The Meyer–Schuster rearrangement for the synthesis of α,β-unsaturated carbonyl compounds

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The Meyer–Schuster rearrangement is the conversion of propargyl alcohols into α,β-unsaturated carbonyl compounds *via* a formal 1,3-hydroxyl shift and tautomerization. The major challenge associated with the Meyer–Schuster reaction is that of selectively promoting the desired rearrangement over the myriad other reaction pathways available to propargyl alcohols. This Perspective Article features recent advances in the Meyer–Schuster reaction, including several demonstrated techniques for improving the scope. Strengths and weaknesses of each technique are discussed, and outstanding problems that warrant further study are highlighted. The primary motivation for research and development of the Meyer–Schuster rearrangement is as a means of preparing α,β-unsaturated carbonyl compounds as part of a two-stage olefination strategy.

Introduction

The Meyer–Schuster rearrangement[1] is the conversion of propargyl alcohols into α,β-unsaturated carbonyl compounds *via* a formal 1,3-hydroxyl shift and tautomerization (Fig. 1).[2] Propargylic alcohols are valuable intermediates in organic synthesis. They are easy to prepare, especially by nucleophilic addition of terminal alkynes to aldehydes and ketones. As a rearrangement, the Meyer–Schuster reaction is attractive from an atom economy[3] standpoint, converting readily available propargyl alcohols into equally valuable and versatile enone-type structures.

The major challenge associated with the Meyer–Schuster reaction is that of selectively promoting the desired rearrangement over the myriad other reaction pathways available to propargyl alcohols. The propargyl alcohol presents, by definition, two complementary functional group handles in close proximity: the alcohol and the alkyne. Reactions of propargyl alcohols can involve either the alcohol or the alkyne independently. Alternatively, the reactions can involve both functional groups reacting cooperatively. Chemical versatility makes propargyl alcohols attractive for a variety of applications in synthesis (Fig. 2). However, traditional protocols for promoting the Meyer–Schuster rearrangement are

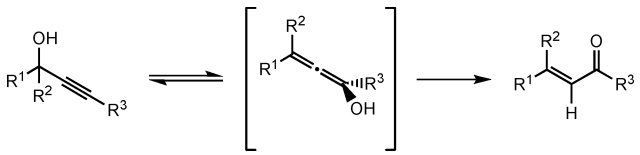

Fig. 1 The Meyer–Schuster rearrangement.

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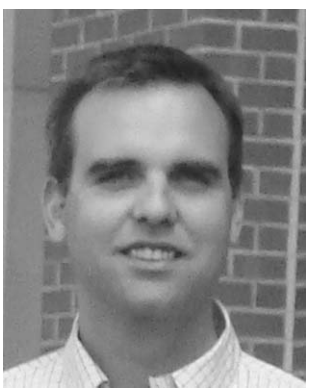


Gregory Dudley

Gregory Dudley received a B.A. from FSU in 1995 and a Ph.D. in 2000 under the direction of Professor Rick Danheiser at MIT. After completing an NIH Postdoctoral Fellowship with Professor Samuel Danishefsky at the Sloan–Kettering Institute for Cancer Research, he returned to FSU as an assistant professor in 2002. Professor Dudley was promoted to Associate Professor with tenure in 2008. The current mission of his research program is to impact the drug discovery process by contributing fundamental new knowledge to organic synthesis. Recent methodology has focused on novel C–C bond cleavage and rearrangement reactions for target-oriented synthesis.

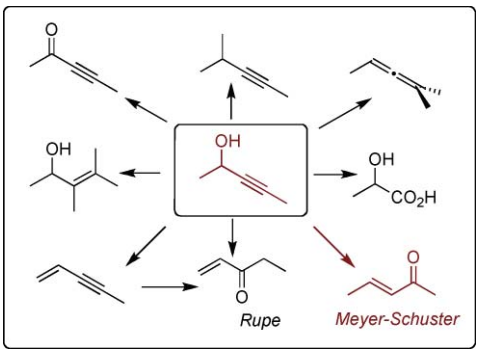


Fig. 2 Common reaction pathways of propargyl alcohols.

strikingly similar to those known to promote the competing Rupe rearrangement,[4] and the Rupe pathway is typically lower in energy (Fig. 3). Therefore, the Meyer–Schuster reaction has been largely limited to substrates for which the Rupe rearrangement is blocked: propargyl alcohols with no β-hydrogens.[1]

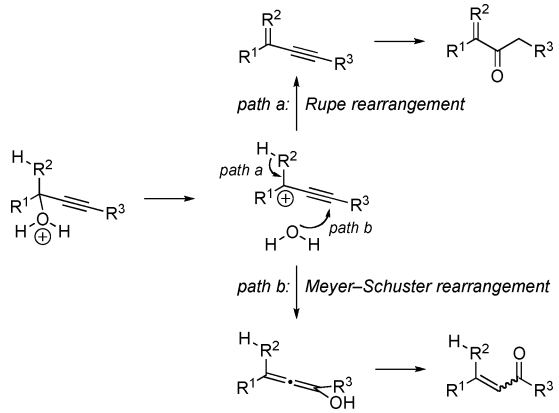


Fig. 3 Competing Rupe and Meyer–Schuster pathways.

The divergence between the two reaction pathways—Rupe and Meyer–Schuster—occurs early on: initial β-elimination of the propargyl alcohol provides an enyne en route to the Rupe product, whereas as γ-substitution generally leads to the Meyer–Schuster product (Fig. 3). Activation of the acetylene unit may be important for imparting selectivity in favor of the Meyer–Schuster pathway. Recent advances in the Meyer–Schuster rearrangement can largely be traced to two innovations: (1) use of "soft" Lewis acid catalysts, which are thought to coordinate preferentially to the alkyne π-system rather than the oxygen atom lone pairs,[5] and (2) electronic activation of the acetylene to enhance coordination of the Lewis acid catalyst to the alkyne π-system.

This Perspective Article features recent advances in the Meyer–Schuster reaction, including several demonstrated techniques for improving the scope. Strengths and weaknesses of each technique are discussed, and outstanding problems that warrant further study are highlighted. The primary motivation for research and development of the Meyer–Schuster rearrangement is as a means of preparing α,β-unsaturated carbonyl compounds as part of a two-stage olefination strategy.

