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

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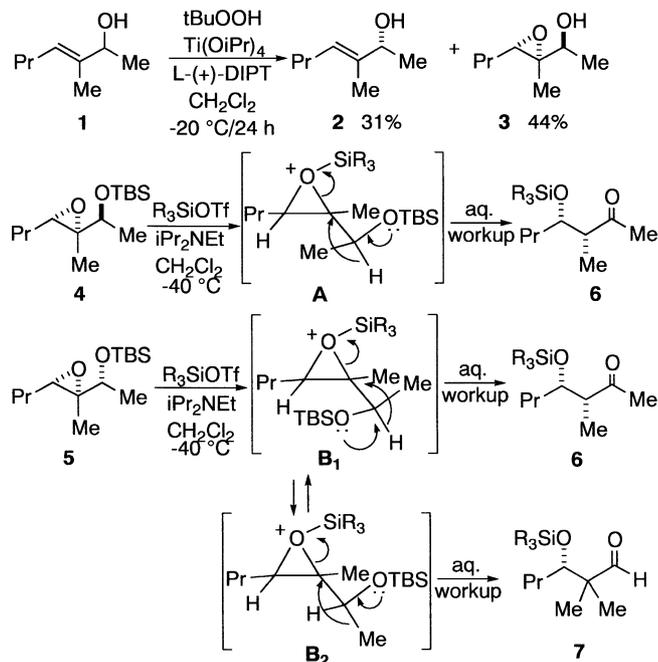
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Abstract—The non-aldol aldol process exhibits diastereoselectivity such that one isomer of a secondary epoxy silyl ether gives only the expected ketone product while the other affords both ketone and aldehyde. We present evidence for a novel silyl triflate-promoted Payne rearrangement of silyloxy epoxides, e.g. $D_3 \leftrightarrow E_3$. 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 reported[1] 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
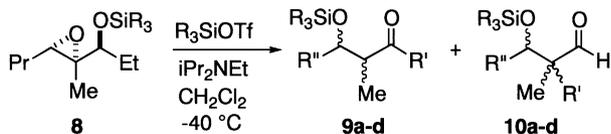
31 and 44% yields, respectively.[3] Conversion of **3** to the silyl ether **4** was straightforward while **5** was prepared by an initial Mitsunobu reaction, hydrolysis and silylation. Treatment of the diastereomer **4** with a silyl triflate in the presence of base afforded the expected non-aldol 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
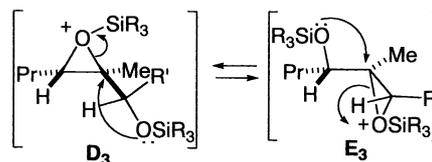

Scheme 1.

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**, **B**$_1$, and **B**$_2$. Thus, in **A** the alignment of the migrating hydrogen atom causes no severe steric problems, whereas in **B**$_1$ the same alignment causes the two methyl groups to be in close proximity and allows for rotation to **B**$_2$, which does not have this methyl–methyl interaction, and permits the migration of the alkyl group instead.[5]
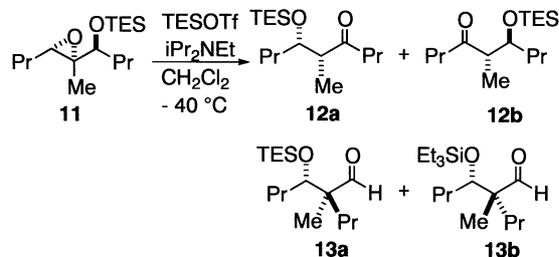
Scheme 2.

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 **D**$_1$ or **D**$_2$) 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 rearrangement[7] had occurred, namely the silyloxy silylated epoxonium ion
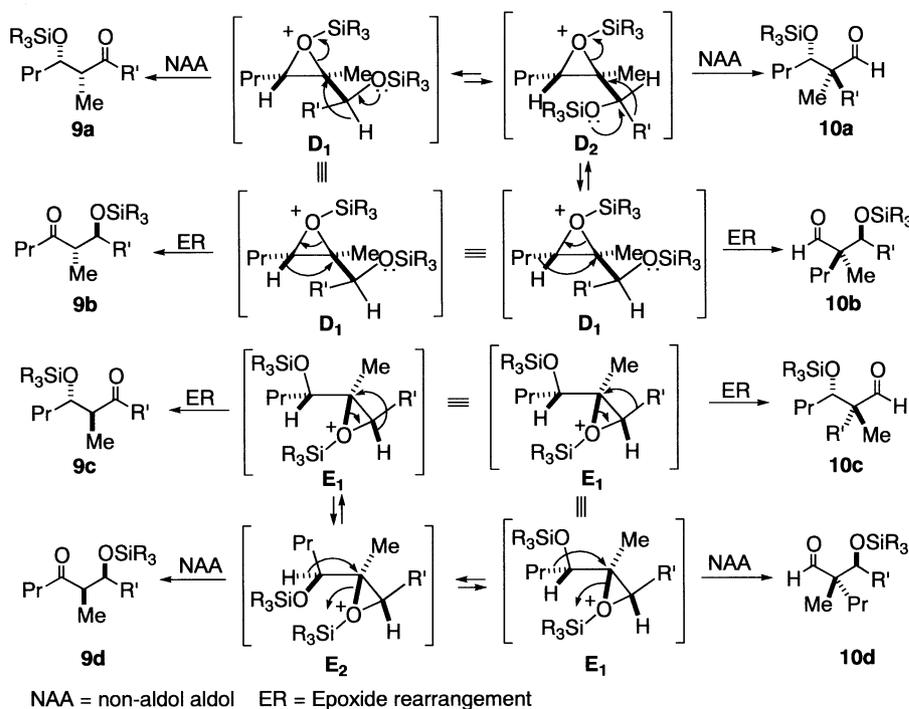
Scheme 4.

