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Silyloxy-Cope Rearrangement of Chiral Aldol Adducts

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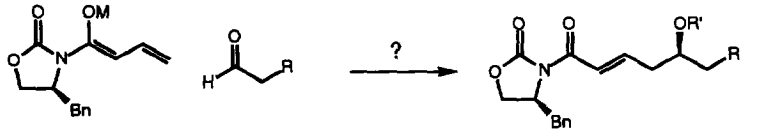
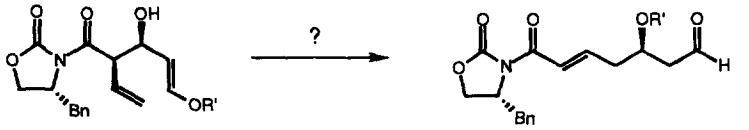
Abstract: The silyloxy-Cope rearrangement of a chiral 1,5-diene generated from aldol condensation proceeds in high yield and selectivity under mild thermal conditions to generate a new stereocenter five atoms removed from the chiral auxiliary.

The construction of remote stereocenters is a continuing problem in organic synthesis. The development of new approaches to remote stereocontrol provides valuable tools for chemists engaged in the synthesis of natural products. The reaction shown in Eq. 1 illustrates the limitations of current methodology. This γ-selective crotonate aldol cannot be performed stereoselectively using existing methods. Yet such a reaction would be desirable as it would allow the chiral auxiliary to be used once to establish the δ-stereocenter and a second time for elaboration of the unsaturated carbonyl using a Michael addition[1] or Diels-Alder reaction.[2]

(1)



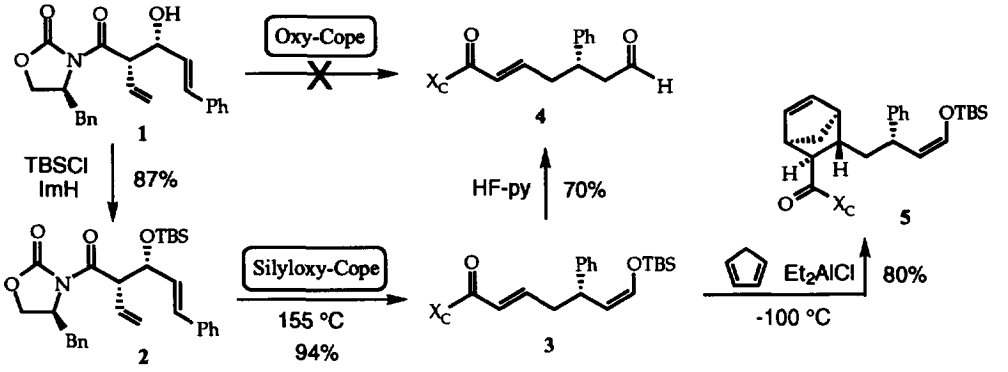
(2)



It has been our goal to define a more direct entry to this type of system using a "transfer of chirality" approach via the oxy-Cope rearrangement of a chiral aldol adduct (Eq. 2). Aldol reactions proceeding with high degrees of stereocontrol are now well-established in the literature, and thus should provide a suitable entry to the required adducts. A major uncertainty, however, was whether these adducts would be stable enough for subsequent manipulation.

To test this approach, a model substrate was prepared by the aldol reaction of a crotonyl imide with cinnamaldehyde using the method of Evans[3] (Scheme 1). The boron dienolate reacts from the α-position to provide the 1,5-diene **1**. We then attempted the oxy-Cope rearrangement of this substrate under both thermal and anionic conditions, but observed only retro-aldol products. However, by first silylating the aldol adduct to give **2**, the thermal rearrangement proceeded extremely well to provide 94% of the silyl enol ether **3** along with 4% of a minor isomer (*vide infra*). The lack of side-products from this reaction was noteworthy: no evidence of retro aldol, alcohol dehydration or olefin conjugation with the carbonyl was observed. Treatment of the silyl enol ether **3** with HF•pyridine then provided the corresponding aldehyde **4**. In order to establish the synthetic utility of this intermediate, **3** was treated with cyclopentadiene under the conditions of Evans[2] (Et_2AlCl, CH_2Cl_2, -100 °C) to provide Diels-Alder adduct **5** without affecting the silyl enol ether moiety.[4]

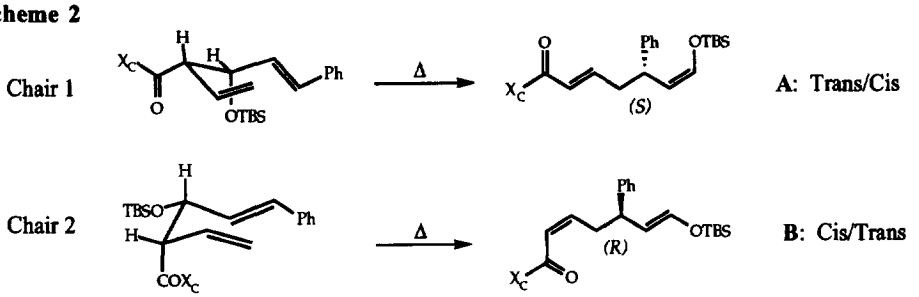
Scheme 1



Assignment of Stereochemistry.

