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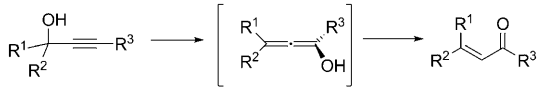
# A Simple and Versatile Re-Catalyzed Meyer–Schuster Rearrangement of Propargylic Alcohols to α,β-Unsaturated Carbonyl Compounds

**Massimo Stefanoni, Marco Luparia, Alessio Porta, Giuseppe Zanoni, and Giovanni Vidari*[a]**

α,β-Unsaturated carbonyl groups are found in a large number of biologically active natural products and their importance in organic synthesis as substrates for countless transformations can be hardly underestimated.[1] Their traditional preparations through well-known protocols, such as aldol-like condensations, Wittig and Horner–Wadsworth–Emmons olefinations,[2] usually require basic conditions, which might be incompatible with the presence of different functional groups and/or preservation of the original stereochemistry. Moreover, these procedures are often multistep sequences and exhibit low atom economy.[2] By contrast, the Meyer–Schuster (M.S.) rearrangement of propargylic alcohols to α,β-unsaturated carbonyl compounds (Scheme 1),[3] intrinsically complies with the principles of atom economy.[4] Moreover, considering the easy access to starting propargylic alcohols,[5] this methodology is synthetically very attractive. However, the M.S. rearrangement has seldom been used in total synthesis so far due to different drawbacks inherent in present methodologies.




Scheme 1. Meyer–Schuster rearrangement of propargylic alcohols.

Strong protic or Lewis acids were mostly used as promoters in the earliest versions of the M.S. reaction,[3] which generally afforded products in poor yields, due to unselective rearrangements and side reactions. More recent procedures are based on catalytic organometallic species. Thus, gold(I)[6] or mercury(II)[7] species catalyze the ready rearrangement of esters of propargylic alcohols to allenic esters and ultimately to the corresponding α,β-unsatured carbonyl compounds; however, the atom and step economy of the overall transformations are obviously only moderate. Alternatively, Ru complexes promote the direct M.S. rearrangement of propargylic alcohols;[8] however, this reaction is limited to the conversion of terminal alkynes to the corresponding enals. On the contrary, α,β-enones have been prepared by means of silver(I)/$CO_2$[9] or gold(I)-/silver(I)[10]-catalyzed isomerization of propargylic alcohols, albeit with general moderate stereoselectivity. $Au^{III}$ also catalyzes the rearrangement, but often in low yields and in competition with nucleophilic substitution of the propargylic alcohol.[11]

Finally, different oxo complexes of transition metals [vanadium(V),[12] molybdenum(VI),[13] titanium(IV)/copper(I),[14] rhenium(VII)[15] promote the M.S. rearrangement in a catalytic fashion. These reactions are envisioned to proceed via a [3,3]-sigmatropic rearrangement of an initially formed metal–alkoxide, followed by protonation of the isomerized species to afford the desired product (Scheme 2).[12,13] Although the last procedures require temperatures $\geq 100\,^{\circ}C$ and/or acidic conditions, often resulting in moderate yields and low stereoselectivity,[16] we were attracted by the high air and moisture tolerance of high oxidation-state metal–oxo complexes which, in addition, might be recovered at the end of the reaction and reused.

Recently, during their studies on rhenium(V)-catalyzed nucleophilic substitution reactions of propargylic alcohols, Toste et al. occasionally detected the formation of the M.S. products as the result of an undesired side-reaction.[17d] This observation was, however, not followed by other attempts to optimize and generalize the formation of α,β-unsaturated carbonyl compounds. Since rhenium(V) is endowed with a rich coordination chemistry,[17] and catalyst recovery has been observed in some cases,[17c] we envisaged the possibility to develop an efficient M.S. rearrangement based on a rhenium(V)–oxo complex, by finely tuning the steric and elec-

[a] M. Stefanoni, Dr. M. Luparia, Dr. A. Porta, Dr. G. Zanoni, Prof. G. Vidari
Dipartimento di Chimica Organica, Università di Pavia
Via Taramelli 10, Pavia (Italy)
Fax: (+39) 0382-987322
E-mail: vidari@unipv.it