Olefination strategies

α,β-Unsaturated carbonyl compounds are commonly prepared by olefination reactions. Typical olefinations involve homologation of aldehydes or ketones using one of several addition/elimination strategies formally derived from the aldol condensation.[6]

The aldol condensation provides α,β-unsaturated carbonyl compounds from aldehydes or ketones with water as the only by-product, but harsh conditions and modest yields discourage its widespread use for the olefination of complex substrates. Designer reagents, often bulky organophosphorus compounds, generally offer superior results. Common olefination methods for the synthesis of α,β-unsaturated carbonyls include the Wittig,[7] Horner–Wadsworth–Emmons (HWE),[8] Horner–Wittig,[8] and Peterson[9] reactions. These methods involve milder conditions than does the simple aldol condensation and often provide higher yields of the desired α,β-unsaturated carbonyl compounds. However, these advantages over the simple aldol condensation come with the costs of requiring costlier reagents, of generating noxious waste by-products, and of high sensitivity to steric congestion around the aldehydes or ketone. In fact, homologation of hindered ketones to α,β-unsaturated carbonyl compounds poses synthetic challenges that typically cannot be overcome using phosphorus-based or other designer olefination reagents.

In contrast to the aforementioned addition/elimination strategies using designer olefination reagents, addition/*rearrangement* strategies involving alkynes offer the prospects of perfect reaction efficiency (as defined in atom economical terms) and broader scope (Fig. 4). Highly electron-rich alkynes (*i.e.*, ynolates,[10] ynamines,[11] and ynamides[12]) undergo a formal [2+2] cycloaddition with the carbonyl group to produce an oxetene intermediate, which then undergoes electrocyclic ring opening to give the homologated enoate, amide, or imide (Fig. 4a). Alternatively, terminal alkynes can participate in a two-step sequence of 1,2-addition to carbonyl groups to give a propargyl alcohol, followed by Meyer–Schuster rearrangement (Fig. 4b).[1] Advancements and projected future developments in the Meyer–Schuster rearrangement that enable the practical application of this strategy for the olefination of ketones and aldehydes are featured in this Perspective.

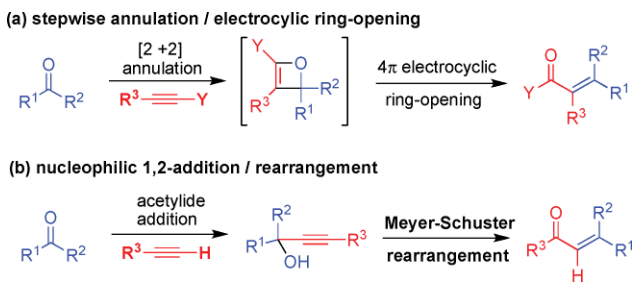


Fig. 4 Addition/rearrangement olefination strategies.

Recent advances in the Meyer–Schuster reaction

The title reaction was first reported by Meyer and Schuster in 1922; it was conducted in acidic media at elevated temperatures.[1a] The requirements of strong acid and high temperatures severely limited the scope of the Meyer–Schuster reaction. Substrates were confined to propargyl alcohols that lacked β-hydrogens. The

presence of β-hydrogens allowed for the Rupe rearrangement[4] (see Fig. 3, above), which generally took precedence over the Meyer–Schuster reaction.

The Meyer–Schuster rearrangement was thoroughly reviewed in 1971 as part of a larger discussion that focused primarily on the Rupe rearrangement.[1b] In recent years, however, interest in the Meyer–Schuster rearrangement has increased as new methods have emerged for promoting it selectively over the Rupe and other competing pathways.

Stoichiometric activation of the alkyne

Electron-donating groups can have a profound impact on the reactivity of π-systems.[13] The Dudley Lab reported in 2006 on the use of ethoxy-activated propargyl alcohols in the gold-catalyzed Meyer–Schuster rearrangement (Fig. 5).[14] The gold(III) catalyst is presumed to promote the reaction through an initial activation of the π-system of the alkyne.[15] Increasing the electron density of the π-system accelerates the transformation, likely by increasing the affinity of the alkyne for the soft alkynophilic catalyst.

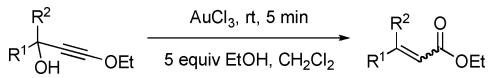
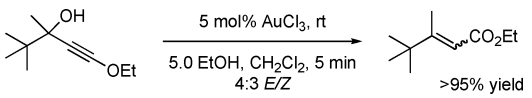


Fig. 5 Gold-catalyzed Meyer–Schuster rearrangement of ethoxyacetylene.

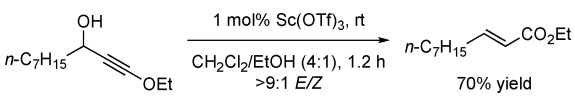
The combined use of oxygen-activated alkynes with alkynophilic catalysts expanded the scope of the reaction to a wider range of substitution patterns. Neither Rupe-type products nor other common side reactions were observed. Preparation of both di- and tri-substituted olefins is supported, and yields are generally excellent (70–99%) (Fig. 5). An attractive feature of these alkoxyacetylene rearrangements is that they can be performed open to air with wet solvents, without sacrificing yield, on a variety of substrates including aliphatic, aromatic, and hindered propargyl alcohols.[14]

Gold(III) chloride gave consistent results, but 5 mol% of the relatively expensive gold catalyst was required, and the catalyst provided little stereochemical control (Eqn 1).[14] The lack of stereochemical control was partially addressed by the use of a mixed catalyst system including Au(I), Ag(I), and 1 equivalent of CSA, which allowed for the preparation of a variety of disubstituted olefins with high (*E*)-selectivity.[16]



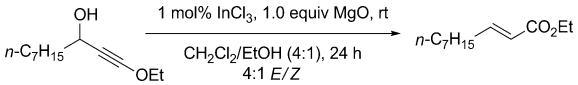
(1)

A screening of various Lewis acids revealed that the less expensive $Sc(OTf)_3$ could be substituted for the precious metal catalysts.[17] Not only did the use of $Sc(OTf)_3$ allow for a lower catalyst loading (1 mol%), it also proved adept in controlling the stereochemistry of the rearrangement (Eqn 2).