The transition state, and thus the stereochemistry, of the Cope rearrangement has been well studied.[5] However, in this case, the preferred chair transition state has one equatorial and one axial substituent, thus introducing some ambiguity as to the stereochemistry of the major product. The initial stereochemical assignment was made by examination of the potential transition states and correlation of the olefin coupling constants with the anticipated product. The reaction is expected to proceed *via* one of two possible chair conformations (Scheme 2). In the case where the imide occupies a pseudo-equatorial position (chair 1), the product would contain a *trans* enone, a *cis* enol ether, with the new stereocenter having the (*S*) configuration (Product **A**). If the silyl ether occupies the pseudo-equatorial position (chair 2), the product would be the corresponding *cis/trans/*(*R*) isomer (Product **B**). If the reaction were to proceed via a boat conformation, the expected product would be the *trans/trans/*(*R*) isomer (substituents equatorial) or *cis/cis/*(*S*) (substituents axial). Thus, a *cis* enol ether will always be accompanied by an (*S*) stereocenter, allowing stereochemical assignment by simple inspection of the NMR spectrum. In the case of the above reaction, HPLC analysis indicated a 26:1 mixture of isomers, with the NMR spectrum of the major isomer showing a silyl enol ether resonance with a 5.8 Hz coupling constant, indicating a *cis* olefin. In contrast, the minor isomer was observed to have a 12.7 Hz coupling constant. After hydrolysis of the chiral auxiliary, the unsaturated carbonyl function in the major isomer was assigned to be *trans* by virtue of its 15.6 Hz coupling constant. This evidence led us to assign the major isomer of the rearrangement to be **A**: *trans/cis/*(*S*).

Scheme 2



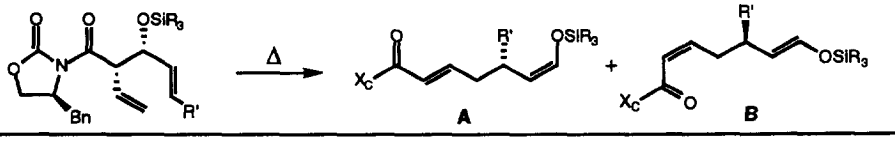
A more rigourous assignment of the new chiral center was made by taking the unpurified product mixture and subjecting it to ozonolysis, followed by treatment of the crude ozonide with sodium borohydride. The resulting 2-phenyl-1,4-butanediol, obtained in 81% yield, had an optical rotation of -25°. The literature value[6] for the (*R*) isomer is +29°, thus confirming our assignment of the stereocenter to be (*S*).

Optimization of Silyloxy-Cope.

Xylene, dodecane and DMF were examined as possible solvents for the thermolysis of **2**. However, it soon became apparent that the highest yields and selectivities could be obtained in the absence of solvent. Thus, reactions were carried out neat in base-washed glassware under a nitrogen atmosphere. Reactions performed at 230 °C proceeded to completion in less than 30 minutes, but provided a mixture of product isomers (A:B:other products = 7:4:1). A reaction temperature of 140 °C was found to provide a high level of stereoselectivity while providing a reasonable reaction rate. These conditions were then used to compare the half-lives and selectivities of differentially substituted substrates. The results are summarized in the Table.

The choice of silyl group for the silyloxy-Cope was found to have an effect on both the selectivity and rate of reaction. A trimethylsilyl ether rearranged more slowly (entry 1, 53 minute half-life) than the corresponding TBS ether (entry 2, 27 minute half-life) and showed somewhat lower selectivity. This effect appeared to be related more to the electronic nature of the silyl group rather than its steric bulk. Thus the more electron-rich TBS and TIPS groups provide significantly faster reactions than the relatively electron-deficient TMS or DPMS groups. For this reason, the TBS group was used for the majority of these studies.

Table. Silyl group and substituent effects on silyloxy-Cope rate and selectivity.



