

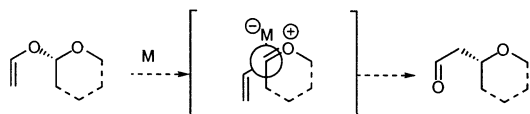
Stereoretentive O-to-C Rearrangement of Vinyl Acetals: Solvent Cage Effects as a Stereocontrol Element

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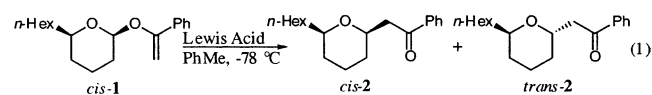
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The Lewis acid-induced rearrangement of vinyl acetals, the Ferrier reaction,¹ has emerged as a powerful synthetic tool.² Stereochemistry in the C–C bond-forming event is dictated by resident chirality and by stereoelectronic features of the oxocarbenium ion intermediate.³ Given that there are numerous means of controlling the C–O bond stereochemistry of glycosides and lactol ethers,⁴ the development of a method to convert a C–O bond into a C–C bond with retention would represent an important advance.⁵ This approach is well-known in concerted reactions such as the Claisen rearrangement⁶ and radical reactions such as the 1,2-Wittig rearrangement.⁷ However, ionic intermediates have rarely been employed in this strategy.^{8,9,10} Herein we report a highly stereoretentive rearrangement of vinyl acetals and present evidence that it proceeds by tight ion pairing in the solvent cage and recombination prior to dissociation.



As a model system to develop conditions to effect the stereoretentive rearrangement, we synthesized the 6-substituted vinyl acetal *cis*-1. Oxocarbenium ions with substitution at the 6-position are known to undergo highly *trans*-selective alkylation.¹¹ Should the generated enolate escape the solvent cage prior to recombination, the *trans* product would predominate. If recombination is faster, the *cis* product will result. A screen of several representative Lewis acids at $-78\text{ }^{\circ}\text{C}$ in toluene revealed that aluminum-based Lewis acids showed the greatest degree of *cis* selectivity. Although Et_3Al afforded the highest selectivities, the results were somewhat erratic.¹² The use of $\text{BF}_3\cdot\text{OEt}_2$ as a second Lewis acid upon initial addition of R_3Al to the vinyl acetal effected a rapid stereoretentive rearrangement of the vinyl acetal, producing *cis*-2 with excellent selectivity and in very good yield, eq 1. In contrast, the use of

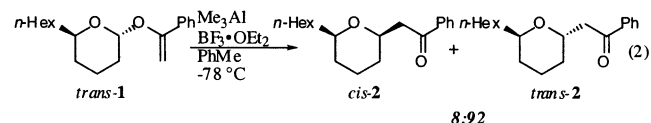


| Lewis Acid | <i>cis</i> / <i>trans</i> | yield |
|---|---------------------------|-------|
| SnCl_4 | 5:95 | 75% |
| $\text{BF}_3\cdot\text{OEt}_2$ | 5:95 | 93% |
| Et_2AlCl | 55:45 | 98% |
| Et_3Al | 95:5 | 38% |
| $\text{Me}_3\text{Al}/\text{BF}_3\cdot\text{OEt}_2$ | 93:7 | 86% |

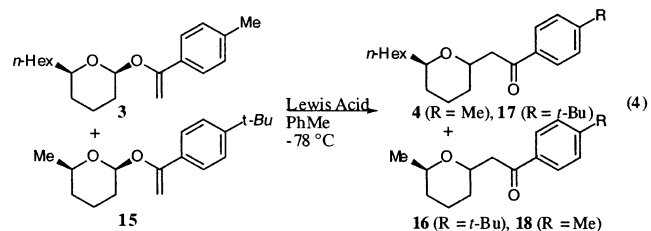
$\text{BF}_3\cdot\text{OEt}_2$ alone effected a highly *trans*-selective rearrangement in good yield. The reaction was found to work best in toluene. The slightly more polar CH_2Cl_2 (93:7) and the Lewis basic and more

polar Et_2O (<5:95, low yield) were less effective as reaction media, following the trend one would expect.¹³