(2)

One other catalyst that bears mentioning is indium chloride. Although indium chloride is less reactive as a catalyst than scandium triflate, indium chloride is significantly cheaper, and it is effective as a catalyst even in the presence of basic additives (Eqn 3).[17] A vanadium oxide catalyst has also proven effective for the Meyer–Schuster rearrangement of ethoxyacetylene-derived propargyl alcohols.[18] Alternatively, Nishizawa and co-workers demonstrated the Hg(II)-catalyzed formation of α,β-unsaturated esters from secondary ethoxyalkynyl acetates (Eqn 4 and 5).[19]



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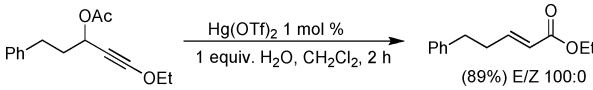
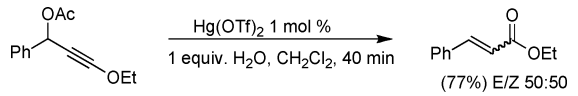
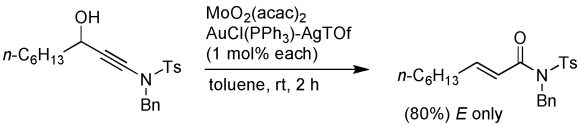


(4)



(5)

Other electron-donating heteroatoms, including sulfur[20] and nitrogen,[21] have been used to activate the π-system. α,β-Unsaturated thioesters have been synthesized by the lab of Kataoka and Yoshimatsu.[20] They were able to convert γ-sulfur-substituted propargyl alcohols to the Meyer–Schuster products using polyphosphoric acid trimethylsilyl ester, albeit in low yield with significant elimination to form enynes. Very recently, the first example of a Meyer–Schuster rearrangement to form an α,β-unsaturated amide was realized by the Akai lab, using a Mo/Au/Ag catalyst system (Eqn 6).[21] The Akai procedure is discussed in more detail in a later section.



(6)

Stoichiometric activation of the propargyl alcohol

Although not a Meyer–Schuster rearrangement in the traditional sense, propargylic acetates and other esters are primed for conversion to α,β-unsaturated carbonyl compounds. Propargyl acetates can undergo a 1,3-migration[22] of the acetate (Fig. 6), yielding Meyer–Schuster products after hydrolysis. Alternatively, a 1,2-migration[23] leads to metal carbenes, which have their own unique chemistry.

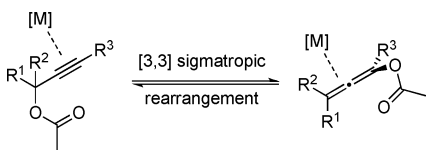
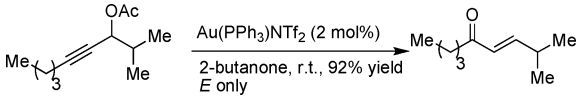


Fig. 6 Rearrangement of propargyl acetates.

Cationic gold catalysts have received attention for their exceptional ability to activate carbon–carbon triple bonds.[15] Zhang and co-workers exploited the affinity of gold salts towards acetylenic π-bonds to convert propargylic esters to α,β-unsaturated carbonyl derivatives at room temperature.[24]

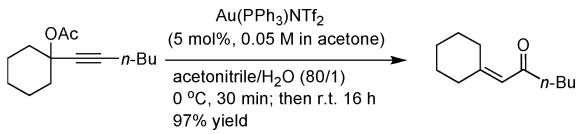
In the initial examination of the reaction, Zhang focused on optimization of the rearrangement of propargyl esters derived from aldehydes, because they were less likely to undergo elimination to form enynes than propargyl esters derived from ketones. A variety

of Au(I) and Au(III) catalysts were screened. $Au(PPh_3)NTf_2$ provided the best results, and all further studies were conducted with this catalyst. Optimization allowed for catalyst loading to be lowered to 2 mol%, without sacrificing yield or selectivity; in almost all reported cases complete (*E*)-selectivity was achieved (Eqn 7).[24]



(7)

Simple extension of these optimized reaction conditions to substrates derived from ketones was not practical, with elimination to form enynes and other side reactions being substantial. Diligent optimization was required before the method was extended to the preparation of β,β-disubstituted-α,β-unsaturated ketones (trisubstituted olefins). Catalyst loading had to be increased to 5 mol% and solvent conditions had to be carefully controlled† (Eqn 8). The limitation in Zhang's methodology is that it does not work for terminal alkynes, which readily undergo Markovnikov hydration under the reaction conditions.



(8)

The reaction is believed to proceed through a gold-catalyzed [3,3] rearrangement[22] of the propargylic ester (Fig. 7), followed by activation of the intermediate allene, giving rise to a vinylgold zwitterion. Hydrolysis and protiodeauration of the vinylgold zwitterion furnishes the Meyer–Schuster product. With a suitable electrophile present, the vinylgold intermediate could be trapped to yield a wide range of products including alkenyl enol esters/carbonates,[25] α-ylidene-β-diketones,[26] cyclopentenones,[27] indoline-fused cyclobutanes,[22a] α-ylidene-β-keto and -malonate esters,[28] indenes,[29] aromatic ketones,[30] and α-haloenones[31] (Fig. 7).

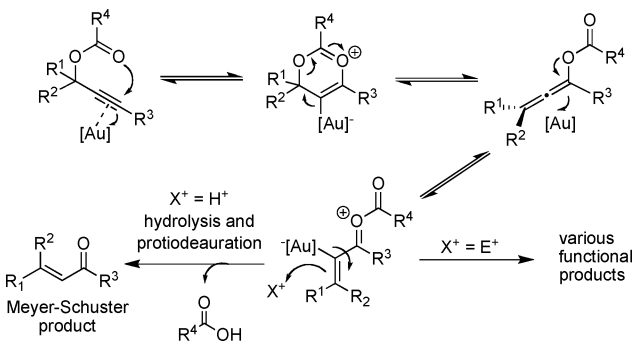
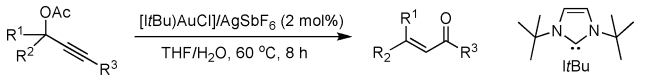


Fig. 7 Proposed mechanism for $Au(Ph_3P)NTf_2$-catalyzed rearrangement.

At the same time as Zhang's work, another gold-based catalyst system was being developed in the lab of Nolan. During their investigation of a Au(I)/Ag(I) catalyst system designed to achieve a tandem [3,3] sigmatropic rearrangement/intramolecular hydroarylation of phenyl-propargyl acetates yielding indenes,[29] Nolan and co-workers noticed Meyer–Schuster by-products when water was present in the reaction. Wishing to capitalize on this observation, the Nolan and Maseras labs modified the original Au(I)/Ag(I) catalyst system to convert a variety of propargyl acetates to their α,β-unsaturated carbonyl counterparts.[32] The optimal conditions were determined to be 2 mol% of both (I*t*Bu)AuCl and $AgSbF_6$, in a 10:1 THF/H_2O solvent system at 60 °C for 8 hours (Table 1).

