Diastereoselectivity in non-aldol aldol reactions: silyl triflate-promoted Payne rearrangements

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Abstract—The non-aldol aldol process exhibits diastereoselectivity such that one isomer of a secondary epoxy silyl ether gives only the expected ketone product while the other affords both ketone and aldehyde. We present evidence for a novel silyl triflate-promoted Payne rearrangement of silyloxy epoxides, e.g. D₃>E₁. Additional examples of the non-aldol aldol process are presented including cyclic examples and one in which an aryl ring participates to give unusual products. © 2002 Elsevier Science Ltd. All rights reserved.

Over the last few years, we have reported¹ on the utility of the rearrangement of optically active tertiary epoxide primary alcohols and silyl ethers derived from 2-methyl allylic alcohols via the Sharpless asymmetric epoxidation.² Treatment of the epoxide prepared from the E-allylic alcohol with a silyl triflate and a hindered base gives the syn 2-methyl-3-trialkylsilyloxyaldehydes whereas similar treatment of those derived from the Z-isomers affords the anti products. We called this sequence the ‘non-aldol aldol’ process since aldol products are prepared in a three-step procedure from aldehydes with no aldol condensation involvement. We report herein the extension of this process to the epoxides of secondary allylic alcohols which is a much more complex process, but which showed reasonable diastereoselectivity. In addition we present evidence for a silyl triflate-promoted Payne rearrangement of epoxy silyl ethers and the existence of two distinct epoxide rearrangement pathways.

We proposed, a priori, that one might observe diastereoselectivity in the rearrangement of the two diastereomeric tertiary epoxide secondary silyl ethers since the position of the hydrogen atom that migrates to the adjacent forming tertiary carbocation center would be spatially different in the two diastereomers. This was indeed the case as shown in Scheme 1. The allylic alcohol 1 (prepared in four steps from butanal) underwent Sharpless kinetic resolution–epoxidation to give the optically active alcohol 2 and the epoxide 3 in 31 and 44% yields, respectively.³ Conversion of 3 to the silyl ether 4 was straightforward while 5 was prepared by an initial Mitsunobu reaction, hydrolysis and silylation. Treatment of the diastereomer 4 with a silyl triflate in the presence of base afforded the expected non-aldol aldol product 6 in good yield.⁴ However, treatment of the diastereomeric epoxy silyl ether 5 under identical conditions gave a mixture of the two

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rearrangement products, the ketone 6 and the aldehyde 7. We assume that the reason for this diastereoselectivity involves the difference in the steric environment of the groups in the likely transition states, A, B₁, and B₂. Thus, in A the alignment of the migrating hydrogen atom causes no severe steric problems, whereas in B₁ the same alignment causes the two methyl groups to be in close proximity and allows for rotation to B₂, which does not have this methyl–methyl interaction, and permits the migration of the alkyl group instead.⁵

The situation is much more complex when a secondary alcohol with a larger alkyl group is used. For example when the ethyl-substituted epoxy silyl ether 8 was treated under the same conditions, a mixture of four ketones 9a–d and four aldehydes 10a–d was formed (Scheme 2)!⁶ We assumed that two ketones and two aldehydes could be formed by the non-aldol aldol pathway and a simple epoxide rearrangement in which either the hydrogen or the propyl group attached to the epoxide could migrate (via D₁ or D₂) to the forming tertiary carbocation center to give, respectively, an aldehyde or a ketone (Scheme 3, top). However, the formation of the other four products required that a silyl triflate-promoted Payne rearrangement⁷ had occurred, namely the silyloxy silylated epoxonium ion had rearranged to the regioisomer E₃ (Scheme 4). This allows the second epoxide rearrangement manifold (Scheme 3, bottom) to occur (via E₁ and E₂) and to afford the other pairs of ketones and aldehydes. As far as we can tell, this is the first example of a silyloxy silylated epoxonium ion equilibration, the silyl analogue of the normal base-catalyzed Payne rearrangement, although Lewis acid-catalyzed epoxy alcohol rearrangements are known.⁸

That this Payne rearrangement was indeed occurring was shown by treatment (Scheme 5) of the correspond-
ing propyl substituted silyl ether 11, which afforded a much simpler mixture of the two ketones 12ab and two aldehydes 13ab due to the symmetry of the system.9

We have also examined cases with different alkyl groups at the β-position of the epoxide with unusual results. Thus, the ethyl-substituted epoxy silyl ether 14 affords the expected non-aldol aldol product 15a and the aldehyde 16 in an 8:1 ratio in good yield (Scheme 6). The structure of the product was proven by conversion into the known hydroxy ketone 15b.10 Cyclic epoxy silyl ethers also undergo the non-aldol aldol rearrangement without difficulty. For example, the epoxy silyl ether derived from cyclohexene–methanol 17 afforded the β-silyloxy cyclohexene–carboxaldehyde 18 in excellent yield and good ee (as determined by the optical rotation of the alcohol 19 prepared by reduction of 18).

