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A Tandem Non-Aldol Aldol Mukaiyama Aldol Reaction

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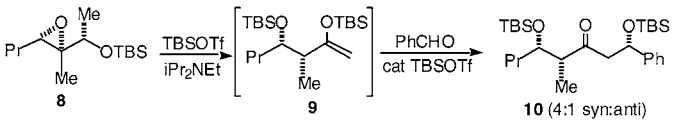
ABSTRACT



A new one-pot tandem aldol process is described in which a secondary epoxy silyl ether is converted into the 1,5-bis-silyloxy-3-alkanone in good yield. Thus, treatment of the epoxy silyl ether 8 with TBSOTf and base affords the silyl enol ether 9 via non-aldol aldol rearrangement and addition of benzaldehyde and TBSOTf gives the ketone 10 with 4:1 syn selectivity. The diastereoselectivity changes to an anti preference for most aldehydes. This anti selectivity overwhelms the normal Felkin–Ahn preference; namely, the 1,5-anti isomer predominates even when it is anti-Felkin–Ahn.

Over the past decade, ongoing research on the non-aldol aldol reaction has been carried out in our group. The non-aldol aldol reaction is an alternative process to obtain aldol products starting with an epoxy alcohol in the presence of a hindered amine base and silyl triflates. We have extended the use of the non-aldol aldol from generating aldehydes to the selective formation of methyl ketones.[1] We have now successfully shown that one can generate in situ a silyl enol ether, which in the presence of an achiral aldehyde and a Lewis acid can undergo a Mukaiyama aldol reaction favoring the formation of the syn 1,5-diol with benzaldehyde and favoring the anti 1,5-diol with many other aldehydes. Both Evans[2] and Paterson[3] showed that the anti 1,5-diols were favored when one used the boron enolate for the aldol reactions. However, when one takes a closer look at the reported reactions, the protecting group on the β-alkoxy group influences greatly the outcome of the reaction and usually favors the anti compound except when this group is *tert*-butyldimethylsilyl (TBS). The choice of the Lewis acid also influences the stereochemical outcome of the aldol reaction.

The non-aldol aldol rearrangement allows one to prepare either the syn or anti aldol products starting from the (*E*)- or (*Z*)-allylic alcohol, respectively. The chirality is introduced using the Sharpless asymmetric epoxidation. The alcohol is protected with a silyl group and then treated with diisopropylethylamine (DIPEA) and a trialkylsilyl triflate (R_3SiOTf). Although the reactions can be carried out with any relatively unhindered silyl triflate, e.g., TMSOTf, TESOTf, or TBSOTf, the cleanest reaction mixtures were obtained using TBSOTf and the TBS-protected alcohol.

The (*E*)-allylic alcohols **1** are easily prepared by Grignard addition to the commercially available 2-methyl-2-pentenal in the case of R = Et. For R = Pr, the 2-methyl-2-hexenal was prepared in three steps starting from butanal and the Wittig reagent, 1-carbethoxyethylidenetriphenylphosphorane (Scheme 1). Reduction and subsequent oxidation afforded the desired 2-methyl-2-hexenal in high yield, which was then reacted with methylmagnesium bromide. A Sharpless asymmetric epoxidation under kinetic resolution conditions afforded the erythro epoxy alcohol **3** as the major product (along with alcohols **2** and **4**). The alcohol **3** was protected with a TBS group and then submitted to the non-aldol aldol conditions. Depending on the workup, one obtains good yields of either the methyl ketone **6** or the silyl enol ether **7** (Scheme 2). Both compounds are presumably formed from

(1) (a) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169−72. (b) Jung, M. E.; van den Heuvel, A.; Leach, A. G.; Houk, K. N. *Org. Lett.* **2003**, *5*, 3375−3378.

(2) Evans, D. A.; Coleman, P. J.; Côté B. *J. Org. Chem.* **1997**, *62*, 788−789.

