Synthetic Methods

DOI: 10.1002/anie.201106381

Heteropoly Compound Catalyzed Synthesis of Both *Z*- and *E*-α,β-Unsaturated Carbonyl Compounds

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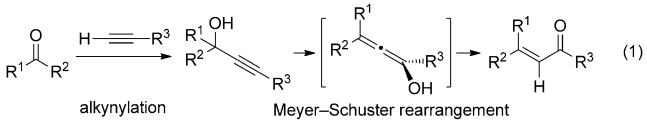
α,β-Unsaturated carbonyl compounds have proven to be versatile components, are present in abundant biologically active natural products, and widely used as intermediates for the manufacture of pharmaceuticals, cosmetics, and chemicals.[1] While various methods for their synthesis have already been reported, the development of a more practical method of preparation having high atom economy is increasingly desired. In this sense, particularly attractive is the 1,3-rearrangement of the readily available propargyl alcohols into α,β-unsaturated carbonyl compounds; the rearrangement is known as the Meyer–Schuster rearrangement.[2] Starting from the carbonyl compounds and the alkynes, the two-step reaction sequence shown in Equation (1) is fascinating because it produces a smaller amount of waste materials, whereas the well-known Wittig and Horner–Wadsworth–Emmons olefinations are inevitably accompanied by the discharge of an equimolar amount of phosphorous by-products.



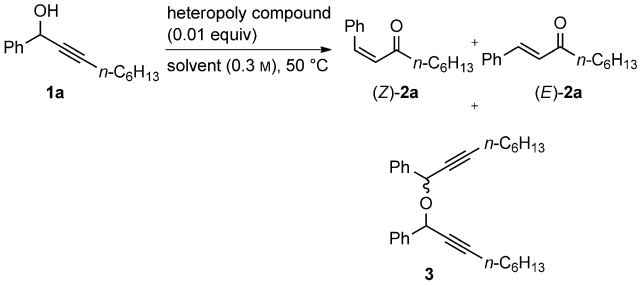
(1)

The Meyer–Schuster rearrangements have traditionally required strong acidic media and elevated temperatures, both of which often result in the formation of a mixture of *E* and *Z* stereoisomers. More recently, the catalysts that include transition metals, such as Au, Re, and Ru, have been shown to be useful for the synthesis of the thermodynamically more stable *E* isomers.[3,4] We also demonstrated an effective method using the combination of oxo-Mo and cationic Au catalysts.[5] In contrast, there have been few effective catalytic systems for the preparation of the less stable *Z* isomers.[6] Therefore, the stereocontrol of the C=C bond still remains a challenge of the Meyer–Schuster rearrangement.

Interestingly, heteropoly acids and their salts have attracted much attention in the fields of chemistry, biology, and materials science.[7] One of the most common heteropoly acids is the Keggin-type compounds with the general formula $H_n[XM_{12}O_{40}]$ in which X is the central heteroatom and M is the addenda atom. They possess a strong acidity and redox properties, both of which can be tuned by simply changing the cationic moiety and the polyanion chemical composition. In addition, they are generally recognized as clean and safe catalysts because of their nontoxicity, high stability, and easy handling. We sought to take advantage of the modular nature and steric effect of these catalysts to promote the 1,3-rearrangement of the propargyl alcohols. We now describe that the heteropoly compounds afford a new entry to both the *Z*- and *E*-configured α,β-unsaturated carbonyl compounds from the same propargyl alcohols.[8] The especially highly selective synthesis of the thermodynamically less stable *Z* isomers under heating conditions is worth noting.

The catalytic applicability of the commercially available $H_3[PMo_{12}O_{40}]\cdot n\,H_2O$ to the Meyer–Schuster rearrangement was initially examined. The reaction of **1a** with $H_3[PMo_{12}O_{40}]\cdot n\,H_2O$ (0.01 equiv) in EtOAc proceeded within 6 hours to afford an 89% yield of the desired enone **2a** and the complete preference for the *E* isomer was observed (Table 1, entry 1). More surprisingly, when using a sodium salt of the same heteropoly acid, (*Z*)-**2a** was obtained in better than a 4:1 ratio with its *E* isomer (entry 2). This remarkable

Table 1: Screening of heteropoly compounds for the Meyer–Schuster rearrangement of **1a**.