Table 1 Selected examples of [(I*t*Bu)AuCl]/$AgSbF_6$ catalyzed rearrangement[a]



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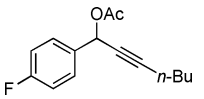
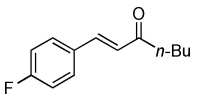
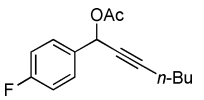
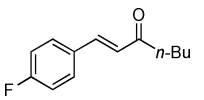
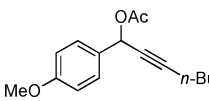
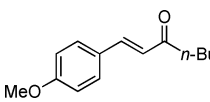
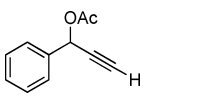
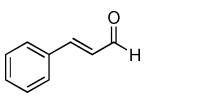
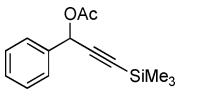
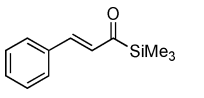
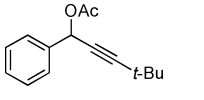
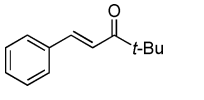
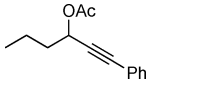
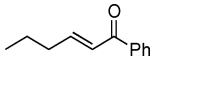
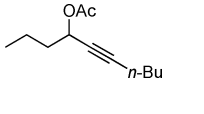
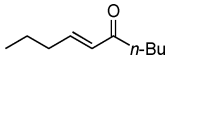
1			91
2[b]			90
3			89
4			90
5			nr
6			nr
7			82 (*E*:*Z*, 12:1)
8			94

[a] Reaction conditions: alkyne (1 mmol), [(I*t*Bu)AuCl]/$AgSbF_6$ (2 mol%), THF (10 mL), H_2O (1 mL). [b] Performed in a microwave at 80 °C, reaction time 12 min.

Nolan *et al.* found that these long reaction times could be avoided by the use of a microwave. Microwave irradiation at 80 °C allowed for the reaction to reach full conversion within 12 minutes, without any negative effect on yield or selectivity (entry 2). A variety of substituents at the propargylic position were tolerated, including electron-rich (entry 3) and electron-deficient (entry 1) aryl groups, as well as simple alkyl groups (entry 7). Alkyl and aryl substituents on the alkyne were also tolerated. Terminal alkynes (entry 4), which have proved to be poor substrates for other methods, could also be used. However, the use of substrates with bulky substituents, such as trimethylsilyl (TMS) and *tert*-butyl

† When 2-butanone was used as a solvent there was always competitive elimination. The use of acetonitrile as the solvent was believed to lessen the reactivity of $Au(PPh_3)NTf_2$ through solvent coordination with the catalyst.

(entries 5 and 6), resulted in no reaction. In most cases, excellent (*E*)-selectivity was observed (*e.g.* entry 7).[32]

Nolan and Maseras investigated the reaction mechanism both experimentally and computationally.[32] Based on their findings, they suggested a S_N2'-type displacement mechanism, instead of the more commonly suggested 1,3-shift of the propargyl acetate.[22] The gold catalyst was believed to activate water, instead of the π-system of the alkyne, to generate [(NHC)AuOH]. The AuOH complex acted as the active catalyst (Fig. 8).[32]

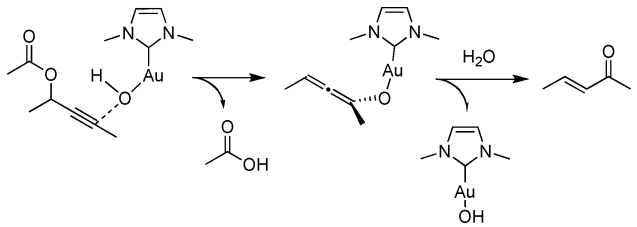


Fig. 8 S_N2'-type mechanistic pathway for the Meyer–Schuster reaction.

Although cationic gold is the most commonly used "soft" Lewis acid catalyst to achieve the Meyer–Schuster rearrangement, many other alkynophilic catalysts are also capable of catalyzing the rearrangement of propargyl acetates. During their investigation into the regioselective hydration of internal alkynes using a $Hg(OTf)_2$ catalyst, Nishizawa and co-workers attempted to influence the reaction site by using neighboring group participation.[33] They examined the reaction of the propargyl acetate shown in Fig. 9 in water with a catalytic amount of $Hg(OTf)_2$. Instead of obtaining the expected hydration products (α- and β-acetoxyketones), the major product was cyclohexylmethyl vinyl ketone. Trace amounts of the divinylmercury diketone were also present (Fig. 9).[32]

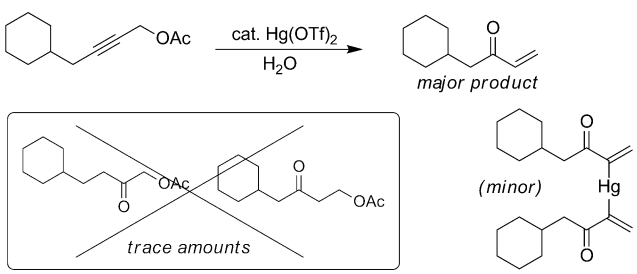
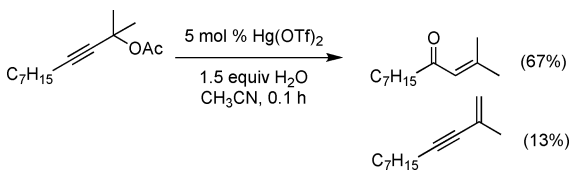


Fig. 9 Attempted acetate-directed regioselective hydration.

