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Lewis acid-catalyzed Meyer–Schuster reactions: methodology for the olefination of aldehydes and ketones

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Abstract

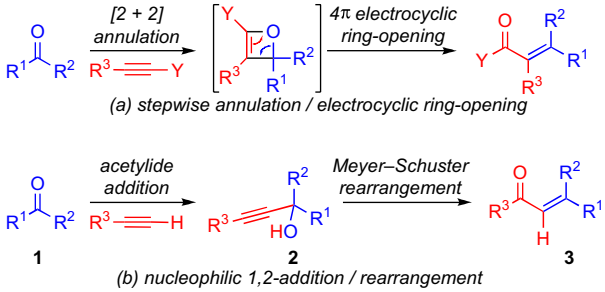
In principle, the most efficient and atom-economical means of converting an aldehyde or ketone into the homologated α,β-unsaturated ester is through addition/rearrangement sequences involving acetylenic π-bonds (Scheme 1). Implementation of such a strategy for the synthesis of α,β-unsaturated esters is presented: addition of ethoxyacetylene followed by scandium(III) triflate-catalyzed Meyer–Schuster rearrangement reaction. Stereoselectivities range from good to excellent in the formation of disubstituted α,β-unsaturated esters from aldehydes (Table 3). The two-stage olefination of even the most hindered ketones proceeds with near perfect efficiency (Table 4).

Keywords: Meyer–Schuster; Scandium(III) triflate; Ethoxyacetylene; Aldehyde; Ketone; Olefination

1. Introduction

The homologation of aldehydes and ketones to α,β-unsaturated esters, an indispensable tool for generating carbon–carbon bonds, is typically achieved using aldol condensation,[1] Wittig, Horner–Wadsworth–Emmons (HWE), or other olefination method.[2] Of these, the aldol condensation is most attractive from an atom economy[3] standpoint in that water is the only by-product, but Wittig or HWE reaction using stoichiometric phosphines, phosphine oxides, or phosphonates often provides higher yields of α,β-unsaturated ester products. Furthermore, these reactions produce phosphorus by-products that can interfere with the isolation of the desired products. Whether using designer olefination reagents or a traditional aldol condensation protocol, these homologation reactions are sensitive to steric congestion around the carbonyl, such that olefination of hindered ketones can be problematic.

In principle, an efficient and atom-economical means of converting an aldehyde or ketone into the homologated α,β-unsaturated ester is through addition/rearrangement sequences involving acetylenic π-bonds (Scheme 1). Realization of this strategy depends on the nature of the alkyne. Highly electron-rich alkynes (i.e., ynolates,[4] ynamines,[5] or ynamides,[6] Scheme 1a) react with carbonyl compounds via an annulation (formal [2+2] cycloaddition) process to produce an intermediate oxetene, which can undergo electrocyclic ring opening to produce the homologated enoate/amide. Notably, Shindo recently extended the use of ynolates to the homologation (olefination) of esters (Y=OLi, R^1=OR).[7]



Scheme 1. Atom-economical carbonyl olefination strategies.

Terminal alkynes offer an alternative addition/rearrangement pathway for the homologation of aldehydes and ketones that can be executed in the two-stage process outlined in Scheme 1b: (1) alkyne addition to the carbonyl and (2)

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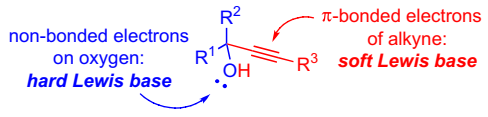


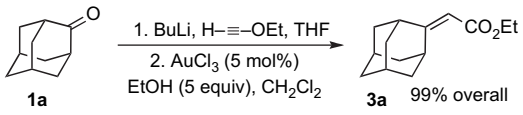
Figure 1. Lewis basic sites on a propargyl alcohol.

Meyer–Schuster rearrangement.[8] The strength of this latter approach stems from the use of acetylide nucleophiles to generate the initial carbon–carbon bond; acetylide nucleophiles are suitable for addition to even the most hindered of carbonyl systems. Therefore, step (1) of the two-step process is quite general. The Meyer–Schuster rearrangement, on the other hand, has received little attention[9] over the years due to the limited scope, harsh conditions, and the competing Rupe rearrangement pathway.[10]

Efficient methods for promoting Meyer–Schuster rearrangements thereby enable progress in the olefination of aldehydes and ketones, including hindered ketones that may not be suitable substrates for any of the other olefination strategies listed above. The recent emergence of 'soft' Lewis acids[11–13]—often late transition metal salts with an affinity for π-bonds over nonbonded electron pairs—brings attention to alternative Lewis basic sites (Fig. 1) and suggests the possibility of exploiting a previously unexplored mechanism for promoting the Meyer–Schuster rearrangement: activation of the propargylic alcohol via the alkyne π-bond rather than the hydroxyl group.[14]

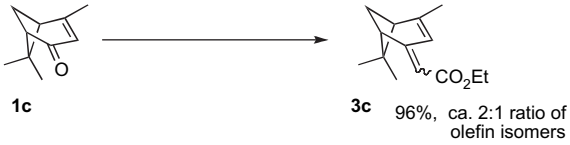
1.1. Gold-catalyzed Meyer–Schuster reaction of ethoxyalkynyl carbinols

In 2006, we reported gold-catalyzed Meyer–Schuster reactions of tertiary ethoxyalkynyl carbinols for the synthesis of α,β-unsaturated ethyl esters (Eqs. 1–3).[15,16] In conjunction with ethoxyacetylide addition to ketones, this work provided the blueprint for general implementation of the two-stage olefination strategy outlined above (**1**→**3**, R^3=OEt, Scheme 1b) for the synthesis of α,β-unsaturated esters.



