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Mo−Au Combo Catalysis for Rapid 1,3-Rearrangement of Propargyl Alcohols into α,*β*-Unsaturated Carbonyl Compounds

Masahiro Egi, Yoshiko Yamaguchi, Noboru Fujiwara, and Shuji Akai*

School of Pharmaceutical Sciences, University of Shizuoka, 52-1, Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan

akai@u-shizuoka-ken.ac.jp

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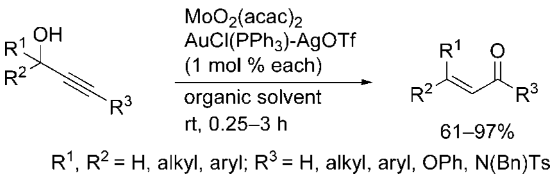
ABSTRACT

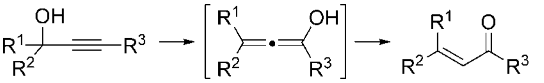


The combination of Mo and cationic Au catalysts dramatically accelerated the rearrangement of diverse propargyl alcohols, which includes a short reaction time, mild conditions, and high product yields. A practical application to the highly challenging primary propargyl alcohols and the *N*-alkynyl amides is achieved.

α,*β*-Unsaturated carbonyl compounds are versatile intermediates for the synthesis of biologically active natural products, pharmaceuticals, agrochemicals, and other useful materials. One of the main methods to prepare such compounds is the 1,3-rearrangement of propargyl alcohols, which is known as the Meyer−Schuster rearrangement (Scheme 1).[1]

Especially, due to its high atom economy, extensive efforts have been devoted to the development of efficient catalysts. Protic and Lewis acids have been widely utilized; however, they often showed low selectivities leading to poor yields.[1a,c] Such rearrangements were better catalyzed by transition metals, such as oxovanadium,[2] oxomolybdenum,[3] and Ti(O-Bu)$_4$/CuCl,[4] which required elevated temperature (>100 °C). Although nBu$_4$NReO$_4$ was employed to catalyze the reaction under milder conditions, the relatively high loading of the catalyst was used and dehydrated compounds were produced as side products.[5] The rearrangements were also mediated by Ru complexes, which went through a mechanism different than that of the above-mentioned acid- or transition-metal-catalyzed reactions;[6] however, the Ru-assisted rearrangement required 50−100 °C and acidic conditions which often led to poor yields of the products. Very recently, the transformations mediated by Au[7] and Ag[8] at room temperature have been published. Nonetheless, there is yet no adequate or

Scheme 1. The 1,3-Rearrangement of Propargyl Alcohols (the Meyer−Schuster Rearrangement)



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(3) Lorber, C. Y.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 853.

(4) Mercier, C.; Chabardes, P. *Pure Appl. Chem.* **1994**, *66*, 1509.

(5) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059.

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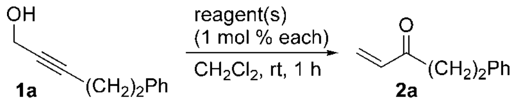
practical method used for the primary alcohols. On the other hand, the rearrangement of the corresponding propargyl esters has also been investigated.[1b] While Zhang's group developed Au-catalyzed reactions under mild conditions, which gave good yields of the products,[9] Nishizawa and co-workers demonstrated an example of the efficient 1,3-rearrangement of the primary propargyl esters using $Hg(OTf)_2$.[10] However, the 1,3-rearrangement of the propagyl alcohols is still more advantageous from the perspective of the atom economy and synthetic aspects. Herein, we describe a novel and practical method by the combined use of Mo, Au, and Ag compounds, which dramatically accelerates the 1,3-rearrangement even at room temperature and affords a diverse range of α,β-unsaturated carbonyl compounds in good to excellent yields.