Based on the initial findings, the Nishizawa lab chose to optimize the reaction for the formation of α,β-enones. A screening process revealed the optimal conditions to be 5 mol% $Hg(OTf)_2$ with 1.5 equivalents of water in acetonitrile, at room temperature for 4 hours. Yields were generally moderate and side reactions could not be avoided[33] (Eqn 9). As mentioned in the previous section, the mercury-catalyzed rearrangement of secondary ethoxyalkynylmethyl acetates was also demonstrated.[19]



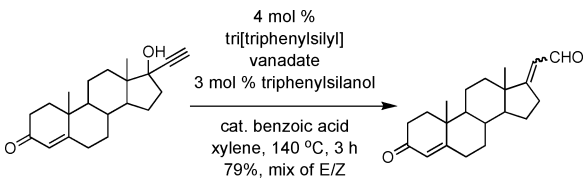
(9)

There are several examples of propargyl *ethers* (as opposed to esters) being successfully converted into α,β-unsaturated carbonyl compounds.[34] These processes typically involve hydration of the alkyne, followed by β-elimination of the ether alkoxide to generate the α,β-unsaturated carbonyl. Although the end result is the same, the reactions are not strictly Meyer–Schuster rearrangements, and they involve distinct synthetic challenges.

Catalytic activation of the propargyl alcohol

Much of the early work in the Meyer–Schuster rearrangement focused on catalytic activation of the hydroxyl group. Among the more effective methods were those that featured the use of metal oxides, with vanadium being among the first transition metals to show promise. Chabardes and Querou demonstrated that trialkyl orthovanadates could be used to prepare aliphatic α,β-unsaturated aldehydes from propargyl alcohols with a terminal alkyne.[35] While avoiding the need for strong acid, temperatures in excess of 140 °C were still necessary to promote rearrangement. At these high temperatures catalyst degradation was problematic.

Catalyst decomposition was partially addressed by Pauling and co-workers, who developed more stable tris[triarylsilyl] vanadates.[36] The tris[triarylsilyl] vanadate catalysts were also limited to the preparation of α,β-unsaturated aldehydes.[37] Catalyst stability was advanced further by the Vol'pin lab with the development of a polymeric silyl vanadate catalyst.[38] The polymeric catalyst showed much greater stability than its monomeric counterpart. The new catalyst allowed for lower catalyst loadings, but it did nothing to address the high temperature requirements. Despite its shortcomings, this novel vanadate chemistry was used by Hoffmann–La Roche in a variety of terpenoid syntheses[39] (Eqn 10).



(10)

The orthovanadate-catalyzed rearrangement is thought to proceed by formation of an intermediate vanadate ester (Fig. 10), which can then undergo a [3,3] sigmatropic rearrangement to give an allenyl vanadate ester. The allene then undergoes transesterification (hydrolysis) with tautomerization to the α,β-enone (Fig. 10).

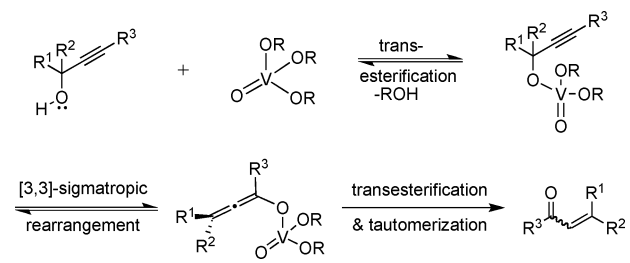


Fig. 10 Proposed mechanism of the orthovanadate-catalyzed reaction.

Attempting to expand the scope of this potentially useful reaction, Chabardes and co-workers performed a comprehensive study on the use of a variety of oxo derivatives of vanadium, molybdenum,[40] rhenium, and tungsten to catalyze the rearrangement.[41] Ultimately, low transformation rates and harsh reaction conditions limited the utility of the reaction.

The early oxovanadium work saw little use outside of the aforementioned industrial applications, until it was resurrected by Chung and Trost in 2006 (Fig. 11). They found that in the presence of suitable electrophiles (initial work focused on imines), the vanadium allene intermediate could be trapped to yield aldol-type products, instead of undergoing hydrolysis to the Meyer–Schuster products.[42]

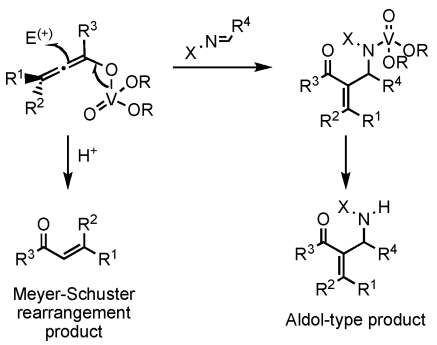
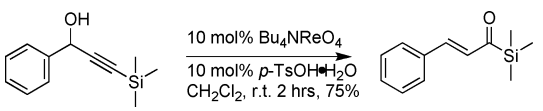


Fig. 11 Trapping of allenyl vanadate ester.

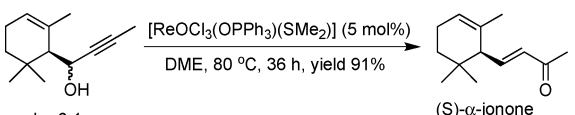
Other early catalyst systems that were explored to activate the propargyl alcohol included a Ti/Cu system[43] (which activated both the propargyl alcohol and the alkyne) and a vanadium-pillared montmorillonite system.[44] Both catalyst systems improved the yield and lowered the reaction time of the rearrangement, but neither addressed the high temperature requirements.

It was not until the development of a tetrabutylammonium perrhenate(VII)/*p*-toluenesulfonic acid catalyst system, in the early 1990's by the Narasaka Lab, that the rearrangement could be carried out at room temperature without sacrificing yield (Eqn 11).[45] An attractive feature of this catalyst system is its ability to generate α,β-unsaturated acylsilanes (Eqn 11) in addition to α,β-enones.



(11)

Recently, there has been a re-emergence in the use of high oxidation state metal-oxo complexes to catalyze the Meyer–Schuster rearrangement. In their investigation into the rhenium(V)-catalyzed nucleophilic substitution of propargyl alcohols, the Toste lab noticed the formation of Meyer–Schuster by-products.[46] Using this as a starting point, Vidari and co-workers developed an efficient rhenium(V)-oxo catalyst to effect the Meyer–Schuster rearrangement of both alkyl and aryl substituted alkynols[47] (Eqn 12).