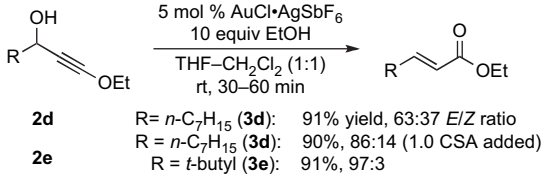
(1)

(2)



(3)

The combination of the electron-rich ethoxyacetylenic π-system and soft gold(III) chloride catalyst[17] provided excellent reactivity in the Meyer–Schuster reaction: consumption of the intermediate tertiary ethoxyalkynyl carbinols occurred within minutes of adding the catalyst. The Meyer–Schuster reactions were conducted open to the air without external heating or cooling. Yields for both the acetylide addition and the formal rearrangement[18] were essentially quantitative in the majority of cases, but stereocontrol of the olefin geometry was nonexistent. The second drawback of the reported conditions is the requirement for 5 mol % of the (expensive) gold catalyst. At 5 mol % catalyst loading, the reactions were complete within minutes, but at 1 mol %, the reaction failed to reach full conversion even after prolonged reaction times.[15]



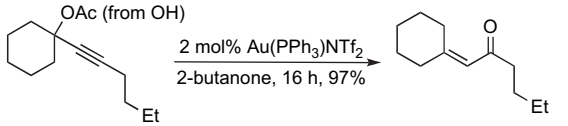
Scheme 2. Gold-catalyzed Meyer–Schuster reactions of secondary ethoxyalkynyl carbinols **2**.

Secondary ethoxyalkynyl carbinols could be converted into the corresponding ethyl *trans*-α,β-unsaturated esters with moderate to good stereocontrol using a mixed catalyst system of gold(I) chloride and silver(I) hexafluoroantimonate (Scheme 2); [19] inclusion of camphorsulfonic acid as a co-catalyst resulted in better selectivity for the trans isomer.

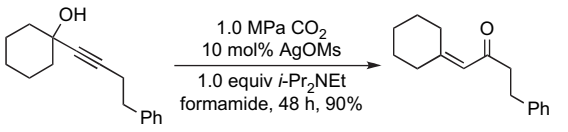
1.2. Recent advances in the Meyer–Schuster reaction

The last few years have seen a surge of interest in the Meyer–Schuster reaction.[20] Whereas our Laboratory has focused on electronically activated propargyl alcohols for the synthesis of α,β-unsaturated esters,[15,19] Zhang and co-workers reported a method for obtaining α,β-unsaturated ketones through independent activation of both of the aforementioned Lewis basic sites of electronically neutral propargyl alcohols (Eq. 4).[20d] They and others[20f] have shown that pre-activation of the hydroxyl group as an acetate ester followed by a gold-catalyzed hydrolysis process[21] of the propargyl acetate delivers Meyer–Schuster products.[22,23] The Yamada Lab used high-pressure carbon dioxide, base, and a silver catalyst to merge this multi-step process into a single operation (Eq. 5).[20i]

A major advantage of using the acetylide addition/Meyer–Schuster reaction strategy for the olefination of aldehydes and



(4)



(5)

ketones (see Scheme 1b, above) is the efficiency of the initial carbon–carbon bond-forming reaction: alkyne addition. However, the second stage of this strategy—the Meyer–Schuster reaction—is generally limiting. Therefore, advances in the Meyer–Schuster reaction translate directly into advances in olefination methods.

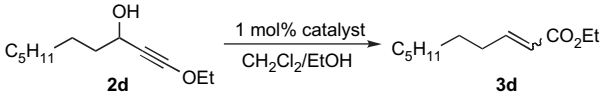
In summary, the emergence of late transition metal 'soft' Lewis acids has contributed to a renewed interest in the Meyer–Schuster reaction. Several tactics have been employed to broaden the scope of this reaction and minimize competing pathways like the Rupe rearrangement, and they all feature the use of late transition metal (gold, silver, and/or mercury) salts.

This paper describes recent advances in our methodology for the olefination of aldehydes and ketones using the Meyer–Schuster reaction of ethoxyacetylenes. Data and observations reported herein include (1) alternative catalysts that are more economical and widely available than gold or silver salts, (2) lower catalyst loadings than our previously reported methods using gold and silver salts, (3) excellent stereoselectivity in the formation of the *E*-alkene isomer for most disubstituted alkenes, and (4) new mechanistic data suggesting that the higher stereoselectivity associated with the new catalysts may stem from a subtle alteration of the reaction mechanism.

2. Results and discussion

The use of cationic gold and other precious metal catalysts offers many advantages in synthesis.[24] One of the general advantages of palladium, platinum, gold, and other precious metal catalysts is their ability to engage in redox chemistry through easy interconversion between oxidation states. In some cases, however, such as when specific π-Lewis acidity is desired, this versatility becomes unnecessary and can even be confounding with respect to understanding the reaction mechanism and predicting new reactivity. Furthermore, the high cost of precious metals places a premium on maximizing the number and frequency of catalyst turnovers.

