Atom Economy. Aldol-Type Products by Vanadium-Catalyzed Additions of Allenic Alcohols and Aldehydes

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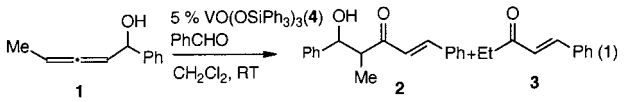
Increasing our repertoire of simple addition reactions will improve synthetic efficiency.[1] The importance of aldol products led us to consider nonconventional ways for their creation by simple additions.[2,3] The 1,3-transposition of allylic and propargylic alcohols have been widely studied and are catalyzed by a wide variety of oxo metal complexes including those derived from vanadium,[4] molybdenum,[5] tungsten,[6] and rhenium.[7] Surprisingly, the corresponding 1,3-transposition of the readily available allenic alcohols has been virtually ignored. The ready availability of allenols, such as by the LAH reduction of the mono THP ethers of butyne-1,4-diols, makes such a strategy very attractive.[10]

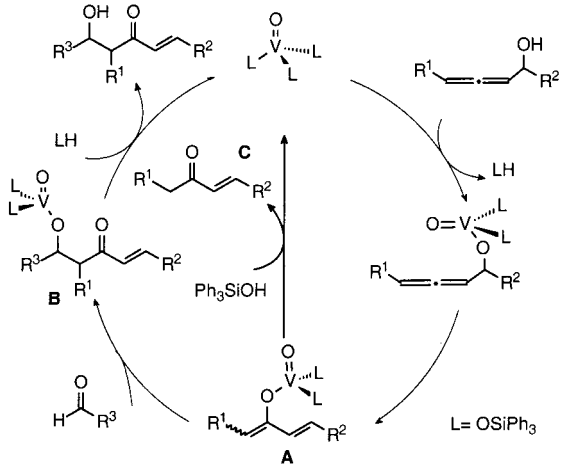
In continuation of our program directed toward the development of atom economical reactions catalyzed by vanadium, we initiated a study of vanadium-catalyzed additions of allenic alcohols and aldehydes which can generate aldol-type adducts formally derived from an α,*β*-unsaturated ketone and an aldehyde, a particularly versatile juxtaposition of functionality, a type of aldol process that is virtually unknown.[9] The proposed route for such a reaction is given in Scheme 1. The key becomes the interception of intermediate **A** by an aldehyde to give aldol **B** vs protonation to enone **C**.

We first studied the reaction of allenic alcohol **1** having a phenyl group α to the alcohol since this has shown some promising result in the aldol-type reactions with propargylic alcohols.[8] The reaction of allenic alcohol **1**[10] (1 equiv), which is a nearly 1:1 diastereomeric mixture, with benzaldehyde (1.2 equiv) in the presence of 5 mol % $VO(OSiPh_3)_3$ (**4**) in CH_2Cl_2 (2.5 M) at 55 °C was investigated (eq 1). The reaction was finished after



18 h and gave aldol product **2**[11] (66%), together with the rearranged product **3** (ratio 75:25). Lowering the temperature to room temperature resulted in an improved reaction, and only the aldol product **2** was isolated in 86% yield with a *syn/anti* selectivity of 80/20.[12] That this diastereoselectivity does not derive from the diastereomeric nature of the allenol was established by using nearly diastereomerically pure allenol and obtaining the identical result. We only observed the *E*-double bond isomer which was in accordance with the results reported by Takai.[8] A few other solvents (THF and toluene) were also screened in order to see if the *syn/anti* selectivity could be improved. The reaction in CH_2Cl_2, however, proved to be the best. Increasing the concentration of the reaction did not improve the selectivity either. Changing the catalyst to $MoO_2(acac)_2$ resulted in a mixture of aldol product **2** and rearranged product **3** (ratio 80:20). The more electron rich vanadium catalyst $VO(OiPr)_3$ gave no reaction at all. Using $VO(OTMS)_3$ gave a much slower reaction, and aldol product **2** could only be isolated in 21% yield after 72 h with a *syn/anti* selectivity of 74/26.

