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ENOL VARIANTS OF THE COPE REARRANGEMENT OF *CIS*-2,3-DIVINYL EPOXIDES AND THE FURTHER FUNCTIONALIZATION OF THE OXEPIN NUCLEUS

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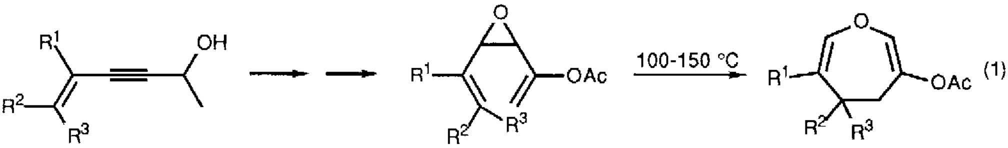
Summary: The Cope rearrangement *cis*-2,3-divinyl epoxides containing a silyl enol ether or enol triflate leads to 4,5-dihydrooxepins that are functionalized to allow for the further elaboration of the oxepin ring.

We recently reported a five step synthesis of 4,5-dihydrooxepins from enynols, the key step being the [3,3] sigmatropic rearrangement of *cis*-2,3-divinyl epoxides (equation 1).[1] One notable feature of this

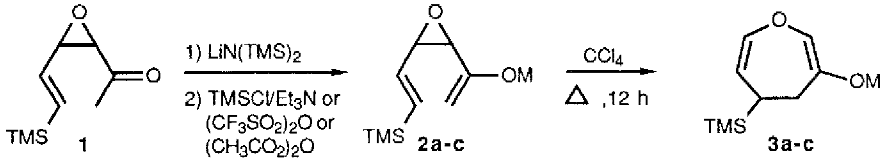


approach is that the enol acetate moiety is not destroyed in the rearrangement, since a new enol acetate is regiospecifically generated in the oxepin product. Enol acetates have limited usefulness,[2] but alternative enol derivatives such as silyl enol ethers[3] and enol triflates[4] would be useful in the further functionaliztion of the oxepin nucleus following the rearrangement. Given that our methodology would easily allow for the preparation of such enol derivatives, it was of interest to see if they would also undergo the Cope rearrangement. We report herein the preparation and Cope rearrangement of such alternative enol derivatives along with a preliminary investigation into their chemistry.

The enol derivatives **2a-b** were readily prepared by quenching the lithium enolate of epoxy ketone **1**[1] (3 equiv LiN(TMS)$_2$, THF, -70 °C) with an excess of the appropriate electrophile.[5-8] Like its enol acetate counterpart, silyl enol ether **2b** underwent smooth Cope rearrangement upon heating (CCl$_4$, 0.1-0.4 M) to give the corresponding 4,5-dihydrooxepins **3a** in good yield. However, the Cope rearrangement of the enol triflate **2b** was at first problematic, as on several occasions the reaction would suddenly turn black with the complete loss of both **2b** and **3b**. This decomposition may have arisen from the presence of a small amount of water, which led to the generation of an exiguous amount of CF$_3$SO$_3$H from the partial hydrolysis of either enol triflate **2b** or **3b**. By simply adding two equivalents of triethylamine, the Cope rearrangement of enol triflate **2b** proceeded reproducibly to give the 4,5-dihydrooxepin **3b**. These results are summarized in Table I, along with those from enol acetate **2c**.[1] In comparing the relative ease of the Cope rearrangements of **2a-c**, there did not appear to a large substituent effect at C.2 of the 1,5-diene, although the substrate with the most electron-withdrawing group, the enol triflate **2b**, rearranged under the mildest conditions.

The availability of **3a** provided the opportunity to study the chemistry of its silyl enol and the possibility

Table I. Preparation and Rearrangement of Enol Ethers of cis-2,3-Divinyl Epoxides



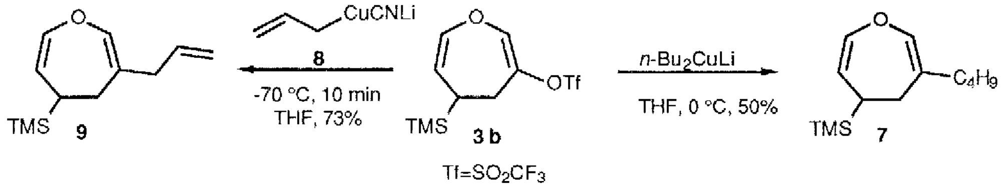
entry	M	Yield of 2 (%)[a]	T (°C)	Yield of 3 (%)[a]
a	TMS	76	120	78
b	Tf	66	90[b]	77
c[c]	Ac	70	135	94