Entry	Silyl Group (R_3Si) [a]	Substituent (R')	Temperature (°C)	Half-Life (min) [b]	% Yield (A + B)	Selectivity [c]
1	TMS	Ph	139.3	53	96	18:1
2	TBS	Ph	142.2	27	98	26:1
3	TIPS	Ph	139.8	29	96	28:1
4	DPMS	Ph	139.3	59	94	19:1
5	TBS	4-MeOPh	139.0	29	96	16:1
6	TBS	4-NO_2Ph	140.5	21	84	23:1
7	TBS	2-Npth	140.8	23	95	20:1
8	TBS	CH_3	140.8	86	98	7:1
9	TBS	CF_3	140.3	83	90	3:1
10	TBS	SPh	139.8	218	92	29:1
11	TBS	OPh	141.9	101	86	31:1

Notes: (a) TMS = Trimethylsilyl; TBS = t-Butyldimethylsilyl; TIPS = Triisopropylsilyl; DPMS = Diphenylmethylsilyl. (b) Determined by ^1H NMR analysis of starting material/product mixtures of aliquots taking at appropriate reaction times. (c) The ratio of Product **A** (trans/cis/S) to Product **B** (cis/trans/R) as determined by HPLC using a refractive index detector following 14h thermolysis.

Substituent Effects.

A number of variations were made in the aldehyde-derived vinyl substituent (R'), since the group that occupies the new chiral center was of greatest synthetic interest. Electronic effects did not appear to be important in this position, as both electron-rich substituents (4-methoxyphenyl, entry 5) and electron-deficient substituents (4-nitrophenyl, entry 6) proceeded with similar rates and selectivities. A simple alkyl substituent (entry 8) gave a slower rearrangement, possibly indicating the importance of conjugation in the transition state. The rearrangement with the trifluoromethyl group (entry 9) had a similar half-life to that with the methyl group, indicating the insensitivity of this position to inductive effects. The lower selectivity in these cases is likely the result of a smaller steric demand in the transition state.

The extension of this reaction to heteroatom substituents was of particular interest to us, as we felt that these cases would have the greatest applicability to natural product synthesis. We were gratified to find that the thiophenyl-substituted system rearranged with excellent selectivity to provide the chiral sulfide (entry 10). Likewise, the phenol-substitued system (entry 11) rearranged very cleanly to provide the desired phenyl ether product as a 31:1 mixture of isomers.[7] The success with this oxygen substituent indicates that this reaction can be used to prepare γ-crotonate aldol systems with high stereoselectivity.

The silyloxy-Cope rearrangement of a chiral aldol adduct provides ready access to highly functionalized molecules with a high degree of stereocontrol at a center five atoms removed from the chiral auxiliary. Subsequent elaboration of the molecule can take advantage of the chiral auxiliary to introduce further complexity that may be applicable to natural product synthesis.

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References and Notes.

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4. ^{1}H NMR for compound **5** (300 MHz, CD_3COCD_3) δ 7.4 - 7.1 (m, 10H), 6.29 (dd, J = 5.8, 0.8 Hz, 1H), 6.24 (m, 1H), 5.85 (m, 1H), 4.72 (m, 1H), 4.63 (dd, J = 9.8, 5.6 Hz, 1H), 4.34 (dd, J = 8.9, 8.3 Hz, 1H), 4.22 (dd, J = 8.9, 3.2 Hz, 1H), 3.96 (m, 1H), 3.64 (dd, J = 4.6, 3.4 Hz, 1H), 3.31 (m, 1H), 3.09 (dd, J = 13.4, 3.2 Hz, 1H), 2.85 (dd, J = 13.4, 8.7 Hz, 1H), 2.71 (m, 1H), 2.12 (m, 1H), 1.83 (m, 2H), 1.66 (m, 1H), 1.40 (m, 1H), 0.95 (s, 9H), 0.17 (s, 3H), 0.11 (s, 3H).
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6. Bettoni, G.; Cellucci, C.; Tortorella, V. *J. Heterocyclic Chem.* **1976**, *13*, 1053-55.
7. 3-Phenoxypropenal and 3-thiophenylpropenal were prepared by phenol or thiophenol addition to propynal in the presence of triethylamine. Alternatively, 3-thiophenylpropenal could be prepared using literature methods (Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173-181). The aldol reactions of these heteroatom-substituted aldehydes provided mixed results. With the thiophenyl- and phenol-substituted aldehydes, the aldol reactions (unoptimized) proceeded in 75% and 46% yield respectively, while attempts at the aldol reaction using or ethoxy- or *N*-methylaniline-substituted aldehydes were unsuccessful.

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