First, to develop a more effective catalytic system, a highly challenging primary propargyl alcohol **1a** was used as the substrate. When the rearrangement of **1a** was carried out in CH_2Cl_2 at room temperature for 1 h, no observable reaction occurred in the presence of only the Mo, Au, or Ag catalyst (entries 2−4, Table 1). Moreover, all combinations of two catalysts among them afforded no or poor yields of the desired compound **2a** (entries 5−7). However, in stark contrast, the use of all these catalysts showed a significant improvement in the rate and the yield of **2a**. That is, the reaction was completed within 1 h to provide **2a** in 92% yield (entry 1). Subsequently, the effect of each metal catalyst on this reaction was further surveyed. Among a variety of oxo-metal compounds and gold catalysts, $MoO_2(acac)_2$ and $AuCl(PPh_3)$ were determined to be the most effective for generating **2a**. No significant difference in efficiency was noted among the silver catalysts such as AgOTf, $AgClO_4$, $AgBF_4$, and $AgPF_6$, all of which produced **2a** in NMR yields between 84 and 92%. The screening of solvents also revealed that toluene and CH_2Cl_2 showed comparable effects, although toluene was somewhat superior (99% as measured by NMR).

Table 1. Preliminary Survey for the Rearrangement of **1a**[a]



entry	$MoO_2(acac)_2$	$AuCl(PPh_3)$	AgOTf	NMR yield (%)[b]
1	+	+	+	92
2	+	−	−	0
3	−	+	−	0
4	−	−	+	0
5	+	+	−	4
6	−	+	+	25
7	+	−	+	0

[a] +: with, −: without. [b] NMR yield using 1,1,2,2-tetrachloroethane as the internal standard.

Next, the reactivity of diverse propargyl alcohols was tested using the combination of 1 mol % each of $MoO_2(acac)_2$, $AuCl(PPh_3)$, and AgOTf in toluene at room temperature. The results are depicted in Table 2. Our protocol showed an excellent generality and provided good to excellent isolated yields of unsaturated ketones **2a**−**n** from primary, secondary, and tertiary propargyl alcohols **1a**−**n**. The time required to reach completion was typically less than 1 h, while 3 h was sufficient for the less reactive tertiary substrates **1i**−**m**. Furthermore, the oxidation of a hydroxyl group did not occur at all.[3] Even in the case when the catalyst loading was reduced to 0.5 mol %, excellent yields were obtained, although a slightly longer reaction time was needed (entries 2 and 4). Besides, the rearrangement of secondary propargyl alcohols **1d**−**g** produced β-monosubstituted compounds **2d**−**g** with a high *E*-selectivity (entries 6−9). Entries 1, 3, 5, 7, 11, and 14 show that the yields are higher and the times are shorter than the reactions conducted with $Hg(OTf)_2$,[10a] AgOMs,[8] $NaAuCl_4{\cdot}2H_2O$,[7a] or Bu_4NReO_4.[5] It is notable that our method has an advantage over the previous applications, especially for the primary propargyl alcohol.

The developed method was also useful for the rearrangement of the propargyl alcohols bearing proton **1o**−**p**, oxygen **1q**−**r**, and nitrogen groups **1s** at the end of the acetylene functionality to give the α,β-unsaturated aldehydes **2o**,**p**, the phenyl esters **2q**,**r**,[11] and the amide **2s**, respectively. In these cases, the choice of a proper solvent brought about high yields of the products. To the best of our knowledge, this is the first example of the 1,3-rearrangement of the *N*-alkynyl amide, and **2s** was produced with complete *E*-selectivity. The substrates (**1o** and **1p**) were conveniently prepared by the reaction of carbonyl compounds with ethynylmagnesium bromide. Similarly, the preparation of **1q**−**s** was also effectively achieved by the reaction of the lithiated phenoxyacetylene **3a**[12] or the lithiated N-substituted ynamine **3b**[13] with aldehydes or ketones (Table 3).

α,β-Unsaturated aldehydes, esters, and amides have so far been synthesized by the aldol condensation,[14] Wittig and Horner−Wadsworth−Emmons reactions,[15] and Peterson reaction.[16] For the aldol reactions, either an acidic or a basic catalyst was required, and self-condensation often

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(6) (a) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Tetrahedron Lett.* **2002**, *43*, 7531. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J. *Adv. Synth. Catal.* **2006**, *348*, 101.

(7) (a) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (b) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949. (c) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, 2107.

(8) Sugawara, Y.; Yamada, W.; Yoshida, S.; Ikeno, T.; Yamada, T. *J. Am. Chem. Soc.* **2007**, *129*, 12902.