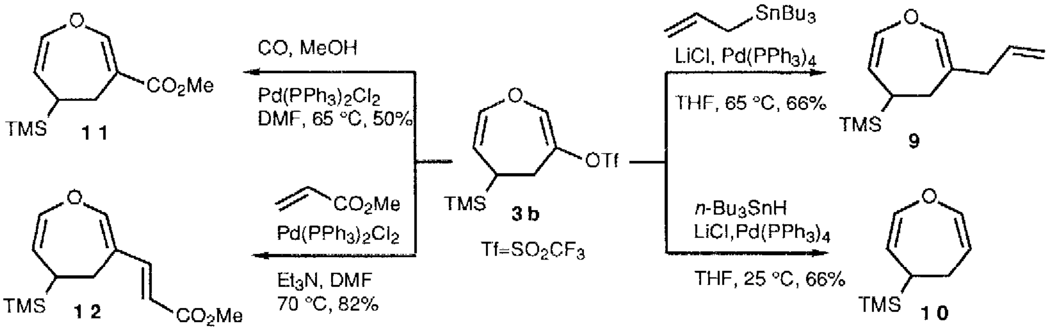
[a] Isolated yield after flash chromatography on either silica gel or Florisil. See reference 7. [b] The rearrangement of **2b** was conducted in the presence of two equivalents of Et_3N. [c] Data for **3a** and **3b** from reference 1.

of selectively functionalizing C.2 of the oxepin ring. Such silyl enol ethers are virtually unprecedented in oxepin chemistry,[9a] and few strategies for the generation of a nucleophilic center at C.2 of a 3-oxoperhydrooxepin exist.[9b,c] In a preliminary study, it was found that the Si-O bond of the TMS enol ether can be selectively cleaved with methyllithium (3 equiv MeLi, -25 °C, 20 min) to give the corresponding lithium enolate. This enolate, in turn, underwent directed aldol condensation[10] with a series of aldehydes (2 equiv $ZnCl_2$, THF, -60 °C, 5 min; 3 equiv RCHO, -60 °C, 30 min) to give the β-hxdroxyketones **4-6**. The relative stereochemistry of the aldol products has not been determined, but the diastereoselectivity was modest. For **4** and **5**, two diastereomers were isolated in ratios of 8:1 and 3:1, respectively. **6** was isolated as a mixture of four diastereomers, indicating less facial selectivity of crotonaldehyde for this enolate.

	R	Yield (%)
4	Ph	56
5	$(CH_3)_2CH$-	69
6	(*E*)-CH_3CH=CH-	76

Replacement of the triflate group in enol triflates by organocopper reagents or in reactions mediated by palladium catalysts has made this functional group very useful in organic synthesis.[4] Enol triflate **3b** has been found to undergo a variety of these substitution reactions, allowing for the easy functionalization of C.3 of the oxepin ring.[11] For example, reaction of enol triflate **3b** with *n*-Bu_2CuLi or the mixed cyanocuprate **8**[12] gave oxepins **7** and **9**, respectively. Alternatively, oxepin **9** was prepared by the palladium-mediated allylation with allyltributylstannane.[13] The use of tributylstannane in this latter reaction led to substitution of the triflate with a hydrogen to give oxepin **10**.[14] Carboxylation of the triflate led to the ester **11**,[15] while a Heck reaction with methyl acrylate led to ester **12**.[16]





In conclusion, the incorporation of a silyl enol ether or enol triflate into the 1,5-diene of a *cis*-2,3-divinyl epoxide significantly extends the utility of their Cope rearrangement, as the rearranged enol derivatives allow for the subsequent functionalization of the oxepin ring at C.2 and C.3. Further studies are in progress, and will be reported in due course.

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References

(1) Clark, D. L.; Chou, W.-N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975-7.

(2) Enol acetates have been used to prepare lithium enolates. See: House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502-12.

(3) Rasmussen, J. K. *Synthesis* **1977**, 91-110.

(4) For reviews, see: (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-24. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47-54.