Table 1
Screening of alternative catalysts



Entry	Catalyst	Time (h)	Conversion	*E*/*Z* Ratio[a]
1	CSA	24	0	—
2	$NiCl_2 \cdot xH_2O$	24	0	—
3	CuI	24	0	—
4	$Cu(OAc)_2$	24	Trace	n.d.
5	$CeCl_3 \cdot 7H_2O$	24	0	—
6	$HfCl_4$	24	Trace	n.d.
7	$ZrCl_4$	24	Trace	n.d.
8	$Cu(C_5H_4F_3O_2)_2$[b]	24	0	—
9	$Hg(CF_3CO_2)_2$	24	Trace	n.d.
10	$NaReO_4$	24	0	—
11	*$Cu(OTf)_2$*	*1.5*	*100%*	*89:11*
12	*$InCl_3$*	*24*	*100%*	*84:16*
13	$Ag(OTf)_2$	0.3	100%	43:57
14	$Pd(OAc)_2$	24	<100%[c]	63:37
15	*$Sc(OTf)_3$*	*1.2*	*100%*	*90:10*
16	$PtCl_4$	24	Trace	n.d.
17	$AuCl_3$	24	<100%[c]	>20:1

[a] As observed by ^1H NMR.
[b] Copper(II) trifluoroacetylacetonate.
[c] Ethoxyacetylene **2d** could be detected by TLC analysis but not by ^1H NMR after workup.

2.1. Alternative catalysts for the Meyer–Schuster reaction

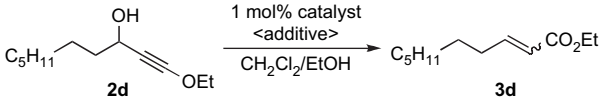
Under the hypothesis that late transition metal-catalysis of the Meyer–Schuster reaction of ethoxyalkynyl carbinols is strictly derived from Lewis acid/base interactions, we became interested in identifying similar (or better) catalytic activity in other Lewis acids. Table 1 provides a summary of our catalyst screenings, which focused primarily (though not exclusively) on soft transition metal salts.[16]

In an open reaction vessel, ethoxyacetylene **2d** was dissolved in methylene chloride and treated with reagent-grade ethanol (ca. 5–10 equiv) and 1 mol % of various Lewis acid catalysts (and one protic acid, camphorsulfonic acid, entry 1) at room temperature. Reactions were allowed to continue for up to 24 h or until TLC analysis indicated that no **2d** remained. The lone protic acid (CSA) is listed first; the rest of the table is arranged by the typical cost of the catalysts (per mole), from lowest to highest.

From this general catalyst screening emerged three top choices: copper(II) triflate, indium(III) chloride, and scandium(III) triflate. Of these, indium(III) chloride is the least reactive; the copper and scandium catalysts are comparable in reactivity. All three are air-stable powders and are convenient to handle and use.

Further information on these Lewis acid-catalyzed Meyer–Schuster reactions was gleaned by observing the effect of additives on the reaction rate (qualitatively) and stereoselectivity (quantitatively). Table 2 recounts the outcome of a small

Table 2
Effect of additives



Entry	Catalyst	Additive	Amount	Time (h)	*E*/*Z* Ratio[a]
1	*$InCl_3$*	*None*	—	*24*	*84:16*
2	$InCl_3$	CSA	1 mol %	6	67:33
3	$InCl_3$	DTBMP	1 mol %	24	75:25
4	$InCl_3$	AcOH	1.0 equiv	24	91:9
5	$InCl_3$	MgO	1.0 equiv	24	78:22
6	*$Cu(OTf)_2$*	*None*	—	*1.5*	*89:11*
7	$Cu(OTf)_2$	CSA	1 mol %	1.5	86:14
8	$Cu(OTf)_2$	DTBMP	1 mol %	24	76:24
9	$Cu(OTf)_2$	AcOH	1.0 equiv	<1	89:11
10	$Cu(OTf)_2$	MgO	1.0 equiv	24[b]	76:24
11	*$Sc(OTf)_3$*	*None*	—	*1.2*	*90:10*
12	$Sc(OTf)_3$	CSA	1 mol %	<1	92:8
13	$Sc(OTf)_3$	DTBMP	1 mol %	4	91:9
14	$Sc(OTf)_3$	AcOH	1.0 equiv	<1	92:8
15	$Sc(OTf)_3$	MgO	1.0 equiv	24[c]	n.d.

[a] As observed by ^1H NMR.
[b] Conversion (60%).
[c] Conversion (30%).

grid of reactions in which the three top Lewis acid catalyst choices were each coupled with two acidic and two basic additives: 1 mol % CSA, 1.0 equiv acetic acid (AcOH), 1 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), and 1.0 equiv magnesium oxide (MgO).

Studying the effect of additives aids in the identification of optimal conditions, and it provides insight into the reaction mechanism. Lewis and protic acids catalyze the Meyer–Schuster reaction, so one would expect acidic additives to accelerate the reaction and basic additives to quench or retard the reaction. This hypothesis is supported by the data presented in Table 2. However, the fact that basic additives retard *but do not quench* the reaction suggests that protic acid, though helpful, is not required for catalytic activity. Therefore, one can choose between a short reaction time (e.g., entries 9 or 14) and reaction conditions that are presumably free of protic acid (e.g., entry 5).