Scheme 1. Proposed Additon of Allenic Alcohols and Aldehydes



Using the conditions stated above (eq 1), we explored the generality of the reaction by varying the aldehyde (Table 1, entries 1−8).[13] When we employed aromatic aldehydes (entries 1 and 2) or heteroaromatic aldehydes (entries 3−5), complete conversions into aldol products **6**−**10** were generally observed within 36−48 h. The isolated yields were good, and usually none or a trace amount (<10%) of the simple rearranged product **3** (eq 1) was observed. It was necessary to protect the amine in 2-pyrrolecarboxaldehyde to obtain a good yield (entry 5). Running the reaction with the free amine resulted in a complex mixture of products. Aliphatic aldehydes also seem to be efficiently converted to the aldol products. Performing the reaction in the presence of butyraldehyde gave aldol product **11** in 79% yield with a *syn/anti* ratio of 78/22 (Table 1, entry 6). More sterically hindered aldehydes gave lower yields and a corresponding significant

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(10) The allenic alcohols were prepared according to known procedures. (a) Kimura, M.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689. (b) Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720. (c) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943. Further methods: (d) Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1979**, 859. (e) Katsuhira, T.; Harada, T.; Oku, A. *J. Org. Chem.* **1994**, *59*, 4010. (f) Masauyama, Y.; Watabe, A.; Ito, A.; Kurusu, Y. *Chem. Commun.* **2000**, 2009. (g) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632. (h) Isaac, M. B.; Chan, T.-H. *Chem. Commun.* **1995**, 1003.

(11) New compounds have been characterized spectroscopically, and elemental composition has been established by high-resolution mass spectroscopy and combustion analysis.

(12) The *syn/anti* selectivity was determined by comparing the coupling constants for the *syn* and *anti* isomers with similar compounds. Examples: (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *29*, 8739. (c) Kawakami, T.; Miyatake, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **1996**, *61*, 376.

(13) A general procedure follows: In a screw-cap reaction vessel with a Miniert syringe valve, aldehyde (1.2 equiv) and allenic alcohol (1.0 equiv) were added to a solution of $VO(OSiPh_3)_3$ (5 mol %) in CH_2Cl_2 (2.5 M). After the solution was stirred for 36−48 h, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography to give pure products.

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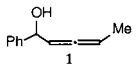
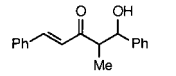
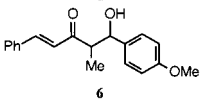
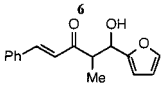
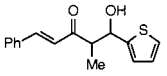
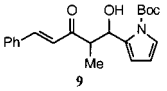
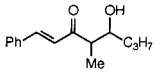
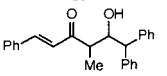
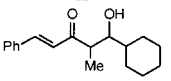
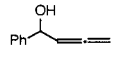
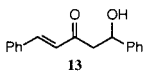
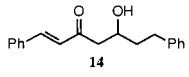
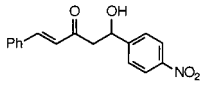
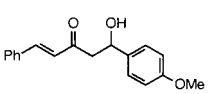
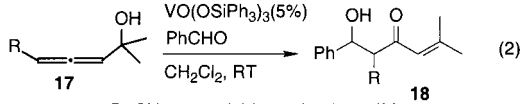
Table 1. Vanadium-Catalyzed Additions of Allenic Alcohols and Aldehydes[a]

Entry	Allenic alcohol	Aldehyde	Product	Yield[b]	*Syn/Anti*[c]
1	 **1**	PhCHO	 **2**	86%	80/20
2	**1**		 **6**	83%	42/58
3	**1**		 **7**	88%	67/33
4	**1**		 **8**	86%	68/32
5	**1**		 **9**	88%	70/30
6	**1**	C_3H_7CHO	 **10**	79%	78/22
7	**1**		 **11**	60% 71%[d]	80/20
8	**1**		 **12**	61%	66/33
9	 **5**	PhCHO	 **13**	85%	-
10	**5**		 **14**	70%	-
11	**5**		 **15**	83%	-
12	**5**		 **16**	64%	-

[a] In a typical procedure the reactions were carried out at room temperature in dichloromethane (2.5 M) employing 5 mol % of $VO(OSiPh)_3$, 1.2 equiv of aldehyde, and 1.0 equiv of allenic alcohol under an atmospheric pressure of argon. The reaction times varied from 24 to 48 h. [b] Isolated yield after flash chromatography. [c] The *syn/anti* ratio was determined by ^1H NMR. [d] The allenic alcohol was added slowly over a period of 6 h.