(5) All new compounds gave satisfactory spectroscopic (^{1}H and ^{13}C NMR, IR, LRMS) and analytical data. ^{13}C NMR data are reported in reference 6.

(6) ^{13}C NMR (55.3 Hz, CDCl$_3$) data reported relative to the center line of CDCl$_3$ as δ 77.0. **2a**: δ 152.4, 139.3, 139.0, 92.5, 60.4, 58.0, 0.21, -1.48. **2b**: δ 149.5, 140.6, 136.2, 118.4, 106.7, 60.6, 55.3, -1.67; **3a**: δ 142.6, 142.0, 132.8, 109.0, 33.8, 25.2, 0.22, -2.76. **3b**: δ 140.4, 140.3, 138.0, 118.5, 111.3, 32.5, 24.6, -2.70. **4**: δ (major diastereomer) 212.8, 145.1, 140.3, 128.3, 127.8, 126.3, 114.6, 92.0, 74.4, 40.2, 26.1, -3.54. **5**: δ (major diastereomer) 216.2, 143.7, 114.6, 89.1, 74.6, 40.4, 29.1, 26.6, 19.4, 15.3, -3.16; (minor diastereomer) 214.3, 145.5, 114.4, 89.6, 76.5, 40.2, 29.1, 26.0, 19.4, 16.8, -3.56. **6**: δ (four diastereomers) 213.1, 145.1, 129.2, 128.9, 114.7, 91.7, 73.5, 40.1, 26.2, 17.8, -3.84; 213.8, 143.8, 129.8, 128.4, 114.5, 91.4, 72.4, 40.6, 26.4, 17.8, -3.10; 212.9, 144.3, 129.3, 128.8, 113.8, 91.3, 73.1, 41.4, 26.1, 17.8, -2.92; 212.2, 145.3, 130.1, 127.8, 114.6, 92.0, 73.3, 40.0, 26.1, 17.8, -3.55. **7**: δ 140.8, 139.2, 122.0, 108.9, 35.6, 30.9, 30.6, 28.4, 22.3, 14.0, -2.39. **9**: δ 140.6, 139.9, 136.6, 119.5, 116.2, 109.2, 40.4, 30.8, 28.3, -2.36. **10**: δ 142.6, 139.8, 109.4, 107.3, 29.7, 27.4, -2.30. **11**: δ 168.8, 154.1, 138.8, 113.0, 105.8, 51.8, 28.9, 27.3, -2.20. **12**: δ 168.0, 152.1, 147.0, 139.3, 119.2, 112.7, 112.0, 51.4, 28.2, 26.6, -2.03.

(7) Silyl enol ethers **2a** and **3a** are sensitive to silica gel, and are best purified by flash chromatography on Florisil (100-200 mesh, Fischer Scientific). Though less sensitive, the enol triflates **2b** and **3b** were also purified on Florisil.

(8) (Tf)$_2$NPh can be substituted for (Tf)$_2$O in the preparation of **2b** (see: McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979-82), but the use of (Tf)$_2$O/2,6-di-*t*-butyl-4-methylpyridine (see: Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283-4) led to decomposition.

(9) (a) Davies, M. J.; Heslin, J. C.; Moody, C. J. *J. Chem. Soc. Perkin Trans. I* **1989**, 2473-84. (b) Davies, M. J.; Moody, C. J.; Taylor, R. J. *Syn. Lett.* **1990**, 93-4. (c) Davies, M. J.; Moody, C. J. *ibid* **1990**, 95-6.

(10) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310-24.

(11) Enol triflates derived from ε-caprolactones have recently been found to undergo substitution with Gilman reagents, leading to substitution at C.2 of the oxepin ring. See: Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313-6.

(12) Lower-order cuprate **8** was prepared by mixing at -70 °C a solution of 3 equiv each of allyltributylstannane and MeLi with a solution at -70 °C of 3 equiv of CuCN·LiCl in THF. It has recently been reported (Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695-6) that enol triflates can be substituted by higher-order allylcyanocuprtates.

(13) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-40.

(14) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630-2. This method worked better than an alternative method using Pd(OAc)$_2$, PPh$_3$, *n*-Bu$_3$N, HCO$_2$H; see: Cacchi, S.; Morera, E.; Ortar, G. *Org. Syn.* **1989**, *68*, 138-47.

(15) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109-12.

(16) Scott, W. J.; Peña, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302-8.

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