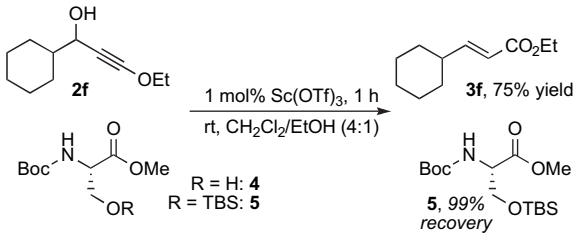
All of these experiments were conducted on an exploratory scale to gauge reactivity and selectivity. Because the scandium(III) and copper(II) catalysts in the absence of additives were significantly more reactive and slightly more selective than indium(III) chloride, the triflate salts were employed throughout the next stage of the methodology (Table 3).

2.2. Two-stage olefination of aldehydes and ketones

When performed immediately following addition of ethoxyacetylene to a carbonyl compound, the Meyer–Schuster reactions described above complete a two-stage olefination of aldehydes and ketones. Illustrative examples are presented in this section.

Scandium(III) and copper(II)-catalyzed Meyer–Schuster reactions of secondary and tertiary propargyl alcohols are shown in Table 3 (**2**→**3**). In all cases, both catalysts provided similar results, with scandium(III) triflate consistently (albeit perhaps insignificantly) out-performing copper(II) triflate. From an industrial perspective, the scarcity of scandium salts is off-set by the fact that scandium(III) triflate is water-soluble, recoverable after aqueous workup, and reusable without noticeable loss of activity.[25]

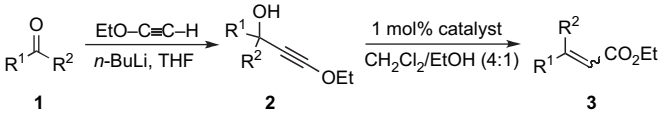
Entries 1–4 in Table 3 document the comparison between including ethanol as an additive (5 equiv, as in our earlier studies)[15,19] and employing ethanol as a co-solvent, which provided superior results under the current conditions (entries 3 and 4). Aliphatic substituents on the propargyl alcohols were universally tolerated, whether the substituent was linear (**2d**), branched (**2f**), or even quaternary (**2e**). Some erosion of stereoselectivity was observed in the benzylic case (**2g**→**3g**, entries 11 and 12). Entries 7–10 reveal that stereoselectivity was better for disubstituted alkenes than trisubstituted alkenes.



(6)

The experiment outlined in Eq. 6 provides insight into the compatibility of the Meyer–Schuster reaction conditions with common functionality. *N*-Boc-serine methyl ester (**4**) was converted into *tert*-butyldimethylsilyl (TBS) ether **5**, which was then included in the reaction mixture during the conversion of **2f** to **3f** (75% yield; cf. Table 3, entry 6). Recovery of **5** from this control experiment in 99% yield indicates that the present Meyer–Schuster reaction conditions will prove to be compatible with typical alkyl esters, amine carbamates, and silyl ethers.

Table 3
Scope and stereoselectivity



Entry	1	2 (Yield %)[a]	Catalyst	R^1	R^2	3	Yield (%)	*E*/*Z* Ratio[a]
1[b]	Octanal (**1d**)	**2d** (>99)	$Cu(OTf)_2$	*n*-Heptyl	H	**3d**	53	91:9
2[b]			$Sc(OTf)_3$				63	(*E* only)
3			$Cu(OTf)_2$				64	97:3
4			$Sc(OTf)_3$				70	(*E* only)
5	Cyclohexane-carboxaldehyde (**1f**)	**2f** (76)	$Cu(OTf)_2$	Cyclohexyl	H	**3f**	71	(*E* only)
6			$Sc(OTf)_3$				75	(*E* only)
7	Pivaldehyde (**1e**)	**2e** (97)	$Cu(OTf)_2$	*tert*-Butyl	H	**3e**	94	(*E* only)
8			$Sc(OTf)_3$				97	(*E* only)
9	Pinacolone (**1b**)	**2b** (83)	$Cu(OTf)_2$	*tert*-Butyl	Me	**3b**	86	57:43
10			$Sc(OTf)_3$				89	58:42
11	Benzaldehyde (**1g**)	**2g** (92)	$Cu(OTf)_2$	Phenyl	H	**3g**	90	76:24
12			$Sc(OTf)_3$				93	77:23

[a] As observed by ^1H NMR.
[b] EtOH (5.0 equiv) in CH_2Cl_2.

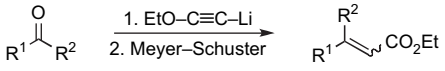
Given the dearth of methods suitable for the homologation of hindered ketones into α,β-unsaturated esters,[26] the two-stage acetylide addition/Meyer–Schuster strategy as applied to hindered ketones is particularly valuable. We earlier investigated the utility of gold(III) chloride (5 mol %) as a catalyst for such processes.[15] Table 4 illustrates that only 1 mol % of the less-expensive scandium(III) triflate provides similarly outstanding results: near-quantitative overall yield for the olefination of menthone (entry 1, **1h**→**3h**, 98%),[26] verbenone (entry 2, **1c**→**3c**, 97%), benzophenone (entry 3, **1i**→**3i**, 99%), and adamantanone (entry 4, **1a**→**3a**, 96%). Verbenone gave rise to **3c** as a 58:42 mixture of olefin isomers, whereas the isomeric mixture of esters **3h** could not be reliably estimated by ^{1}H NMR.