(12)

The rhenium-catalyzed reactions proceeded with high (*E*)-selectivity, which can be attributed to the isomerization of the (*Z*)-isomer to the more stable (*E*)-isomer under the reaction conditions.‡ The conversion of terminal alkynes to the corresponding α,β-unsaturated enals was supported by this catalyst system. Due to the high oxophilicity of the rhenium catalyst, these reactions were performed under strictly anhydrous conditions. The ability of the rhenium catalyst to be recycled without loss of catalytic efficiency added to the appeal of the method.[47]

With the variety of methods available for its mild execution, the Meyer–Schuster rearrangement has been applied to the total synthesis of complex molecules.[48] A representative example can be found in efforts towards the total synthesis of the marine alkaloid chartelline A (Fig. 12).[48d] The Weinreb lab needed to olefinate a γ-lactam in the presence of a β-lactam, and they found that they could add lithio *tert*-butylacetylide chemoselectively to the γ-lactam, which set the stage for the rearrangement. Standard Meyer–Schuster conditions (*i.e.* acid) gave the α,β-unsaturated ketone, but the acidic conditions resulted in removal of the Boc protecting group. Gratifyingly, use of the milder tetrabutylammonium perrhenate/*p*-toluenesulfonic acid catalyst system developed by Narasaka *et. al.*[45] allowed for the rearrangement to take place in quantitative yield without loss of the Boc group (Fig. 12).[48d] Undoubtedly, the application of the Meyer–Schuster reaction to other total syntheses will soon follow.

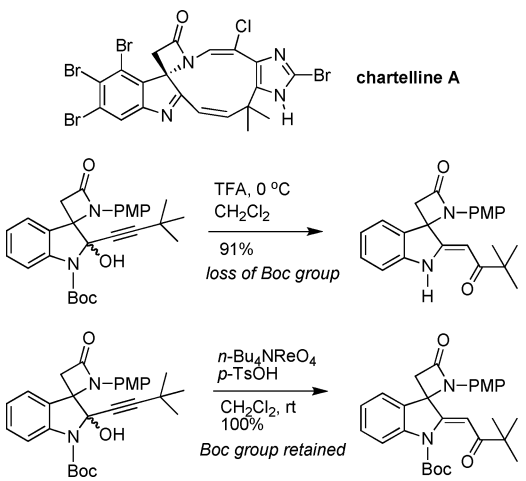


Fig. 12 Recent application in chemical synthesis.

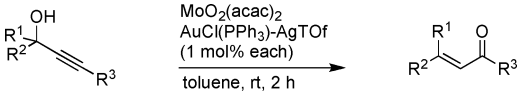
Transition metal oxo-complexes are thought to catalyze the Meyer–Schuster rearrangement through formation of the propargyl metal ester, which then undergoes rearrangement to an allenyl metal ester, followed by hydrolysis and tautomerization to furnish the α,β-unsaturated carbonyl and regenerate the catalyst (refer back to Fig. 10, earlier).

Despite impressive advances, the Rupe rearrangement[4] continues to interfere with this Meyer–Schuster pathway unless somehow restricted by the substrate. As discussed in an earlier section, one solution to this problem is to pre-functionalize the propargyl alcohol as a carboxylate ester, and then use a soft, alkynophilic metal salt to promote rearrangement selectively over elimination. For example, Nolan and co-workers reported gold-catalyzed rearrangements of propargyl acetates, providing Meyer–Schuster products *via* in situ hydrolysis of the allenyl acetate ester.[32]

The Nolan lab later extended this method to the preparation of α,β-unsaturated carbonyls from propargyl alcohols, eliminating the functionalization step, using a similar catalyst system.[49] High conversions were achieved for a variety of substrates; however,

‡ Vidari performed control experiments in which pure (*Z*)-isomer was fully converted to the (*E*)-isomer under the standard reaction conditions.

Table 2 Mo/Au Multi-catalyst system for the synthesis of α,β-unsaturated ketones



Entry	R^1	R^2	R^3	Time (h)	Isolated Yield (%)
1	H	H	$(CH_2)_2Ph$	0.5	93
2	H	H	*n*-C_7H_{15}	0.5	84
3	H	H	Ph	1	61
4	H	Me	*n*-C_6H_{13}	0.25	97 (*E*/*Z* 93:7)
5	Me	Me	Ph	2.5	90
6	Me	$Ph(CH_2)_2$	*n*-C_4H_9	2	94 (*E*/*Z* 67:33)

rearrangement of primary alcohols and terminal alkynes proved unsuccessful.[49]

Primary propargyl alcohols have proven to be very difficult substrates for the Meyer–Schuster reaction.[1b] To address this shortcoming in Meyer–Schuster methodology, Akai and co-workers developed a multi-catalyst system consisting of $MoO_2(acac)_2$, $AuCl(PPh_3)$ and AgOTf, which allowed for the Meyer–Schuster rearrangement to proceed smoothly under mild conditions.[21] Selected examples can be seen in Table 2.

Primary (entries 1–3), secondary (entry 4), and tertiary (entries 5–6) propargyl alcohols all rearrange smoothly and in high yield. The low reaction times, typically less than an hour, and the ability of the rearrangement to proceed at room temperature can be attributed to the double activation of the propargyl alcohol. The Au and Ag catalysts activate the alkyne π-system, while the Mo catalyst activates the alcohol.[15,40,41]

The Chung lab also reported converting propargyl alcohols into α,β-unsaturated ketones using a Au(I) catalyst system. Chung *et al.* screened a variety of Lewis acids including $FeCl_3$, $InCl_3$, $GaCl_3$, $PtCl_2$, Ag(OTf) and $AuCl_3$ before selecting $[Au(PPh_3)](OTf)$.[50] Yields were generally moderate, and side reactions such as the Rupe rearrangement[4] and enyne formation were problematic. Chung suggested a new mechanism for his Au(I) catalyst system featuring a cumulene intermediate, although it was purely speculative (Fig. 13).

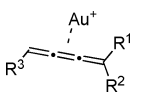


Fig. 13 Chung's postulated cumulene intermediate.

The conversion of propargyl alcohols with a terminal acetylene to α,β-unsaturated enals can be catalyzed by ruthenium complexes.[51] The requirement for terminal alkynes can be explained by the proposed mechanism. The reaction is a two step process. In the first step, a carboxylic acid is added to the alkyne, presumably through a Ru-vinylidene intermediate that can only be formed from a terminal alkyne. The resulting enol esters can be isolated or cleaved with acid to give Meyer–Schuster products (Fig. 14).

Metal oxide catalysis of the Meyer–Schuster rearrangement of unactivated propargyl alcohols has improved dramatically in recent years, but the substrate scope remains limited. Preactivation of the propargyl alcohol as an acetate ester is generally more reliable, but it requires the extra acylation step.