Entry	Heteropoly compound[a]	Solvent	*t* [h]	Yield [%][b] (*Z*)-**2a**	(*E*)-**2a**	**3**
1	$H_3[PMo_{12}O_{40}]$	EtOAc	6	<1[c]	89[c]	0
2	$Na_3[PMo_{12}O_{40}]$	EtOAc	5	67	16	0
3	$Na_4[SiMo_{12}O_{40}]$	EtOAc	5	no reaction		
4	$Na_3[PW_{12}O_{40}]$	EtOAc	5	0	0	70
5	$K_3[PMo_{12}O_{40}]$	EtOAc	5	54	14	18
6	$Cs_3[PMo_{12}O_{40}]$	EtOAc	5	12	1	17
7	$Ag_3[PMo_{12}O_{40}]$	EtOAc	3	66	18	0
8	$Ag_3[PMo_{12}O_{40}]$	acetone	1.5	79	17	0
9	$Ag_3[PMo_{12}O_{40}]$	acetone[d]	1	88[c]	8[c]	0

[a] Using the hydrate of the heteropoly compound. [b] Yield determined by NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. [c] Yield of isolated product. [d] Conducted at a concentration of 0.05 M.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106381.

change in the stereochemistry stimulated us to study the *Z*-selective synthesis of the unsaturated carbonyl compounds. Catalyst screening led to the finding that $[PMo_{12}O_{40}]^{3-}$ was superior to $[SiMo_{12}O_{40}]^{4-}$ and $[PW_{12}O_{40}]^{3-}$ as an anionic moiety to produce a better yield of (*Z*)-**2a** (entries 2–4). In contrast, the $Na_3[PW_{12}O_{40}]\cdot n H_2O$-catalyzed reaction did not afford **2a**, but instead the dimeric ether **3** (entry 4). Among the various cations, a silver salt exhibited higher reactivity and *Z* selectivity (entries 2, and 5–7). The reaction of **1a** with $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ in EtOAc gave (*Z*)-**2a** in 66% yield (NMR spectroscopy); furthermore, the use of the same silver salt in acetone dramatically improved both the yield and the stereoselectivity (entries 7–9).[9]

Under the optimal reaction conditions, we subsequently examined the reactions of a series of secondary propargyl alcohols **1b–g** (Table 2). Using 0.01 equivalents of $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ in acetone (method A), (*Z*)-**2b–g** were selectively prepared in all cases. The tendency of the transformation into *Z* isomers was found to depend on the electronic nature of the aryl substituent at the propargyl position (Table 2, entries 1 and 3 and Table 1, entry 8). Especially, the reaction of **1b**, having an electron-donating group, smoothly proceeded at room temperature within 1 hour to give (*Z*)-**2b** in 90% yield (Table 2, entry 1). Particularly noteworthy is the high *Z* selectivity and chemical yield obtained with **1e**, having a sterically demanding *tert*-butyl group, even though it took longer to complete the reaction. In contrast, the use of $H_3[PMo_{12}O_{40}]\cdot n H_2O$ in EtOAc (method B) for the same substrates **1b–d** allowed the exclusive formation of (*E*)-**2b–d** (entries 2, 4, and 6).

On the basis of several experiments mentioned below, the unprecedented *Z* selectivity can be accounted for by the characteristic bulkiness and acidity of the heteropoly compounds. First, monitoring the reaction of **1a** with $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ by ^1H NMR spectroscopy revealed that (*Z*)-**2a** formed about ten times more quickly than (*E*)-**2a** (Figure 1). Although a large amount of the dimer **3** was

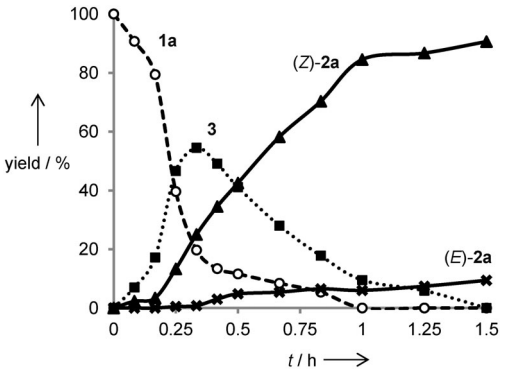


Figure 1. Reaction profile as a function of time for the rearrangement of **1a** using $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$. ○: **1a**, ×: (*E*)-**2a**, ▲: (*Z*)-**2a**, ■: **3**.