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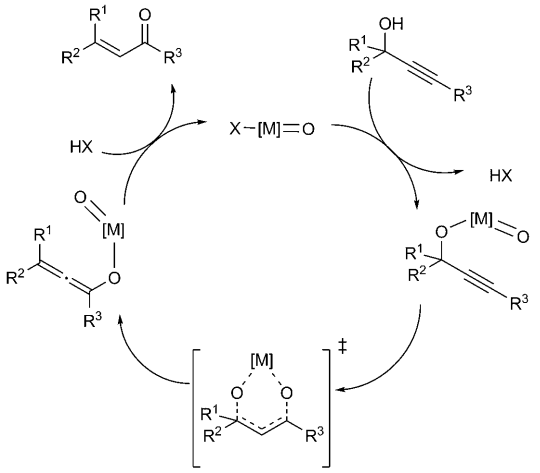
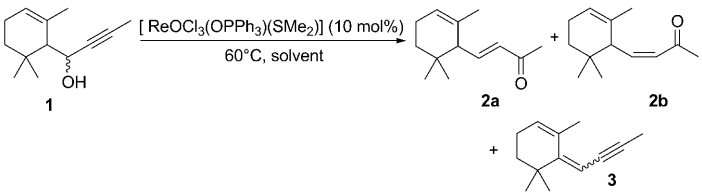


Scheme 2. Mechanism envisioned for the Meyer–Schuster rearrangement catalyzed by oxo-metal complexes.

tronic properties of ligands. In this paper, we describe our efforts in this field, culminating in a new simple protocol of the M.S. rearrangement.

We selected the easily accessible propargylic alcohol **1**[18] as the ideal substrate for studying the rearrangement to enones **2a–b** under highly-demanding steric and electronic conditions. In fact, the OH group resided in a highly crowded environment and simple dehydration could afford a stabilized conjugated dienyne **3**.

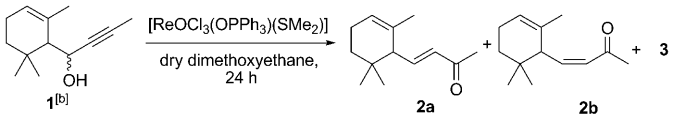
At first, we chose the easily obtainable complex $[ReOCl_3(OPPh_3)(SMe_2)]$ as a viable catalyst,[17b,19] focusing our attention on finding the best reaction solvent (Scheme 3).



Scheme 3. Model reaction for the optimization of solvents in Re-catalyzed Meyer–Schuster rearrangement.

Both $CH_2Cl_2$ and $CHCl_3$ proved to be unsatisfactory, whereas a serious lack of reactivity was noticed in apolar solvents such as hexane. Surprisingly, no reaction was also observed in acetone, while starting material **1** readily decomposed in MeCN or DMSO, without formation of the desired product **2**. We reasoned that these highly coordinating polar solvents might sequester $Re^V$ species while favoring unproductive pathways via cleavage of the propargylic C–OH bond. Consequently, we turned our attention to ethers, which are less coordinating solvents but polar enough to stabilize partially charged species presumably developing during the M.S. rearrangement (see below). Indeed, in THF starting material **1** was almost completely consumed, affording (*E*)-α-ionone **2a** and (*Z*)-α-ionone **2b** in an encouraging 69% combined yield. Addition of $H_2O$ to THF severely inhibited the isomerization, possibly because it competed with alcohol **1** in coordinating the rhenium(V) complex, thus reducing the concentration of the active catalytic species. Further studies were, therefore, performed in dry solvents and in the presence of the catalyst previously dried under vacuum. In dimethoxyethane the reaction proceeded at lower rate than in THF, but afforded less by-products and the yields were significantly higher. By contrast, mostly unreacted starting material **1** was recovered when the reaction was performed in 1,4-dioxane. In conclusion, dry dimethoxyethane was selected as the solvent of choice for further reaction optimization. Next, either the catalyst loading or the temperature of the reaction was changed (Table 1).