(9) (a) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147. (b) Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth. Catal.* **2007**, *349*, 871. (c) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585.

(10) (a) Imagawa, H.; Asai, Y.; Takano, H.; Hamagaki, H.; Nishizawa, M. *Org. Lett.* **2006**, *8*, 447. (b) Nishizawa, M.; Hirakawa, H.; Nakagawa, Y.; Yamamoto, H.; Namba, K.; Imagawa, H. *Org. Lett.* **2007**, *9*, 5577.

(11) We found that the rearrangement of the corresponding ethoxyethynyl derivative using AgOTf (1 mol %) alone was completed at room temperature for 0.5 h; however, that of **1q** with AgOTf (2 mol %) alone gave **2q** in less than 5% NMR yields. Thus, the trimetallic catalytic system was revealed to be highly effective for less activated alkynes. For details, see Supporting Information.

(12) Brückner, D. *Synlett* **2000**, 1402.

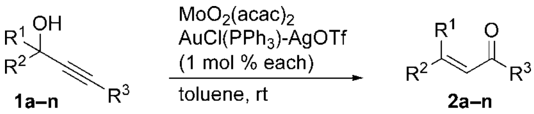
(13) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

(14) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon, Oxford, **1991**; Vol. 2, p, 133.

(15) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(16) Ager, D. J. *Org. React.* **1990**, *38*, 1.

Table 2. Mo−Au Combo Catalysis for Rearrangement of **1** into α,*β*-Unsaturated Ketones **2**

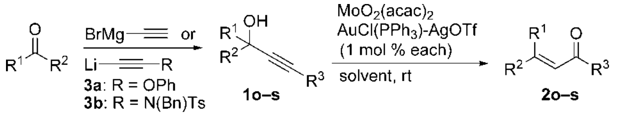


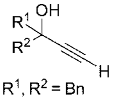
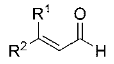
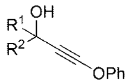
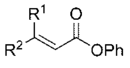
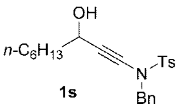
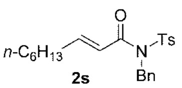
entry	substrate 1				time (h)	product 2	
		R^1	R^2	R^3		isolated yield (%)	
1	**1a**	H	H	$(CH_2)_2Ph$	0.5	**2a**	93
2[a]	**1a**	H	H	$(CH_2)_2Ph$	2	**2a**	92
3	**1b**	H	H	n-C_7H_{15}	0.5	**2b**	84
4[a]	**1b**	H	H	n-C_7H_{15}	1	**2b**	87
5	**1c**	H	H	Ph	1	**2c**	61
6	**1d**	H	Me	n-C_6H_{13}	0.25	**2d**	97 (*E*/*Z* 93:7)
7	**1e**	H	$Ph(CH_2)_2$	n-C_4H_9	0.25	**2e**	94 (*E*/*Z* 93:7)
8	**1f**	H	Ph	n-C_6H_{13}	0.5	**2f**	86 (*E*/*Z* 97:3)
9	**1g**	H	Me	Ph	1	**2g**	88 (*E*/*Z* 82:18)
10	**1h**	Me	Me	n-C_7H_{15}	0.5	**2h**	92
11	**1i**	Me	Me	Ph	2.5	**2i**	90
12	**1j**	Bn	Bn	Me	1.5	**2j**	91
13	**1k**	Me	t-C_4H_9	n-C_4H_9	3	**2k**	88 (*E*/*Z* 75:25)
14	**1l**	Me	$Ph(CH_2)_2$	n-C_4H_9	2	**2l**	94 (*E*/*Z* 67:33)
15	**1m**	$-(CH_2)_5-$		n-C_6H_{13}	1.5	**2m**	88
16	**1n**	$-(CH_2)_6-$		Me	0.5	**2n**	94

[a] Using 0.5 mol % each of the Mo, Au, and Ag catalysts.

occurred, providing poor yields of the products, while all the remaining above-mentioned olefination reactions are accompanied with the discharge of an equimolar amount of phosphorus or silicon compounds. In addition, few direct approaches to prepare unsaturated aldehydes have been reported.[17] In contrast, Table 3 presents another promising method that features the two-step synthesis of the unsaturated carbonyl compounds (**2o−s**) from the carbonyl compounds and the production of smaller amounts of waste materials.