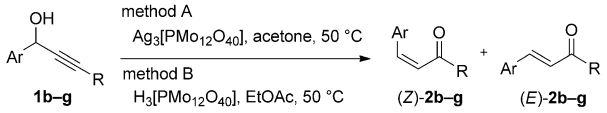
generated at the beginning of the reaction, **3** was found to react with $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ under the same conditions to preferentially afford (*Z*)-**2a** [(*Z*)-**2a**/(*E*)-**2a** ≈ 10:1].[10] We also observed a similar selective formation of (*Z*)-**2a** with $Na_3[PMo_{12}O_{40}]\cdot n H_2O$ as the catalyst. It is worth noting that even $H_3[PMo_{12}O_{40}]\cdot n H_2O$ preferentially generated (*Z*)-**2a** at an early stage of the reaction.[11] Therefore, it is clear that regardless of the kind of counter cation, the heteropoly compound catalyzed rearrangement initially gives (*Z*)-**2**.

Second, in these reactions, it was speculated that the allenolates are initially generated by the 1,3-shift of the hydroxy group of **1**, similar to the conventional Meyer–Schuster rearrangements.[2,4a,b] The stereochemistry of the protonation of the allenolates directly reflects the *Z*/*E*-selectivity of the products **2**. Zimmerman and Pushechnikov reported on the protonation of the allenolate **5**, which is generated from **4** and Bu_4NF, with varous proton sources and found that the bulkiness of the acid had little effect on the stereoselectivity (Scheme 1).[12] In contrast, we found that a similar reaction using $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ achieved a high *Z* selectivity to give a 8.2:1 mixture of (*Z*)- and (*E*)-**2f**. A similar reaction in acetone at 50 °C, using the conditions of method A, produced (*Z*)-**2f** with even higher selectivity (*Z*/*E* = 11.6:1). These results indicate that there is a potential influence of heteropoly compounds as a sterically demanding proton source. It is noteworthy that in spite of reacting at 50 °C, our developed reaction afforded the products with high *Z* selectivities.

Finally, we disclose that the $H_3[PMo_{12}O_{40}]\cdot n H_2O$-catalyzed formation of (*E*)-**2** arose from the isomerization of the primary product (*Z*)-**2**. Actually, a catalytic amount of $H_3[PMo_{12}O_{40}]\cdot n H_2O$ promoted the double bond isomerization of (*Z*)-**2a** into (*E*)-**2a** in EtOAc (Table 3, entry 1), whereas similar treatment of (*Z*)-**2a** with $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ in acetone (entry 3) or without any heteropoly acid in EtOAc retained its stereochemistry (entry 2).

In conclusion, we have demonstrated the stereoselective preparation of both the *Z*- and *E*-α,β-unsaturated ketones by simply changing the cationic moiety of the heteropoly compounds. The use of $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ preferentially produced the

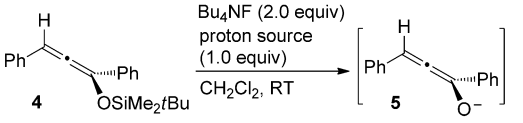
Table 2: Heteropoly compound catalyzed rearrangement of **1b–g** into (*Z*)- and (*E*)-**2b–g**.



1b–g (*Z*)-**2b–g** (*E*)-**2b–g**

Entry	Substrate			Method[a]	*t* [h]		Yield [%][b]	
		Ar	R				*Z*	*E*
1[c]	**1b**	4-MeC_6H_4	*n*-C_6H_{13}	A	1	**2b**	90	8
2[c]	**1b**	4-MeC_6H_4	*n*-C_6H_{13}	B	72	**2b**	1	85
3	**1c**	4-ClC_6H_4	*n*-C_6H_{13}	A	3.5	**2c**	69	11
4	**1c**	4-ClC_6H_4	*n*-C_6H_{13}	B	6	**2c**	1	86
5	**1d**	Ph	Me	A	1.5	**2d**	74	9
6	**1d**	Ph	Me	B	5	**2d**	1	80
7	**1e**	Ph	*t*Bu	A	24	**2e**	79 ($Z/E = 93:7$)[d]	
8	**1f**	Ph	Ph	A	5	**2f**	83 ($Z/E = 80:20$)[d]	
9	**1g**	Ph	1-cyclohexenyl	A	0.33	**2g**	57 ($Z/E = 93:7$)[d]	

[a] Method A: $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ (0.01 equiv), 0.05 M in acetone, 50 °C; method B: $H_3[PMo_{12}O_{40}]\cdot n H_2O$ (0.01 equiv), 0.3 M in EtOAc, 50 °C. [b] Yield of isolated product. [c] Conducted at room temperature. [d] The products were obtained as an inseparable mixture of *Z* and *E* isomers.