D$_3$ had rearranged to the regioisomer **E**$_3$ (Scheme 4). This allows the second epoxide rearrangement manifold (Scheme 3, bottom) to occur (via **E**$_1$ and **E**$_2$) 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-
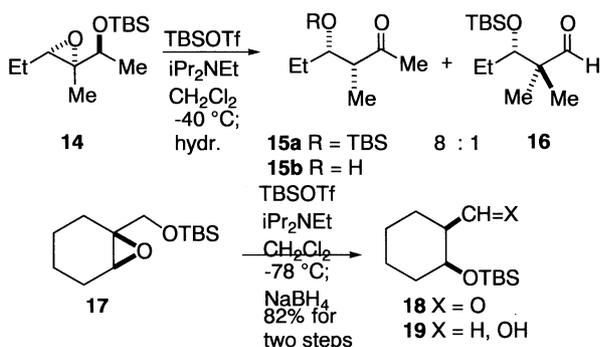
Scheme 5.

NAA = non-aldol aldol　　ER = Epoxide rearrangement
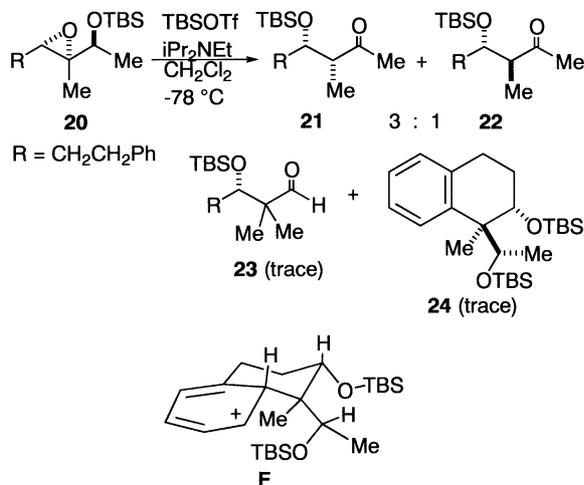
Scheme 3.

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 cyclohexane–carboxaldehyde **18** in excellent yield and good ee (as determined by the optical rotation of the alcohol **19** prepared by reduction of **18**).

Scheme 6.

Finally, we have shown that treatment of a substrate **20** with a phenethyl 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 tetralin bis-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-oxymethyl 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

Scheme 7.

References

1. (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208; (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150; (c) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663; (d) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129; (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307; (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343; (g) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669; (h) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719; (i) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333.
2. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; (b) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp. 193–243; (c) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp. 247–308.
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 triflate 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 triflate and is 4.3:3.3:3:1 when the TBS ether is treated with TBS triflate (TBSOTf). The ketone ratios are similarly dependent of which combination of silyl ether and triflate are used.

7. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

8. See for example: (a) Wen, X.; Norling, H.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 2096; (b) Gillmore, A. T.; Roberts, S. M.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron Lett.* **1998**, *39*, 3315; (c) Tius, M. A.; Reddy, N. K. *Tetrahedron Lett.* **1991**, *32*, 3605.

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.

10. (a) Hoffmann, R. W.; Ditrich, K.; Froech, S. *Liebigs Ann. Chem.* **1987**, *1*, 977; (b) Utaha, M.; Onoue, S.; Takeda, A. *Chem. Lett.* **1987**, 971.

11. Spectroscopic characterization of selected compounds:

(3*R*,4*S*)-4-[(1,1-Dimethyl)ethyldimethylsilyloxy]-3-methyl-heptan-2-one (6, TBS). ^{1}H NMR (400 MHz, CDCl$_3$) 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). ^{13}C NMR (100 MHz, CDCl$_3$) 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}.

(5*S*,6*R*)-6-(Triethylsilyloxy)-5-methylnonan-4-one   (12a). ^{1}H NMR (400 MHz, CDCl$_3$) 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). ^{13}C NMR (126 MHz, CDCl$_3$) 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}.

(1*R*,2*S*)-2-[(1,1-Dimethyl)ethyldimethylsilyloxy]cyclohex-anecarboxaldehyde (18). ^{1}H NMR (500 MHz, CDCl$_3$) 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). ^{13}C NMR (126 MHz, CDCl$_3$) 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}.