Table 1. Optimization of catalyst loading and reaction temperature in the formation of **2a**.[a]



| Entry | Catalyst[c] | *T* [°C] | **2a**[d] | **2b**[d] | Unreacted **1**[d] | **3**[d] |
|---|---|---|---|---|---|---|
| 1 | 10 | 60 | 41 | 24 | 29 | 5 |
| 2 | 10 | 80 | 68 | 17 | 0 | 15 |
| 3 | 20 | 60 | 26 | 24 | 27 | 23 |
| 4 | 5 | 80 | 75 | 20 | 0 | 5 |

[a] Reactions were carried out on a 0.5 mmol scale in a screw plastic cap vial in 1 mL of solvent and heated with an external oil bath set at the indicated temperature. [b] Alkyne **1** was a 6:1 mixture of racemic diastereomeric carbinols. [c] Catalyst loading in mol%. [d] Percentage of each compound in the reaction mixture was estimated by GC-MS analysis.

Increasing the catalyst loading from 10 to 20 mol% resulted in larger amounts of the dehydration product **3** and in only a slightly higher conversion of substrate **1** (Table 1, compare entries 1 and 3). On the other hand, with 10 mol% catalyst, an increase of the temperature from 60 to 80°C, significantly enhanced both the conversion of **1** and the yield of ionones **2**, although the amount of compound **3** increased as well (Table 1, compare entries 1 and 2). Eventually, 5 mol% catalyst and a temperature of 80°C were found to be the optimal conditions, under which model substrate **1** was completely converted in 24 h to 95% **2**, while compound **3** accounted for only 5% (Table 1, entry 4).[20]

We noticed that with the progress of the reaction the amount of (*E*)-**2a** constantly increased at the expense of the (*Z*)-isomer **2b**. Such double-bond isomerization was attributed to a catalytic effect of the rhenium complex. In fact, in a separate experiment, pure (*Z*)-**2b** was completely converted into (*E*)-**2a** upon exposure to 5 mol% $[ReOCl_3(OPPh_3)(SMe_2)]$ in dimethoxyethane at 80°C for 24 h; by contrast, in the absence of the catalyst, no isomerization occurred and (*Z*)-**2b** was recovered unchanged.

In a subsequent pivotal experiment, (*S*)-**2a** was produced in 91% isolated yield and 95% *ee* (chiral GC) upon expo-

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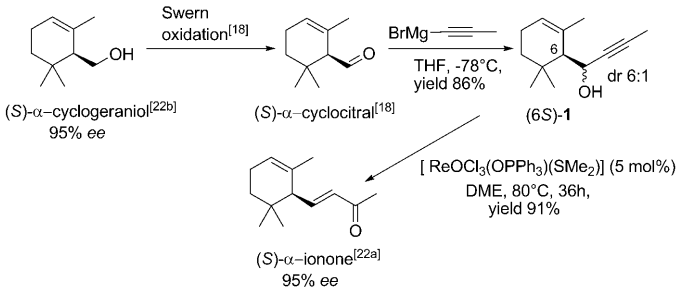
sure of enantioenriched (6*S*)-**1** (95% *ee*, 6:1 mixture of diastereomeric carbinols)[18] to 5 mol% catalyst in dimethoxyethane at 80°C for 36 h (Scheme 4).

This synthesis, further representing the most straightforward enantioselective approach to the important perfume ingredient (*S*)-α-ionone **2a**[21,22] nicely proved the configuration integrity of stereocenters under our conditions for the M.S. rearrangement. Notably, in previous studies of this reaction, this important issue, namely, the stereochemical stability of potentially enolizable stereocenters has never been examined in detail.




Scheme 4. Enantioselective synthesis of (*S*)-α-ionone (**2a**).

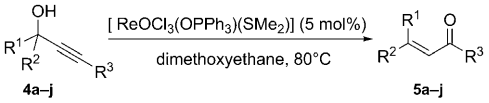
Subsequently, we turned our attention to the M.S. rearrangement of different secondary and tertiary propargylic alcohols to demonstrate the vast applicability of our protocol. Both alkyl and aryl substituted alkynols were well tolerated affording the corresponding α,β-unsaturated carbonyl compounds in high isolated yields (Table 2). Also terminal alkynes led to the corresponding enals in high yield (Table 2, entries 9, 10). Notably, an ester group attached to the alkyne moiety was not of impediment to the reaction (Table 2, entry 7), and even in the presence of a carboxylic acid group the product was formed in acceptable yield (Table 2, entry 8).