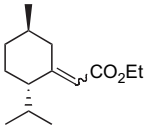
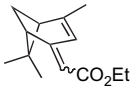
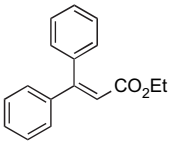
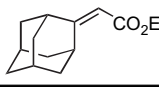
2.3. Mechanistic studies

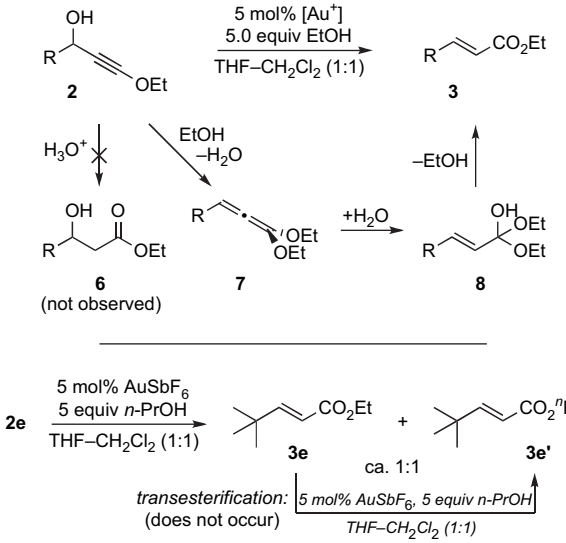
Earlier experiments in our Lab using gold and silver salts to catalyze the Meyer–Schuster reaction of ethoxyalkynyl carbinols support a mechanism in which the alcoholic additive included in the reaction mixture (i.e., ethanol) becomes incorporated into 50% of the product via an intermediate 1,1-diethoxy-allene (**7**, Scheme 3).[19] This gold-catalyzed reaction pathway is distinct from that of analogous reactions catalyzed by protic or hard Lewis acids,[16] which are known[16b,c] to produce β-hydroxy ester by-products (i.e., **6**) from initial hydration of the alkyne. β-Hydroxy esters (**6**) have not been observed in any of the Meyer–Schuster reactions catalyzed by soft Lewis acids in our study.

Perhaps the most compelling observation relevant to the mechanistic hypothesis laid out in Scheme 3 is that when *n*-propanol was used in place of ethanol, the resulting product

Table 4
Two-stage olefination of ketones

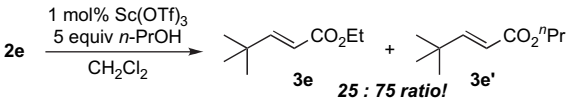


Entry	1	3		Yield (%)
1	Menthone (**1h**)		**3h**	98
2	Verbenone (**1c**)		**3c**	97
3	Benzophenone (**1i**)		**3i**	99
4	Adamantanone (**1a**)		**3a**	96

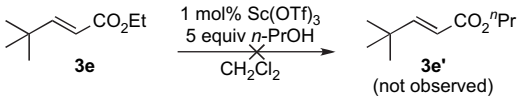


Scheme 3. Hypothesis and data on the mechanism of gold-catalyzed Meyer–Schuster reactions.[19]

mixture comprised ethyl and propyl esters in a roughly 1:1 ratio (**2e**→**3e**+**3e′**, Scheme 3).

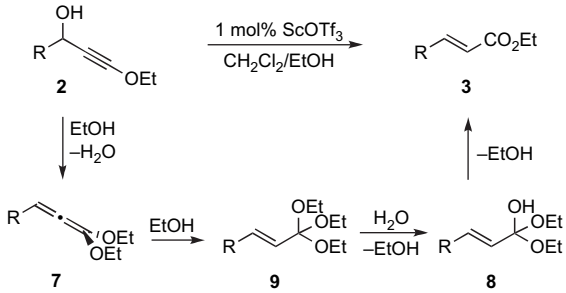


(7)



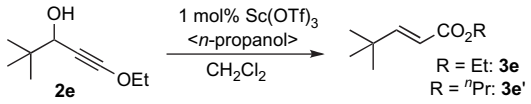
(8)

When this experiment was repeated on **2e** using scandium(III) triflate as the catalyst (Eq. 7), the ratio of ethyl to propyl esters (**3e**:**3e′**) was 25:75 (as estimated by ^{1}H NMR). In other words, there was only about 25% retention of the ethyl ester in the product mixture. According to the mechanism outlined in Scheme 3, however, the ethoxy group should be at least 50% retained, even at high levels of *n*-propanol. Transesterification does not occur under the reaction conditions (Eq. 8), so we conclude that the scandium(III) triflate-catalyzed reactions proceed by a slightly different mechanism than those catalyzed of cationic gold salts. One such potential mechanism is outlined in Scheme 4.



Scheme 4. Revised mechanistic hypothesis for scandium-catalyzed Meyer–Schuster reactions.

Table 5
Incorporation of the external alcohol additive into the product ester



Entry	PrOH (equiv)	**2e**:PrOH	**3e**:**3e′**[a]
1	1	50:50	55:45
2	2	33:67	42:58
3	3	25:75	38:62
4	5	17:83	25:75
5	10	9:91	22:78
6	100	1:99	16:84

[a] As observed by ^{1}H NMR.

