) in 1:1 THF–CH_2Cl_2. Identical results were obtained when this catalyst solution was filtered, decanted, or used with the unknown residue in place.

(14) 2-Butanone is the recommended solvent in a forthcoming study on the transpositional hydrolysis of propargylic acetates (Prof. Liming Zhang, University of Nevada, Reno, private communication; Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth Catal.* **2007**, in press, DOI: 10.1002/adsc.200600579).

(15) In fact, simultaneous addition of the solutions of the gold and silver salts to the reaction mixture provided the enoate products with slightly better selectivity, but we consider the sequential addition protocol to be more easily duplicated and thus preferable.

(16) Isomerization of the *Z*-enoates to the *E*-enoates does not occur under the reaction conditions: extending the reaction time does not have a significant effect on the product ratio, and resubjecting the enoate mixtures to the rearrangement conditions does not change the ratio of stereoisomers. Therefore, we assume that the nonthermodynamic product distribution is purely the result of kinetic control.

(17) To the extent that the additive is incorporated into the product, the Meyer–Schuster reaction is not a true 'rearrangement', although it is generally referred to as such in a formal sense for the sake of simplicity.

(18) Control experiments confirmed that the rearrangement conditions do not promote transesterification between the ethyl and propyl esters, so the incorporation of the propanol additive is most likely occurring during the course of the rearrangement.

(19) For a previous report on the combined use of oxygen-activated alkynes and cationic gold catalysts, see: Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806.