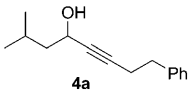
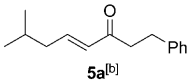
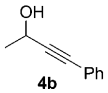
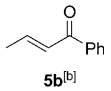
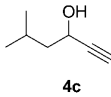
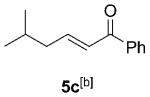
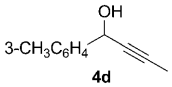
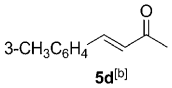
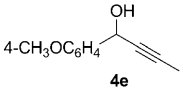
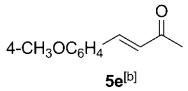
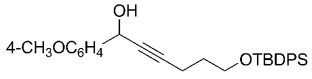
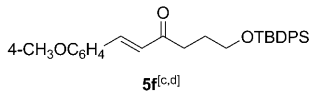
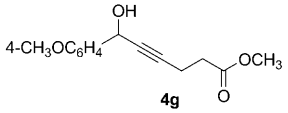
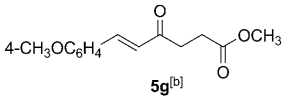
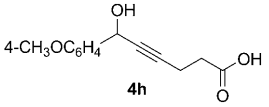
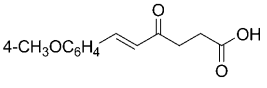
The possibility to recycle the catalyst gives this procedure an additional attractiveness. As an example, in the rearrangement of **4b** (Table 2, entry 2), the rhenium catalyst was recovered by filtration at the end of the reaction and reused two additional consecutive times, with the same catalytic efficiency.

Although still preliminary, additional experiments shed some light on the reaction mechanism. In particular, M.S. rearrangement of *O*-deuterated alcohol **6** afforded [2D]-labelled enone **7** (Scheme 5).[23] On the other hand, treatment of **4b** with stoichiometric amounts of $^{18}O$=Re enriched complex[24] led to significant $^{18}O$ incorporation into rearranged enone **8** (Scheme 5).[23]

Both results were consistent with the catalytic cycle generally accepted for oxo–metal cata-

Table 2. Re-catalyzed Meyer–Schuster rearrangement of propargylic alcohols.[a]




| Entry | Substrate | Product | *t* [h] | Yield [%] |
|---|---|---|---|---|
| 1 |  **4a** |  **5a**[b] | 24 | 90 |
| 2 |  **4b** |  **5b**[b] | 24 | 96 |
| 3 |  **4c** |  **5c**[b] | 24 | 98 |
| 4 |  **4d** |  **5d**[b] | 24 | 94 |
| 5 |  **4e** |  **5e**[b] | 7 | 90 |
| 6 |  **4f** |  **5f**[c,d] | 0.5 | 60 |
| 7 |  **4g** |  **5g**[b] | 1.5 | 98 |
| 8 |  **4h** |  **5h**[c,e] | 3 | 60 |
| 9 |  **4i** |  **5i**[f] | 20 | 94 |
| 10 |  **4j** |  **5j** | 20 | 96 |

[a] A solution of propargylic alcohol **4** (0.5 mmol) in dimethoxyethane (1 mL), placed in a screw plastic cap vial, was heated with an external oil bath at the indicated temperature; yields refer to isolated product (average of two runs). [b] TLC analysis indicated complete disappearance of minor *Z* isomer. [c] The reaction was interrupted before complete disappearance (TLC) of starting alkynol. [d] Products of decomposition were formed on prolonged reaction times. [e] **5h** was characterized as ester **5g**. [f] *E*/*Z* 12.5:1.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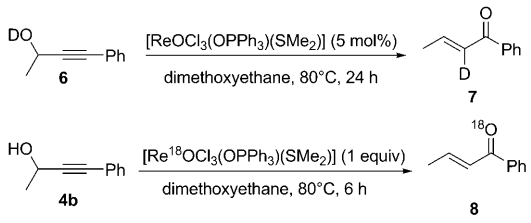
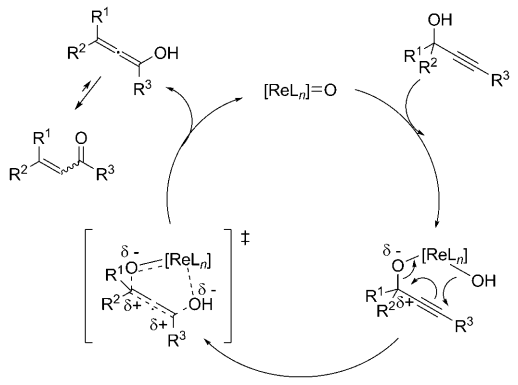