(3) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

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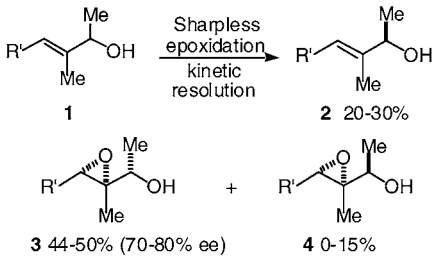
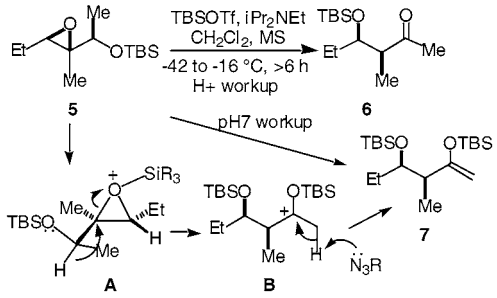
Scheme 1



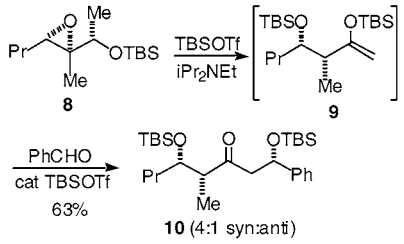
Scheme 2



the rearrangement of **5** (as shown in **A**) via intermediate **B**, which is deprotonated or hydrolyzed.

Since silyl enol ethers are very versatile substrates in organic synthesis, we decided to submit compound **7** to a Mukaiyama aldol reaction. We were able to obtain the desired aldol product **10** favoring the syn 1,5-diol with benzaldehyde and catalytic amounts of TBSOTf (Scheme 3). Only one case of a Mukaiyama aldol reaction using

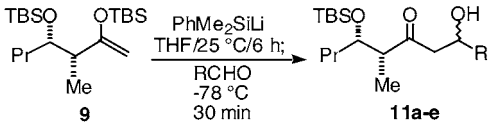
Scheme 3



TMSOTf and benzaldehyde has been reported,[4] while in all other cases the aldehyde was activated as an acetal derivative.[5]

This reaction worked well with non-enolizable aldehydes as shown for benzaldehyde and cinnamaldehyde. In the latter case, the Mukaiyama aldol product was obtained in 52% yield in favor of the syn compound (4:1 syn:anti). Unfortunately, under these same reaction conditions, enolizable aldehydes enolized to afford the silyl enol ether and no longer were reactive toward the silyl enol ether. We were able to circumvent this problem using a two-step procedure. The silyl enol ether **9** was isolated, and then $PhMe_2SiLi$ was used to generate the lithium enolate, which was then reacted with an aldehyde to afford monoprotected 1,5-diols **11** (Scheme 4 and Table 1).[6] The selectivity was again in favor of the

Scheme 4



syn product for benzaldehyde and cyclohexenecarboxaldehyde, but the reactions with all of the other aldehydes were

Table 1. Formation of 1,5-Diols from **9** with $PhMe_2SiLi$

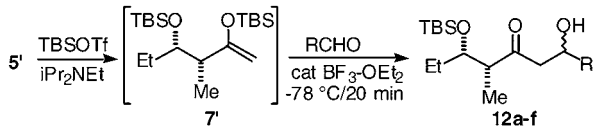
compound	aldehyde (RCHO)	yield (%)[a]	anti:syn
11a	iPr−CHO	59	1.7:1
11b	Pr−CHO	44	1.5:1
11c	$PhCH_2CH_2CHO$	39	2:1
11d	cyclohexenyl−CHO	48	1:1.5
11e	Ph−CHO	21	1:1.7

[a] These are the isolated yields of pure products with the remainder being recovered starting material **9**.

slightly selective for the anti 1,5-diols. Although the reactions proceeded in very low conversion (about 21−59%), the yields of aldol products were essentially quantitative.

We were able to obtain a one-pot NAA (non-aldol aldol) Mukaiyama aldol reaction by generating the silyl enol ether in situ and then adding excess $BF_3{\cdot}OEt_2$ and aldehydes to the reaction mixture (Scheme 5 and Table 2).[7] The methyl

Scheme 5



ketone **6′** always was a side product of this reaction. Some aldehyde was produced via migration of the alkyl group during the non-aldol aldol reaction.[1a] The reaction proceeded

(4) Yukozawa, T.; Yamaguchi, M.; Nakai, T.; Ishikawa, N. *Nippon Kagaku Kaishi* **1985**, *11*, 2202−2204.

(5) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899−3910. (b) Noyori, R.; Murata, S.; Suzuki, M. *J. Am. Chem. Soc.* **1980**, *102*, 3248−3249.

(6) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1209−1214.

(7) (a) Scheidt, K. A.; Banister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981−6990. (b) Roush, W. R.; Banister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275−4283.