Finally, we have shown that treatment of a substrate 20 with a phenyl substituent affords a 3:1 mixture of two ketones, namely the product of the normal non-aldol aldol rearrangement 21 and also the product with retained stereochemistry 22 (along with a trace amount of the aldehyde 23) (Scheme 7). This is the first case of a non-aldol aldol rearrangement with retention of configuration and was a worrisome result until we realized that is almost certainly due to the participation of the phenyl group in opening the activated epoxide and thus proceeds via a double inversion pathway. Evidence for this mechanism comes from the formation of a small amount of the tetrafluorobis-silyl ether 24. Presumably the formation of 24 and 22 both proceed via the reactive intermediate F in which the phenyl ring has opened the silylated epoxide. Loss of a proton would afford 24 while hydride transfer from the silyl-oxyethyl unit would afford 22.

Thus, the non-aldol aldol process proceeds in a diastereoselective manner with one isomer giving only the expected ketone product and the other affording both ketone and aldehyde via competing hydride and alkyl group migrations. In addition we have presented evidence for a novel silyl triflate-promoted Payne rearrangement of silyloxy epoxides. Finally, we have shown the versatility of the non-aldol aldol reaction in several different substrates, including an electrophilic cyclization.11

Acknowledgements

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References


3. The optical purity of the two diastereomers was determined to be about 80% by use of the Alexakis method: Alexakis, A.; Mutti, S.; Mangeney, P. J. Org. Chem. 1992, 57, 1224.

4. The optical purity of the product 6 was identical to that of the starting epoxide indicating a stereospecific rearrangement.

5. The exact ratio of products 6 and 7 of the rearrangement of 5 is somewhat dependent on conditions and the silyl triflate used, with trimethylsilyl and triethylsilyl triflates (TMSOTf and TESOTf) giving about a 2:1 ratio and t-butyldimethylsilyl triflate (TBSOTf) affording about a 1:2 to 1:1 ratio, alkenes and other rearrangement products (vide infra) are formed in all cases.
6. Again the exact ratios of the eight products 9a–d and 10a–d vary depending on the exact conditions and the silyl trflate used. For example, the ratio of the four aldehydic products, 9a–d, is approximately 3:1:6:1.5:1 when the TES ether is treated with TES trflate and is 4.3:3.3:3:1 when the TBS ether is treated with TBS trflate (TBSOTf). The ketone ratios are similarly dependent of which combination of silyl ether and trflate are used.


9. The structures of the two ketones were determined by comparison to authentic samples prepared by the Evans asymmetric aldol reaction, followed by formation of the Weinreb amide and addition of alkyl Grignard reagent.


11. Spectroscopic characterization of selected compounds:

(3R,4S)-4-[(1,1-Dimethyl)dimethylsilyloxy]-3-methylheptan-2-one (6, TBS). 1H NMR (400 MHz, CDCl3) δ: 3.91 (m, 1H), 2.55 (qd, 1H, J = 4.5, 7.0 Hz), 2.18 (s, 3H), 1.33 (m, 4H), 1.04 (d, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 7 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). 13C NMR (100 MHz, CDCl3) δ: 211.6, 73.5, 52.0, 36.9, 30.1, 25.9, 18.8, 18.1, 14.2, 11.5, –4.3, –4.5. IR (neat): 1715 cm⁻¹.

(5S,6R)-6-(Triethylsilyloxy)-5-methylnonan-4-one (12a). 1H NMR (400 MHz, CDCl3) δ: 3.88 (m, 1H), 2.63 (dq, J = 5.3, 7.0 Hz), 2.51 (dt, J = 7.4, 17.3 Hz), 2.42 (dt, 1H, J = 7.2, 17.3 Hz), 1.57 (m, 2H), 1.28 (m, 4H), 1.04 (d, 3H, J = 7.0 Hz), 0.96 (t, 9H, J = 7.9 Hz), 0.90 (2t, 6H, J = 7.4 Hz), 0.60 (q, 6H, J = 7.9 Hz). 13C NMR (126 MHz, CDCl3) δ: 213.5, 73.7, 51.5, 44.7, 37.2, 18.7, 16.8, 14.2, 13.8, 12.3, 6.8, 5.0. IR (neat): 1713 cm⁻¹.

(1R,2S)-2-[(1,1-Dimethyl)dimethylsilyloxy)cyclohexanecarboxaldehyde (18). 1H NMR (500 MHz, CDCl3) δ: 9.71 (s, 1H), 4.38 (m, 1H), 2.23 (m, 1H), 1.88 (m, 1H), 1.8–1.2 (m, 7H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). 13C NMR (126 MHz, CDCl3) δ: 205.4, 67.6, 54.4, 33.4, 25.6, 24.0, 21.0, 20.4, 17.9, –4.4, –5.2. IR (neat): 1732 cm⁻¹.