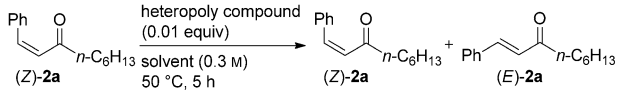
Proton source	Z/E ratio
$Ag_3[PMo_{12}O_{40}]\cdot n H_2O$	8.2 (11.6)[a]
AcOH[12]	2.3
PivOH[12]	2.8
2,6-di-*tert*-butyl-4-methylphenol[12]	2.8
iPr_2NH_2Cl[12]	4.2

(*Z*)-**2f** + (*E*)-**2f**

[a] Run in acetone at 50 °C.

Scheme 1. Effect of $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ on protonation of allenolate **5**.

Table 3: Influence of heteropoly compounds on isomerization of (*Z*)-**2a** to (*E*)-**2a**.



Entry	Heteropoly Compound	Solvent	Yield [%][a]	
			Z	*E*
1	$H_3[PMo_{12}O_{40}]\cdot n H_2O$	EtOAc	4	80
2	None	EtOAc	92	0
3[b]	$Ag_3[PMo_{12}O_{40}]\cdot n H_2O$	acetone	97	2

[a] Yield determined by NMR spectroscopy using 1,4-dimethoxybenzene as the internal standard. [b] Conducted for 1.5 h.

thermodynamically unfavorable *Z* isomers, whose practical synthesis has been limited.[13] To the best of our knowledge this is the first successful transformation of propargyl alcohols into the *Z*-α,β-unsaturated ketones through the Meyer–Schuster rearrangement. It was suggested that the heteropoly compounds could serve not only as an acidic catalyst, but also as a bulky proton source. Because of the facile access to the propargyl alcohols through the additions of alkynes to carbonyl compounds, the two-step process is highly atom economical and produces a reduced amount of waste materials. Additional investigation of the detailed effects of the heteropoly compounds on the reaction and a practical extension of this method is now in progress.

Experimental Section

Procedure for the preparation of $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$: $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ was prepared by a minor modification of Haasnoot's method.[14] To a stirring solution of $H_3[PMo_{12}O_{40}]\cdot n H_2O$ (1.00 g, 0.55 mmol) in water (1.0 mL) was dropwise added a solution of $AgNO_3$ (279 mg, 1.64 mmol) in water (1.0 mL). A yellow precipitate was immediately formed, and separated by centrifugation and washed with acetone. After drying in vacuo at room temperature overnight, $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ (539 mg, 46%) was obtained. The main element contents were analyzed by ICP-AES. Found: Ag 13.9 wt%; P 1.37 wt%; Mo 50.0 wt%. The atom ratio of Ag:P:Mo is equal to 3:1:12.

Rearrangement of propargyl alcohols **1** into α,β-unsaturated ketones **2**:

Z isomer: $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ (5.4 mg, 0.0025 mmol) was added to a solution of the propargyl alcohols **1** (0.25 mmol) in acetone (5.0 mL, 0.05 M). The reaction mixture was stirred at 50 °C or room temperature until complete consumption of both **1** and the dimer **3**, and then quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, usually hexanes/EtOAc = 30:1) to give (*Z*)-**2** and (*E*)-**2**, unless otherwise noted.

E isomer: $H_3[PMo_{12}O_{40}]\cdot n H_2O$ (4.6 mg, 0.0025 mmol) was added to a solution of the propargyl alcohols **1** (0.25 mmol) in EtOAc (0.80 mL, 0.3 M). The reaction mixture was stirred at 50 °C until complete consumption of (*Z*)-**2**, and then quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, usually hexanes/EtOAc = 30:1) to give (*E*)-**2**.

Received: September 8, 2011
Published online: October 25, 2011

Keywords: heteropoly compounds · olefination · alcohols · rearrangements · synthetic methods

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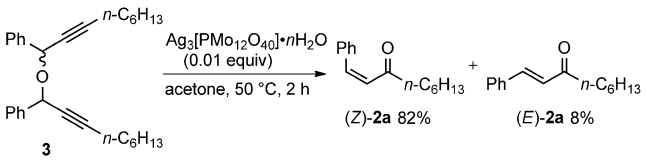
[9] For more information, see the Supporting Information.
[10] The reaction of the dimer **3** with $Ag_3[PMo_{12}O_{40}]\cdot n H_2O$ proceeded within 2 h to give (*Z*)-**2a** (82%) and (*E*)-**2a** (8%).



[11] For the detailed time-course of the rearrangement of **1a** using either $H_3[PMo_{12}O_{40}]\cdot n H_2O$ or $Na_3[PMo_{12}O_{40}]\cdot n H_2O$. See the Supporting Information.
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