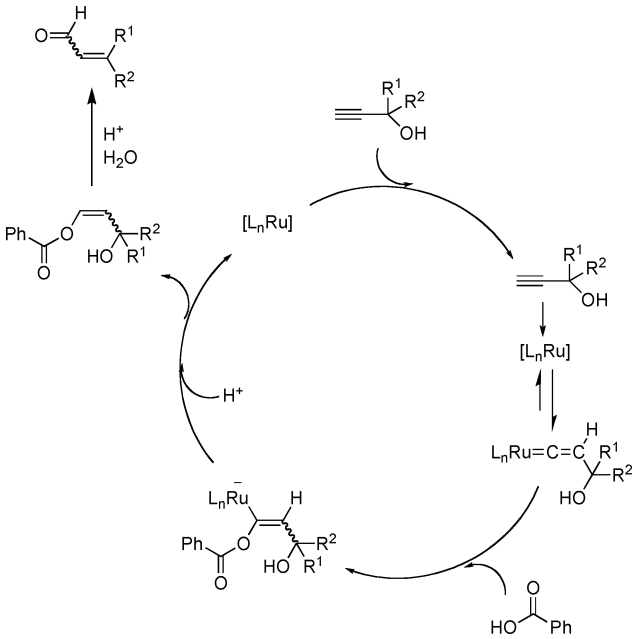


Fig. 14 Proposed mechanism of the Ru-catalyzed isomerization of propargyl acetates into α,β-unsaturated aldehydes.

The Yamada lab has shown that covalent activation of the propargyl alcohol as a carbonate and the rearrangement/hydrolysis sequence can be merged into a single operation using high-pressure carbon dioxide, base, and a silver catalyst[52] (Fig. 15). The propargyl carbonate, generated transiently in situ, undergoes silver-catalyzed rearrangement to an allenyl carbonate, which then releases carbon dioxide and tautomerizes to give the Meyer–Schuster product. The Yamada method is very attractive from a cost and atom economy perspective.

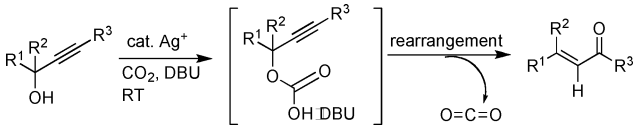


Fig. 15 Rearrangement of in situ-generated propargyl carbonate.

In conclusion, the Meyer–Schuster reaction has evolved from a simple acid-catalyzed rearrangement of tertiary ethynyl carbinols, into an elegant reaction whose reactivity can be precisely controlled by activation of the alcohol and alkynyl moieties independently or cooperatively. Once limited to the formation of α,β-unsaturated ketones and aldehydes that lack γ-hydrogens, recent advances have made general access to α,β-unsaturated esters,[14,33] amides,[21] thioesters,[20] and acylsilanes[45] a reality. Metal salts including Au, Ag, Cu, Ti, Re, V, Mo, W, and Ru have been used to achieve this transformation. The Meyer–Schuster reaction has found use in chemical synthesis.[48d,18,25-31] The variety of protocols now available to execute the Meyer–Schuster rearrangement will undoubtedly lead to an increase in the use of this powerful reaction.

The two-step olefination of ketones and aldehydes using the Meyer–Schuster rearrangement

The Dudley lab interest in the Meyer–Schuster reaction stemmed from the desire to identify and develop a way to olefinate hindered ketones (Fig. 16). As discussed in the previous section, classic olefination techniques such as the Wittig olefination,[7] the Horner–Wadsworth–Emmons (HWE) olefination,[8] and the aldol condensation[6] are sensitive to steric congestion and often fail to work on hindered ketones.

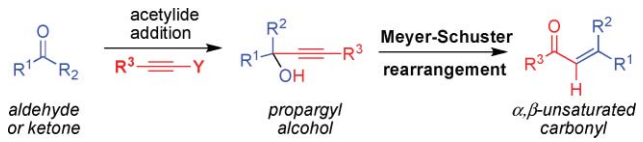


Fig. 16 Two-step olefination strategy.

We applied our Meyer–Schuster methodology as the second step of a two-step strategy for the olefination of aldehydes and ketones (Fig. 16).[14,17] The first step was acetylide addition to a carbonyl substrate. Acetylide addition is relatively insensitive to steric congestion, which allowed for the use of hindered ketones as substrates. Purification of the intermediate propargyl alcohol is not necessary and can be safely omitted. In fact, the use of the crude propargyl alcohol directly in the Meyer–Schuster rearrangement allowed for higher yields over the two steps and greatly reduced the time needed to complete the overall olefination.

Our initial report featured the use of gold(III) chloride to promote the Meyer–Schuster rearrangement, but the catalyst loading could not reliably be lowered below 5 mol%.[17] We later found that the use of 1 mol% of scandium(III) triflate in place of 5 mol% of the more expensive gold(III) chloride had no negative effect.[17] Yields were generally excellent for the two-stage olefination process (Table 3).

A series of trisubstituted olefins were prepared (entries 1–7) in good to excellent yield (Table 3). Although control of stereochemistry was limited (entries 1–2, 7), many of these substrates fall outside the scope of traditional olefination methods for the synthesis of α,β-unsaturated carbonyls. For example, the HWE olefination of menthone (cf. entry 1) has never been reported and was unsuccessful despite repeated attempts in our hands. Entries 1–4 illustrate the utility of this method for olefination of hindered ketones in excellent yields.

A nice feature of this strategy is that more hindered carbonyl compounds have shown to be *better* substrates for olefination using the Meyer–Schuster-based process. This qualitative observation is rationalized by recognizing that (1) acetylide addition is generally feasible across a wide range of hindered ketones, and (2) congested tertiary propargyl alcohols are primed for rearrangement to the α,β-unsaturated carbonyl products.[17]

The Meyer–Schuster-based olefination strategy is similarly effective for the preparation of disubstituted olefins (Table 3, entries 8–12). Excellent (*E*)-selectivity was achieved for aliphatic substituents (entry 8); however, selectivity diminished when aryl (entries 10–12) or vinyl (entry 9) substituents were introduced (exception is entry 12). Both electron-rich (entries 10 and 11) and electron-deficient (entry 12) aryl substituents at the propargyl position were tolerated.[17]

Future directions and challenges to be addressed in the Meyer–Schuster rearrangement

One of the major challenges in any olefination process is control of olefin geometry. Installation of (*E*) α,β-unsaturated carbonyls generally takes advantage of thermodynamic control, and the Horner–Wadsworth–Emmons[8] reaction typically provides good (*E*) selectivity in the olefination of aldehydes. Alternatively, the Still–Gennari modification[53] of the Horner–Wadsworth–Emmons olefination protocol provides (*Z*)-alkenes. Meyer–Schuster rearrangements that provide high (*E*)-selectivity are known, but (*Z*)-selective rearrangements remain elusive.