Based on the consistent lack of β-hydroxy ester by-products (i.e., **6**), the scandium(III) triflate-catalyzed Meyer–Schuster reactions of secondary alcohols **2**[27] likely also proceed via intermediate 1,1-diethoxy-allene **7** (Scheme 4). Addition of a second equivalent of ethanol to allene **7** would give rise to *ortho*-ester **9**, which can then hydrolyze via **8** to reach the α,β-unsaturated ester (**3**). *ortho*-Ester intermediate **9** thus easily accounts for up to 67% incorporation of the alcohol additive, but we observed 75% (nearly statistical) incorporation of *n*-propanol in the experiment recounted in Eq. 7. This high level of incorporation can be explained by dynamic alcohol exchange reactions of *ortho*-ester **9**.

A series of experiments were conducted in which the incorporation of the alcohol additive (propanol) was tracked with respect to the amount of alcohol added (Table 5).[28] In each case, the ratio of propyl and ethyl esters (**3e**:**3e′**) was less than but close to statistical incorporation of propanol. These data are consistent with a hemi-labile intermediate (e.g., **9**) that can undergo partial equilibration before giving way irreversibly to the observed α,β-unsaturated ester (**3**).

An attractive feature of this mechanistic hypothesis is that it can account for the high stereoselectivity observed for the *E*-olefin isomer in the scandium(III) triflate-catalyzed Meyer–Schuster reactions of secondary alcohols.[27] Direct hydrolysis of allene **7** would most likely occur under kinetic control, whereas vinyl *ortho*-ester **9** provides the opportunity for thermodynamic establishment of olefin geometry using the exaggerated steric profile of *ortho*-ester **9**.

3. Conclusion

We have outlined and discussed a strategy for the olefination of aldehydes and ketones using the Meyer–Schuster reaction of ethoxyalkynyl carbinols. The method would appear to be limited only by the ability to access the requisite propargyl alcohols via ethoxyacetylide addition to carbonyls, and such reactions are known to be quite general. Stereoselectivities in the two-stage olefination of aldehydes range from good to excellent, whereas α,β-unsaturated esters derived from ketones are obtained with little to no stereocontrol. Nonetheless, it is for the olefination of ketones, especially hindered ketones, that this method is expected to be most useful.

Many different Lewis and protic acids catalyze Meyer–Schuster reactions of ethoxyacetylenes; Lewis acids that demonstrate an affinity for π-bonds were most effective in our methodology. After a detailed screening of many catalysts, we recommend scandium(III) triflate for the excellent reactivity and optimal stereoselectivity that it provides in the Meyer–Schuster reactions, even at low catalyst loading. This method is likely to find widespread application in organic synthesis, particularly for its unique ability to complete the olefination of hindered ketones in excellent yield.

4. Experimental section

4.1. General information

^{1}H NMR and ^{13}C NMR spectra were recorded on 300 MHz spectrometer using $CDCl_3$ as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to the residual $CHCl_3$ peak (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). The coupling constants (J) were reported in hertz (Hz). IR spectra were recorded on an FTIR spectrometer on NaCl discs. Mass spectra were recorded using chemical ionization (CI) or electron ionization (EI) technique. Yields refer to isolated material judged to be ≥95% pure by ^{1}H NMR spectroscopy following silica gel chromatography. All chemicals were used as received unless otherwise stated. Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were purified by passing through a column of activated alumina. The *n*-BuLi solutions were titrated with menthol dissolved in tetrahydrofuran using 1,10-phenanthroline as the indicator. The purifications were performed by flash chromatography using silica gel F-254 (230–499 mesh particle size).

4.2. General procedure for the preparation of ethoxyalkynyl carbinols (*1*→*2*)

To a THF solution (7 mL) of ethyl ethynyl ether (0.7 g, ca. 40% by weight in hexanes, ca. 9 mmol) was added *n*-BuLi (1.5 mL, 3.4 mmol, 2.3 M) 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. The solution was then recooled to −78 °C and pinacolone (**1b**, 0.30 mL, 2.4 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 h and held at room temperature for an additional 3 h. Saturated aqueous NH_4Cl solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography (gradient elution with 20:1 to 7:1 hexanes/ethyl acetate) to give 1-ethoxy-3-methyl-3-*tert*-butyl-1-propyn-3-ol (**2b**) in 83% yield (0.34 g).

4.2.1. 1-Ethoxy-3-methyl-3-tert-butyl-1-propyn-3-ol (**2b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.37 (t, J=7.1 Hz, 3H), 1.41 (s, 3H), 1.71 (s, 1H), 4.08 (q, J=7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 25.2, 25.6, 38.4, 41.9, 73.9, 74.2, 92.8; IR (neat) 3479, 2971, 2873, 2261, 1481, 1392, 1369, 1219, 1094, 1007, 908, 878 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{19}O_2$ ([M+H]$^+$) 171.1385. Found 171.1390.

4.2.2. 1-Ethoxy-dec-1-yn-3-ol (**2d**)

The title compound was prepared in a similar manner as described above (>99% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.90 (m, 3H), 1.21–1.46 (m, 10H), 1.37 (t, J=7.1 Hz, 3H), 1.56–1.70 (m, 3H), 4.09 (q, J=7.1 Hz, 2H), 4.39 (q, J=6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.2, 22.6, 25.3, 29.2, 29.2, 31.7, 38.7, 39.7, 62.4, 74.4, 93.6; IR (neat) 3381, 2927, 2263, 1722, 1467 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{22}O_2$ (M+H$^+$) 199.1698. Found 199.1692.