To ensure that the *cis* selectivity was not a function of the Lewis acids, *trans*-1 was subjected to the identical reaction conditions. As expected, the *trans* product predominated, with a 92:8 selectivity, eq 2. Furthermore, the *trans* product does not epimerize to give *cis* product under these reaction conditions.¹⁴



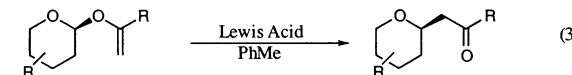
Investigations into the scope of this transformation revealed some dependence of selectivity on enolate nucleophilicity, Table 1. The electron-rich *p*-tolylvinyl acetal **3** underwent the rearrangement with 96:4 selectivity (*cis*/*trans*) while the progressively less electron-rich phenyl and *p*-bromophenyl were each less selective (93:7 and 90:10, respectively), entries 1–3 Table 1. This trend was further reinforced by vinyl acetal **7**, which rearranged with only 81:19 selectivity. Surprisingly, cooling the reaction temperature to $-90\text{ }^{\circ}\text{C}$ resulted in decreased *cis* selectivity, while warming the reaction to $-55\text{ }^{\circ}\text{C}$ provided optimal selectivity, affording the *cis* product in 89:11 selectivity, a clear example of an inverse Eyring relationship.¹⁵ We have observed this trend with other substrates as well (cf. entries 10 vs 11 and 12 vs 13). A possible rationale for this effect may lie in the observation that contact ion pairs are disfavored relative to solvent-separated ion pairs at lower temperatures.¹⁶ Last, we have rearranged *cis*-1 on 2 mmol scale providing **2** in 92% yield and 97:3 *cis*:*trans* selectivity.



| Lewis Acid | <i>cis</i> -4 | <i>trans</i> -4 | <i>cis</i> -16 | <i>trans</i> -16 | <i>cis</i> -17 | <i>trans</i> -17 | <i>cis</i> -18 | <i>trans</i> -18 |
|---|---------------|-----------------|----------------|------------------|----------------|------------------|----------------|------------------|
| $\text{BF}_3\cdot\text{OEt}_2$ | 0.5 | 23.0 | 0.3 | 36.0 | 0.6 | 20.8 | 0.1 | 15.3 |
| $\text{Me}_3\text{Al}/\text{BF}_3\cdot\text{OEt}_2$ | 48.8 | 1.4 | 42.8 | 6.8 | 0 | 0.3 | 0 | <0.2 |

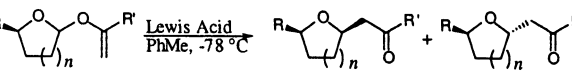
In search of conclusive proof that tight ion-pair binding in the solvent cage is the factor responsible for high stereoretention in this reaction, we conducted a crossover experiment. We subjected substrates **3** and **15** to our standard reaction conditions ($\text{Me}_3\text{Al}/\text{BF}_3\cdot\text{OEt}_2$ in PhMe at $-78\text{ }^{\circ}\text{C}$), eq 4. If ion pairing is the operative effect, the enolate generated from **3** should not combine with the oxocarbenium ion derived from **15** (and vice versa) and no

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Table 1. Scope of the Vinyl Acetal Rearrangement


| Entry ^a | Vinyl Acetal | Temp (°C) | Product | <i>cis/trans</i> (isolated yield) ^b | |
|--------------------|-----------------|-----------|---------|--|--|
| | | | | BF ₃ ·OEt ₂ | Me ₃ Al/BF ₃ ·OEt ₂ |
| | | | | | |
| 1 | 1 Ar = Ph | -78 | 2 | 5:95 (93%) | 93:7 (86%) |
| 2 | 3 Ar = (4-Me)Ph | -78 | 4 | 7:93 (90%) | 96:4 (92%) |
| 3 | 5 Ar = (4-Br)Ph | -78 | 6 | 5:95 (90%) | 90:10 (80%) |
| | | | | | |
| 4 | 7 | -78 | 8 | 5:95 (88%) | 81:19 |
| 5 | 7 | -90 | 8 | - | 55:45 |
| 6 | 7 | -55 | 8 | - | 89:11 (82%) |
| 7 | 7 | -32 | 8 | - | 79:21 |
| | | | | | |
| 8 | 9 | -78 | 10 | 5:95 (90%) | 50:50 |
| 9 | 9 | -32 | 10 | - | 90:10 (83%) |
| | | | | | |
| 10 | 11 | -78 | 12 | 9:5:5 (95%) ^c | 60:40 |
| 11 | 11 | -25 | 12 | - | 10:90 (85%) |
| | | | | | |
| 12 | 13 | -78 | 14 | 5:95 (92%) | 33:67 |
| 13 | 13 | -25 | 14 | - | 89:11 (78%) |