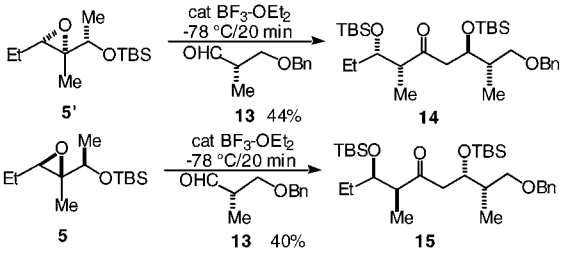
Table 2. Formation of 1,5-Diols from **5′** with BF_3-OEt_2

compound	aldehyde (RCHO)	yield (%)	anti:syn
12a	PhCHO	42	1:1.5
12b	$C_5H_{11}-CHO$	61	2.5:1
12c	iPr−CHO	56	1:1
12d	$PhCH_2CH_2CHO$	45	1.75:1
12e	PhCH=CH−CHO	20	2:1
12f	cyclohexenyl−CHO	20	1.2:1

to give mainly the anti product **12** for all aldehydes except benzaldehyde and cyclohexenecarboxaldehyde (Table 2). The best results were obtained using hexanal as the aldehyde.

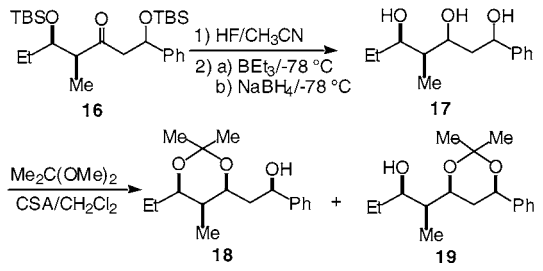
Reaction of **5** or **5′** with the optically active aldehyde **13** gave compounds **14** and **15** as the major products (**14**, 2:1; **15**, 3:1), which indicates that this 1,5 anti stereoinduction from the chiral enolate is more important than the chirality of the aldehyde (Felkin−Anh preference) (Scheme 6).

Scheme 6



The stereochemistry was proven for the benzaldehyde and hexanal derivatives. The stereochemistry of the other products was assigned by the similarity of their NMR spectra to that of the hexanal product. The ketodiol derived from **16** was selectively reduced using the Et_3B·THF/$NaBH_4$ procedure to afford one major compound **17**. The compound was then subjected to acetalization conditions to afford two syn acetonides **18** and **19** as major compounds (Scheme 7).[8] The

Scheme 7



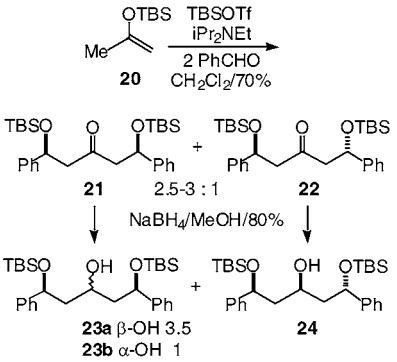
stereochemistry was assigned by NOESY experiments and ^{13}C NMR shifts.[9]

The following results also support the assignment of syn stereochemistry for the major diastereomer. When the TBS enol ether of acetone **20** was treated with 2 equiv each of benzaldehyde, TBSOTf, and Hünig's base, we isolated a 70% yield of a 2.5−3:1 ratio of the syn **21** and anti **22** double-Mukaiyama aldol products. The structures of these two isomers were proven by hydride reduction: the syn isomer **21** gave a 3.5:1 ratio of the two alcohols **23ab**, while the anti isomer **22** gave the sole alcohol **24** (the only possible product), both in 80% yield. Thus, the syn stereochemistry is favored even without the additional α-stereocenter in the silyl ether.

We propose that the mechanism of the Mukaiyama aldol with most aldehydes, e.g., hexanal and the optically active aldehyde **12**, proceeds via an open transition state in accord with the work of Evans[3,10] and Paterson[4] in the case of boron enolate where the anti 1,5-diol is favored. The aldol reaction with benzaldehyde is anomalous, and the formation of the syn-1,5 diol may be due to some unknown electronic effect. Work is underway to try to better understand and improve the diastereoselectivity of this process.

In conclusion, we have shown that we can selectively obtain anti 1,5-diols in a one-pot reaction starting from an epoxy alcohol via non-aldol aldol rearrangement and Mukaiyama aldol. The reaction with benzaldehyde is catalytic and favors the syn 1,5-diol. For enolizable aldehydes, the reactions require the addition of an excess BF_3·OEt_2 and aldehyde.

Scheme 8



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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915−2917.
(9) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.
(10) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343 and references therein. (b) Evans, D. A., Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577−4580.