4.2.3. 1-Ethoxy-4,4-dimethyl-pent-1-yn-3-ol (**2e**)

The title compound was prepared in a similar manner as described above (97% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.38 (t, J=7.1 Hz, 3H), 4.03 (d, J=6.0 Hz, 1H), 4.10 (q, J=7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 25.2, 35.8, 38.0, 71.0, 74.3, 94.0; IR (neat) 3431, 2956, 2714, 2264, 1629 cm^{-1}; HRMS (EI) calcd for $C_9H_{16}O_2$ (M$^+$) 156.1150. Found 156.1103.

4.2.4. 1-Cyclohexyl-3-ethoxy-prop-2-yn-1-ol (**2f**)

The title compound was prepared in a similar manner as described above (76% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–1.3 (m, 6H), 1.38 (t, J=7.1 Hz, 3H), 1.57–1.84 (m, 6H), 4.10 (q, J=7.1 Hz, 2H), 4.18 (t, J=5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 25.9, 25.9, 26.4, 28.1, 28.6, 38.3, 44.6, 67.0, 74.5, 94.3; IR (neat) 3411, 2980, 2460, 1719, 1450 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{18}O_2$ (M+H$^+$) 183.1385. Found 183.1390.

4.2.5. 3-Ethoxy-1-phenyl-prop-2-yn-1-ol (**2g**)

The title compound was prepared in a similar manner as described above (92% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H), 2.02 (d, J=6.0 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 5.51 (d, J=6.0 Hz, 1H), 7.31–7.40 (m, 3H), 7.52–7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 38.8, 64.6, 74.8, 95.4, 126.5, 128.0, 128.5, 129.2; IR (neat) 3401, 2981, 2226, 1718, 1450 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{12}O_2$ (M$^+$) 176.0834. Found 176.0837.

4.3. General procedure for the preparation of α,β-unsaturated esters (**2**→**3**)

To a 4:1 v/v CH_2Cl_2/ethanol solution (10 mL) of 1-ethoxy-dec-1-yn-3-ol (**2d**, 0.10 g, 0.51 mmol) in an open flask was added $Sc(OTf)_3$ (2.5 mg, 0.005 mmol). Progress of the reaction was monitored by TLC analysis. After 1 h, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (hexanes/ethyl acetate, 50:1) to give ethyl (*E*)-dec-2-enoate (**3d**) in 70% yield (70 mg).

4.3.1. (E/Z)-3,4,4-Trimethyl-1-pent-2-enoic acid ethyl ester (**3b**)

The title compound was prepared in a similar manner as described above (89% yield, *E*/*Z* ratio, 58:42); ^{1}H NMR (300 MHz, $CDCl_3$, *E* isomer) δ 1.10 (s, 9H), 1.28 (t, J=7.1 Hz, 3H), 2.16 (br d, J=1.1 Hz, 3H), 4.14 (q, J=7.1 Hz, 2H), 5.74 (q, J=1.1 Hz, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, *Z* isomer) δ 1.20 (s, 9H), 1.28 (t, J=7.1 Hz, 3H), 1.84 (br d, J=1.3 Hz, 3H), 4.14 (q, J=7.1 Hz, 2H), 5.63 (q, J=1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, *E*/*Z* mixture) δ 14.1, 14.3, 15.1, 23.9, 28.5, 29.0, 36.4, 37.9, 59.4, 60.0, 112.9, 116.6, 158.5, 167.2, 167.5, 167.9; IR (neat, *E*/*Z* mixture) 2970, 2873, 1719, 1634, 1466, 1372, 1262, 1182, 1123, 1054, 868 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{18}O_2$ (M$^+$) 170.1307. Found 170.1306.

4.3.2. (E)-Dec-2-enoic acid ethyl ester (**3d**)

The title compound was prepared as described above (70% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–0.90 (m, 3H), 1.26–1.31 (m, 8H), 1.28 (t, J=7.1 Hz, 3H), 1.42–1.47 (m, 2H), 2.19 (ddd, J=14.6, 7.1, 1.2 Hz, 2H), 4.18 (q, J=7.1 Hz, 2H), 5.80 (br d, J=15.6 Hz, 1H), 6.96 (dt, J=15.6, 7.0 Hz, 1H).[29]

4.3.3. (E)-4,4-Dimethyl-pent-2-enoic acid ethyl ester (**3e**)

The title compound was prepared in a similar manner as described above (97% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.29 (t, J=7.1 Hz, 3H), 4.19 (q, J=7.1 Hz, 2H), 5.73 (d, J=15.9 Hz, 1H), 6.97 (d, J=15.9 Hz, 1H).[30]

4.3.4. (E)-3-Cyclohexyl-acrylic acid ethyl ester (**3f**)

The title compound was prepared in a similar manner as described above (75% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12–1.31 (m, 5H), 1.29 (t, J=7.1 Hz, 3H), 1.64–1.77 (m, 5H), 2.04–2.17 (m, 1H), 4.18 (q, J=7.1 Hz, 2H), 5.75 (dd, J=15.8, 1.4 Hz, 1H), 6.91 (dd, J=15.8, 6.7 Hz).[29]

4.3.5. (E/Z)-3-Phenyl-2-propenoic acid ethyl ester (**3g**)