Table 3. Two-step Preparation of α,*β*-Unsaturated Aldehydes, Esters, and Amide from Carbonyl Compounds



entry	product 1	yield 1 (%)	product 2	time (h)	yield 2 (%)
					
1	**1o**: R^1, R^2 = Bn	92	**2o**: R^1, R^2 = Bn	1	92[a]
2	**1p**: R^1 = Me, R^2 = $Ph(CH_2)_2$	82	**2p**: R^1 = Me, R^2 = $Ph(CH_2)_2$	3	83[a,b] (*E*/*Z* 63:37)
					
3	**1q**: R^1, R^2 = n-C_4H_9	82	**2q**: R^1, R^2 = n-C_4H_9	0.5	81[c]
4	**1r**: R^1 = H, R^2 = c-C_6H_{11}	84	**2r**: R^1 = H, R^2 = c-C_6H_{11}	0.25	87[c] (*E*/*Z* 92:8)
5	 **1s**	66	 **2s**	2	80[d] (*E* only)

[a] Run in CH_2Cl_2. [b] Run at 35 °C using $MoO_2(acac)_2$ (5 mol %), $AuCl(PPh_3)$ (1 mol %), and AgOTf (1 mol %). [c] Run in acetone. [d] Run in toluene.

In conclusion, we have disclosed that the combination of 1 mol % each of $MoO_2(acac)_2$, $AuCl(PPh_3)$, and AgOTf provides a highly powerful catalytic system for the rapid 1,3-rearrangement of propargyl alcohols.[18] The reactions proceed at room temperature within 1 h in most cases to afford a variety of α,*β*-unsaturated carbonyl compounds in excellent yields. Especially, it is noteworthy that it is applicable to primary propargyl alcohols and *N*-alkynyl amides as the substrate. Although we have not yet conducted detailed mechanistic studies, we consider a synergetic mechanism in

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[17] In general, α,*β*-unsaturated aldehydes are synthesized by a few reaction steps; viz., the reaction of carbonyl compounds with $(EtO)_2POCH_2CO_2Et$ or $(EtO)_2POCH_2CN$, followed by reduction (and oxidation). For the recent use of this approach, see: (a) Hong, B.-C.; Tseng, H.-C.; Chen, S.-H. *Tetrahedron* **2007**, *63*, 2840. (b) Maddess, M. L.; Tackett, M. N.; Watanabe, H.; Brennan, P. E.; Spilling, C. D.; Scott, J. S.; Osborn, D. P.; Ley, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 591. Alternative condensation reactions using acetaldehyde equivalents have also been developed; however, they produce wastes and/or byproducts. (c) Cabezas, J. A.; Oehlschlager, A. C. *Tetrahedron Lett.* **1995**, *36*, 5127. (d) Mahata, P. K.; Barun, O.; Ila, H.; Junjappa, H. *Synlett* **2000**, 1345.

[18] Typical Experimental Procedure: $MoO_2(acac)_2$ (2.1 mg, 0.0063 mmol), $AuCl(PPh_3)$ (3.1 mg, 0.0063 mmol), and AgOTf (1.6 mg, 0.0063 mmol) were added in this order to a solution of 5-phenyl-2-pentyn-1-ol **1a** (0.10 g, 0.63 mmol) in toluene (1.6 mL) at room temperature. The reaction mixture was stirred for 30 min and then quenched with saturated aqueous NH_4Cl. The organic materials were extracted with Et_2O, and the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/Et_2O 10:1) to give 5-phenyl-1-penten-3-one **2a** (93 mg, 93%) as a colorless oil.

which a cationic Au catalyst, generated from AuCl(PPh_3) and AgOTf, activates the acetylene bond, while $MoO_2(acac)_2$ isomerizes the propargyl alcohol via the rearrangement of an intermediate molybdate. Further developments of this method and elucidation of the mechanism are now in progress in our laboratory.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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