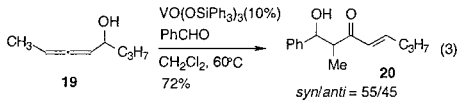
increase in the amount of the rearranged product **3** (Table 1, entries 7, 8). The yield of the reaction of **1** with diphenylacetaldehyde was, however, improved from 60% to 70% by adding the allenic alcohol slowly over 6 h. We also examined the reaction with an unsubstituted allenic alcohol **5** (Table 1 entries 9−12). Using the latter conditions, a range of aldehydes was shown to undergo the vanadium-catalyzed aldol-type reaction. Most notable, in entry 12, when *p*-anisaldehyde was used as the trapping agent, a substantial amount of dehydrated product was observed, and the aldol product **16** was only isolated in 64% yield. This is the only case where we have seen the dehydrated product.

During the course of this study, we considered the possibility of extending the reaction to include nonaromatic allenic alcohols. Indeed, nonaromatic disubstituted allenic alcohol **17a** reacted under the standard conditions with benzaldehyde (eq 2) to give the aldol product **18a** in 86% yield and a *syn/anti* ratio of 77/23.



a: R=CH_3, 86% yield, *syn/anti* = 77/23
b: R=*i*-C_3H_9, 57% yield, *syn/anti* = 88/12

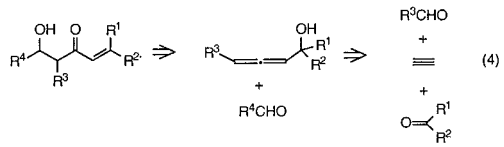
Encouraged by this result, we subjected the nonaromatic monosubstituted allenic alcohol **19**, a type of substitution pattern that failed in the case of propargylic alcohols, to the same conditions. Initially this reaction gave only recovered starting material, but, by increasing the temperature to 60 °C and using 10% of $VO(OSiPh_3)_3$, we were able to push the reaction to completion, and aldol product **20** could be isolated in 72% yield (eq 3).



19 20
syn/anti = 55/45

It was also of interest to see if the reaction could be performed with a more sterically hindered substituent on the allene. Thus, allenic alcohol **17b** was prepared and subjected to the standard conditions. This gave the aldol product **18b** in 57% yield together with a substantial amount of untrapped rearranged product. The *syn/anti* selectivity was 88/12 (eq 2). From this observation and the fact that the more sterically hindered aldehydes (Table 1, entries 7, 8) also gave a lot of untrapped rearranged product, we can conclude that the reaction is quite sensitive to steric hindrance. The rate of aldehyde interception decreases when the substituent on either the allene or the aldehyde becomes too large and protonation of the dienyl oxometalate (**A**, Scheme 1) becomes a major side reaction.

In conclusion, we have presented a new synthetic strategy for the synthesis of unusual aldol-type products consisting of both an α,β-unsaturated ketone and a β-hydroxyketone, which cannot easily be obtained by other methods in a highly atom economic fashion. For example, the only report of **13** involves a circuitous route via a phosphonate olefination[14]—not a direct aldol addition of benzylideneacetone to benzaldehyde, which produces the dehydrated product dibenzylideneacetone.[15] The product **14** is a simple natural product, (±)-yashabushiketol,[16] and this route represents a simpler protocol than that previously recorded.[14] Given the ease of synthesis of the allenols from aldehydes and propargyl alcohols, this new strategy can be summarized as in eq 4 involving a series of additions and one reduction such that



the starting materials are from components—acetylene, aldehyde-1, aldehyde-2, and either an aldehyde-3 or a ketone. Further investigations to improve the *syn/anti* selectivity and to develop the reaction into an asymmetric version are underway.

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Supporting Information Available: Experimental details and characterization data for compounds **1**−**20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Asakawa, Y.; Genjida, F.; Hayashi, S.; Matsuura, T. *Tetrahedron Lett.* **1969**, 3235. (b) Asakawa, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1970.