The title compound was prepared in a similar manner as described above (93% yield, *E*/*Z* ratio, 77:23); ^{1}H NMR (300 MHz, $CDCl_3$, *E* isomer) δ 1.34 (t, J=7.1 Hz, 3H), 4.27 (q, J=7.1 Hz, 2H), 6.44 (d, J=16.0 Hz, 1H), 7.37–7.40 (m, 3H), 7.51–7.54 (m, 2H), 7.69 (d, J=16.0 Hz, 1H);[30] ^{1}H NMR (300 MHz, $CDCl_3$, *Z* isomer) δ 1.24 (t, J=7.1 Hz, 3H), 4.17 (q, J=7.1 Hz, 2H), 5.95 (d, J=12.6 Hz, 1H), 6.95 (d, J=12.6 Hz, 1H), 7.33–7.38 (m, 3H), 7.56–7.59 (m, 2H).[31]

4.4. General two-step procedure for the preparation of α,β-unsaturated esters (**1**→**3**)

To a THF solution (2.6 mL) of ethyl ethynyl ether (0.13 g, ca. 40% by weight in hexanes, ca. 2 mmol) was added *n*-BuLi (0.40 mL, 0.75 mmol, 2.0 M) 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. The solution was then recooled to −78 °C and 2-adamantanone (**1a**, 75 mg, 0.50 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 h and

held at room temperature for an additional 3 h. Saturated aqueous NH_4Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the concentrated mixture in an open flask were added CH_2Cl_2 (8 mL), absolute ethanol (2 mL), and $Sc(OTf)_3$ (2.5 mg, 0.005 mmol). After 6 h, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (hexanes/ethyl acetate, 50:1) to give adamantan-2-ylidene-acetic acid ethyl ester (**3a**) in 96% yield over two steps (106 mg).

*4.4.1. Adamantan-2-ylidene-acetic acid ethyl ester (**3a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J=7.1 Hz, 3H), 1.86 (br s, 6H), 1.93–1.96 (m, 6H), 2.43 (br s, 1H), 4.07 (br s, 1H), 4.13 (q, J=7.1 Hz, 2H), 5.58 (s, 1H).[32]

*4.4.2. (4,6,6-Trimethyl-bicyclo[3.1.1]hept-3-en-(2E/Z)-ylidene)-acetic acid ester (**3c**)*

Title compound was prepared in a similar manner as described above (97% yield); ^{1}H NMR (300 MHz, $CDCl_3$, minor isomer) δ 0.86 (s, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.40 (s, 3H), 1.68 (d, J=7.9 Hz, 1H), 1.90 (d, J=1.5 Hz, 3H), 2.20–2.45 (m, 1H), 2.53–2.63 (m, 2H), 4.08–4.20 (m, 2H), 5.32 (s, 1H), 7.13 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 0.84 (s, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.44 (s, 3H), 1.58 (d, J=8.8 Hz, 1H), 1.86 (d, J=1.4 Hz, 3H), 2.20–2.45 (m, 1H), 2.53–2.63 (m, 2H), 4.08–4.20 (m, 2H), 5.46 (s, 1H), 5.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, *E/Z* mixture) δ 14.3, 14.4, 21.7, 21.8, 23.2, 23.6, 26.4, 26.5, 37.5, 38.1, 45.3, 47.8, 48.2, 49.0, 49.1, 53.1, 59.2, 59.3, 107.6, 110.0, 117.6, 121.6, 156.9, 158.0, 159.6, 161.2, 166.8, 167.4; IR (neat) 2979, 2930, 2870, 1708, 1622, 1466, 1443, 1380, 1370, 1226, 1164, 1040, 874, 705 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{20}O_2$ (M^+) 220.1463. Found 220.1462.

*4.4.3. (2-Isopropyl-5-methyl-cyclohexylidiene)-acetic acid ethyl ester (**3h**)*

The title compound was prepared in a similar manner as described above (98% yield); ^{1}H NMR (300 MHz, $CDCl_3$, *E/Z* mixture, diagnostic peaks) δ 2.55 (ddd, J=12.9, 5.5, 1.5 Hz), 3.14 (dd, J=12.9, 4.3 Hz), 3.48–3.52 (m), 4.13 (q, J=7.1 Hz), 4.14 (q, J=7.1 Hz), 5.63 (br s); ^{13}C NMR (75 MHz, $CDCl_3$, *E/Z* mixture) δ 14.3, 18.1, 19.5, 20.5, 20.8, 21.8, 23.4, 26.1, 26.8, 27.0, 27.6, 30.4, 31.6, 33.6, 33.9, 35.4, 36.1, 40.0, 43.5, 50.8, 52.6, 55.9, 59.3, 59.4, 113.3, 116.3, 164.8, 167.1.

*4.4.4. Ethyl 3,3-diphenylpropenoate (**3i**)*

The title compound was prepared in a similar manner as described above (99% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J=7.1 Hz, 3H), 4.05 (q, J=7.1 Hz, 2H), 6.37 (s, 1H), 7.20–7.23 (m, 2H), 7.30–7.39 (m, 8H).[33]

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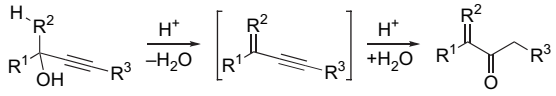

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26. For example, it was our inability to achieve Horner–Wadsworth–Emmons olefination reactions on either menthone (cf. **1h**→**3h**) or menthone derivatives that initially prompted our interest in Meyer–Schuster reaction methodology. For more information on the steric congestion of menthone derivatives, see: Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007**, *9*, 2839–2842.
27. The Meyer–Schuster reactions of tertiary alcohols **2** may take a different course. Further investigations are planned and will be communicated in due course.
28. Reactions conducted with less than a full equivalent of propanol were slow and inefficient, and are omitted from Table 5.
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