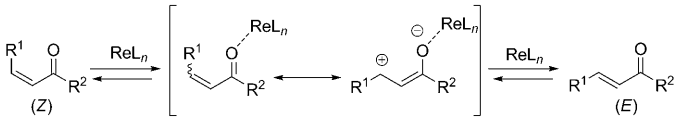

Scheme 5. Formation of [D]- and $^{18}O$-labelled enones.

lyzed M.S. rearrangements (Scheme 2);[12,13] however, no free acid could be detected in the reaction mixture,[25] contrarily to what was expected to arise from the chlorine–alkoxy ligand exchange in the first step of the cycle (Scheme 2). On the basis of these evidences, we propose a slightly different mechanism for the M.S. rearrangement catalyzed by $[ReOCl_3(OPPh_3)(SMe_2)]$ (Scheme 6). In the first step, the propargylic -OH group adds across the Re=O bond of the catalyst, forming a monoalkoxy complex with the alcohol.[17b] Likely, this complexation strongly polarizes the C–ORe bond, facilitating its cleavage. The partial positive charge developing on the propargylic carbon then boosts a concerted six-electron bond migration,[26] which ultimately results in regeneration of the oxo–rhenium catalyst along with concurrent delivery of the OH group, initially bound to Re, to the adjacent terminus of the incipient allene moiety. The allenol thus formed eventually rearranges to an α,β-unsaturated carbonyl product via a ready prototropic shift (Scheme 6).




Scheme 6. Mechanism envisioned for the Meyer–Schuster rearrangement catalyzed by the $[ReOCl_3(OPPh_3)(SMe_2)]$ complex.

Formation of a mixture of (*E*)- and (*Z*)-olefins at the early stages of the reaction appears to be due to a kinetically controlled tautomerization of the intermediate allenol derivative (Scheme 6). By contrast, without excluding other mechanistic hypotheses, stereoconvergence of α,β-unsaturated carbonyl compounds to the thermodynamically more stable *E* isomer on prolonged heating, could be explained by complexation of the carbonyl oxygen to the rhenium complex.[17a] This Lewis acid-like catalysis might be expected to stabilize a dipolar intermediate (enolate, allyl cation), allowing $Z \rightarrow E$ enone isomerization (Scheme 7).




Scheme 7. Mechanism envisioned for the catalyzed isomerisation of (*E*)/(*Z*)-unsaturated carbonyl compounds.

In summary, using the readily available $[ReOCl_3(OPPh_3)(SMe_2)]$ complex,[17b,19] we have developed a new general catalytic procedure for the rapid and efficient 1,3-rearrangement of free secondary and tertiary propargylic alcohols to the corresponding α,β-unsaturated carbonyl compounds. with virtually complete *E* stereoselectivity. The reaction proceeds under neutral conditions and no racemization of potentially enolizable stereocenters was observed. Given its simplicity and reliability, we anticipate that this new version of the Meyer–Schuster rearrangement will find ample application in organic synthesis. Our efforts are now aimed at developing the use of this protocol in one-pot multistep reaction sequences.

## Experimental Section

**Typical reaction procedure**: $[ReOCl_3(OPPh_3)(SMe_2)]$ (18 mg, 0.026 mmol), propargylic alcohol **1** (100 mg, 0.52 mmol), dimethoxyethane (1.05 mL) were placed in a screw cap vial and heated under stirring in an oil bath at 80 °C. After 36 h, the undissolved catalyst was filtered off and the solvent was evaporated under vacuum. Column chromatography of the residue on silica gel afforded, by elution with hexane/$Et_2O$ 98:2, chromatographically pure (*E*)-α,β-enone **2a** (91 mg, 91 %), identical with a commercial authentic sample.

## Acknowledgements

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**Keywords:** carbonyl compounds · Meyer–Schuster isomerization · propargylic alcohols · rearrangement · rhenium

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[26] The unsatisfactory M.S. rearrangement of primary propargylic alcohols catalyzed by the $[ReOCl_3(OPPh_3)(SMe_2)]$ complex might be due to the difficulty for a positive charge to develop on a primary carbon.

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