^a All reactions conducted in PhMe for 30 min at the indicated temperature. BF₃·OEt₂: 1.2 equiv. Me₃Al/BF₃·OEt₂: 4 equiv Me₃Al, 1.2 equiv BF₃·OEt₂. ^b Diastereoselectivity determined by ¹H NMR analysis of the unpurified reaction mixture. Isolated yield refers to the major diastereomer. ^c Trans/*cis* selectivity of 5-substituted oxocarbenium is complementary to 6- or 4-substituted oxocarbeniums. See ref 13.

Table 2. Effect of Ring Size on Rearrangement


| entry ^a | vinyl acetal | n | BF ₃ ·OEt ₂ | | Me ₃ Al/BF ₃ ·OEt ₂ | |
|--------------------|---|---|---|--|--|--|
| | | | <i>cis/trans</i> (% yield) ^b | | <i>cis/trans</i> (% yield) ^b | |
| 1 | <i>cis</i> - 19 (R = heptyl, R' = Me) | 3 | 3:97 (92) | | 86:14 (84) | |
| 2 | <i>cis</i> - 21 (R = butyl, R' = Ph) | 1 | 67:33 (92) | | 92:8 (85) | |
| 3 | <i>trans</i> - 21 (R = butyl, R' = Ph) | 1 | 67:33 (90) | | 4:96 (89) | |

^{a,b} See Table 1.

crossover product should be evident. In the event, the reaction generated only products **4** and **16**, with the crossover products **17** and **18** not evident by ¹H NMR or MS (<0.3% by GC-MS). The use of BF₃·OEt₂ alone, a Lewis acid that induces the *trans* products upon rearrangement that presumably signifies ion-pair dissociation, resulted in the formation of all four possible products. This experiment provides further evidence that ion pairing is determining the stereochemistry in this reaction.

Application of this method to other ring sizes is feasible. The oxepanylvinyl acetal **19**, readily prepared using the method of Rychnovsky,¹⁷ undergoes a retentive rearrangement to provide *cis*-**20** in high yield and good selectivity, entry 1 in Table 2. The tetrahydrofuran substrates *cis*-**21** and *trans*-**21** also undergo rearrangement with high selectivity. Importantly, the use of BF₃·OEt₂ alone provides only 2:1 selectivity favoring *cis*-**22**.

In summary, we have developed a Lewis acid-mediated stereo-retentive rearrangement of vinyl acetals, wherein the selectivity is

controlled by tight ion pairing. A single chiral acetal may be rearranged to form either diastereomer by simple choice of Lewis acid and reaction temperature. Studies aimed at elucidating the exact role and requirement of the two Lewis acids as well as application of this methodology to the synthesis of complex natural products are ongoing.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) The selectivity and reactivity obtained with Et₃Al as a Lewis acid were irreproducible. We suspected that impurities present in the starting material, reagents, or solvent were responsible. Screening for the effect of a number of potential impurities revealed that Et₃Al induced the rearrangement in the presence of alumina, which may have been present in the solvents derived from a solvent purification system.
- (13) Hexanes did not fit this trend (81:19); however, the reaction mixture was found to be heterogeneous under these conditions.
- (14) Ley has reported that the use of TMSOTf at ambient temperature results in isomerization of *trans*-**2a** to *cis*-**2a**; see ref 10. We have found that isomerization of *trans*-**10** to *cis*-**10** does not occur using Me₃Al/BF₃·OEt₂ even at ambient temperature.
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