There may be opportunities to generate the contra-steric (*Z*) geometry by taking advantage of the presumed allene intermediate in the Meyer–Schuster rearrangement (Fig. 17). The diethoxyallene intermediate offers two alternative directions of approach for electrophiles (*e.g.*, H^+). Approach *syn* to the smaller (R^S) substituent places the carbonyl *cis* to the larger (R^L) substituent. If conditions were to be identified in which the stereochemistry-determining step is protonation of the allene, and if that protonation occurs through an early transition state that resembles the allene, then the α-hydrogen would be installed *syn* to the smaller β-substituent, leading to the (*Z*)-alkene. Other electrophiles (*i.e.*, metal salts) would be similarly suitable, so long as the vinylmetal intermediate could be protonated stereospecifically with retention of alkene geometry. We have seen preliminary indications of (*Z*)-selectivity in certain cases (*e.g.*, Table 3, entry 11), but the general factors have yet to be harnessed productively in the (*Z*)-selective Meyer–Schuster rearrangement.

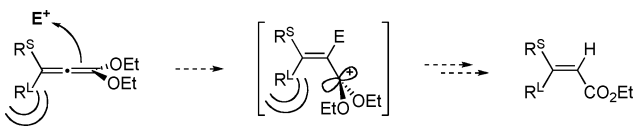
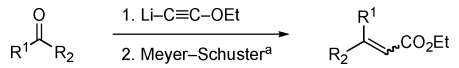


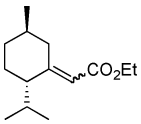
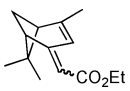
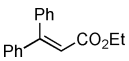
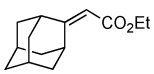
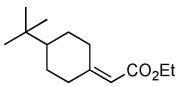
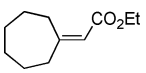
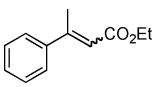
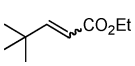
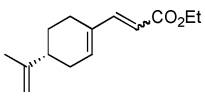
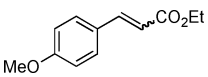
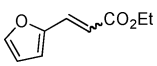
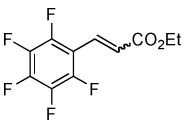
Fig. 17 Potential for *Z*-selective Meyer–Schuster rearrangement.

The scope and chemoselectivity of the Meyer–Schuster rearrangement are two areas in which great strides have been made in recent years, but more progress needs to be made. As the scope of the Meyer–Schuster reaction increases, so too does its appeal as part of a two-step olefination strategy for aldehydes and ketones. The strategy is further enhanced by new and improved methods for making propargyl alcohols by addition of terminal alkynes to carbonyls. Carreira and co-workers' catalytic asymmetric alkyne addition to aldehydes[54] is one such method, but enantiocontrol is not relevant in the Meyer–Schuster olefination strategy. Downey and co-workers recently reported simplified procedures for the zinc-catalyzed addition of terminal alkynes to aldehydes and ketones.[55] If successfully coupled with the Meyer–Schuster rearrangement of propargyl alcohols, then an atom-economical olefination protocol would emerge.

New bi-functional catalysts or multi-catalyst systems could lead to a one-pot, atom-economical olefination strategy based on the Meyer–Schuster rearrangement (Fig. 18). We showed in our recent study that the Lewis acid-catalyzed Meyer–Schuster rearrangement of ethoxyalkynyl carbinols occurs in the presence of Bronsted bases, albeit at a diminished rate.[17] Similar catalyst

Table 3 Two-stage olefination of ketones and aldehydes



Entry	Substrate	Product	Yield (%)[b]	*E*/*Z* Ratio[c]
1	(–)-menthone		98	n.d.[e]
2	verbenone		97	n.d.[e]
3	benzophenone		99	–
4	adamantanone		96	–
5	4-*tert*-butyl cyclohexane		60	–
6	cycloheptanone		78	–
7	acetophenone		93	39:61
8	pivaldehyde		80	*E* only
9	(–)-perillaldehyde		94	89:11
10	4-methoxybenzaldehyde		94	89:11[d]
11	2-furaldehyde		97	36:61[d]
12	pentafluorobenzaldehyde		80	*E* only

[a] 1 mol% $Sc(OTf)_3$, CH_2Cl_2/EtOH (4:1) [b] Isolated yield [c] Determined by ^1H NMR unless otherwise stated [d] *E* and *Z* isomers were isolated separately [e] Unable to determine the *E*/*Z* ratio by ^1H NMR

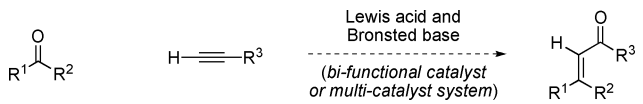


Fig. 18 One-pot, atom economical olefination strategy.

combinations promote alkyne addition to aldehydes and ketones. The foundation for atom economical Horner–Wadsworth–Emmons-type olefination reactions is in place, but has not yet been realized.

Conclusions

Recent advances in the Meyer–Schuster rearrangement are bringing this nearly forgotten process back to the fore. A SciFinder search in May 2009 on "Meyer–Schuster" resulted in 65 unique hits in the 84-year span of time from 1922 until 2005, inclusive (0.77 hits per year). From 2006 until 2008, however, SciFinder identified an additional 22 hits (7.3 hits per year). This acceleration serves as circumstantial evidence of a growing appreciation for the Meyer–Schuster rearrangement and its role in organic chemistry.

New applications are emerging at a steady pace. The presumed allene intermediate has been diverted in several productive directions, further increasing the value of efficient control over the Meyer–Schuster rearrangement pathway. The Meyer–Schuster-based olefination strategy is uniquely effective for many hindered ketones. With continued advances in the Meyer–Schuster rearrangement, the two-stage addition/rearrangement sequence may emerge as the method of choice for homologation of aldehydes and ketones into α,β-unsaturated carbonyls.

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