A Ligand Assisted Claisen Rearrangement

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Abstract: The Ireland ester enolate Claisen rearrangement gives rise to Z-trisubstituted alkenes via heteroatom mediated substrate pre-organization prior to rearrangement.

The Claisen rearrangement of allyl vinyl ethers to give γ , δ -unsaturated carbonyl compounds is a widely used reaction in organic synthesis.¹ An important modification, the Ireland ester enolate Claisen rearrangement,² resulted in improved selectivity and greatly accelerated rates at or below ambient temperature. Numerous reports testify to the value of this contribution.¹ The Claisen rearrangement, either the thermal or Ireland modification, normally yields (E)-alkenes. The observed E-selectivity can be rationalized on the basis of reaction via a chair-

MOTRA HOMANS. MOTA

pseudoequatorial

pseudoaxial

like conformation of the cyclic transition state which places the more bulky group at the carbinol carbon in the pseudo-equatorial orientation. Most of the previous studies have focused on the relative stereochemistry at the α,β -centers of the resulting γ,δ -unsaturated carboxylic acid, and have shown the stereochemistry to be strongly dependent on both enolate and alkene geometry.¹⁻⁵ A new direction for the now classical Ireland ester enolate accelerated Claisen rearrangement is a ligand assisted version which yields Z-trisubstituted alkenes as a result of heteroatom enforced control during the rearrangement.^{6,7}

Our approach to alkene selectivity utilizes coordination of an ether oxygen (at the carbinol center) to the enolate metal to provide pre-organization of the substrate, via a seven membered chelate, prior to rearrangement (eq 1). A very high degree of selectivity has been achieved in reactions of tertiary carbinol esters. The results are listed in the Table. Oxygen very effectively acts as a control element placing the ethereal sidechain in the pseudoaxial orientation prior to rearrangement.

Reactions with numerous different metals using oxygen as the control element were investigated, for example M = Li, Cp₂ZrCl, ZnBr and TiCl₃. None of the combinations gave a Z:E ratio greater than 80:20. Different solvents, ether, THF, toluene and combinations thereof did not significantly improve the ratio. The highest selectivity in the rearrangement ultimately was obtained after ester deprotonation at -10 °C using BrMgN(Et)₂⁸ in a 2:1 mixture of Et₂O:THF in the presence of 1 equiv of HMPA and stirring for 15 h at 0 °C. Higher temperatures decreased the selectivity as did the use of more HMPA.



5,7,9 R'=MOM



2,4 E R'=Me 6.8.10 E R'=MOM



The examples in the Table show that both methoxymethyl and methyl ethers direct equally well. Large groups at the carbinol center, i.e. $R=cy-C_6H_{11}$, provided even more enhanced selectivity. The effectiveness of the metal mediated pre-organization is illustrated in the Table by a comparison of the results of rearrangement of the bromomagnesium enolate and the corresponding trimethylsilylketene acetal.^{10,11} If the carbinol center is tertiary, then no steric preference should be observed and a mixture of E and Z isomers would be expected upon rearrangement in the absence of ligand direction. In fact, essentially no selectivity was observed upon thermal rearrangement of the trimethylsilylketene acetal of esters of tertiary carbinols. Ester **11** rearranged to give only

the tetrasubstituted alkene 12Z.¹⁰ Rearrangement of ester 13 gave rise to 14Z exclusively. We have been unsuccessful in our attempts to trap the magnesium enolate as the ketene acetal. Therefore, at this time, we do not know if it is the E-enolate which rearranges through a chair-like conformation of the transition state or the Z enolate rearranging through a boat-like conformation of the transition state to give the observed result. The stereochemistry of 14Z was assigned following ¹H NOE NMR spectroscopic studies on the corresponding bromolactones 19 and 20.



Using the current set of reaction conditions, rearrangement of esters of secondary alcohols gave only mixtures of E/Z isomers in low yields and significant amounts of ester cleavage and Claisen condensation occurred. Use of sulfur in place of oxygen as the control element resulted in a significant loss of selectivity. In addition, an increase in the chain length between the carbinol center and the coordinating ligand was also detrimental to the efficiency and selectivity of the reaction.¹²

Hydrolysis of the MOM ether¹³ was accompanied by concomitant lactone formation (eq 2). This provided not only a verification of the alkene geometry, but also a means of purification and separation of the Claisen rearrangement product.



Methods for controlling the stereochemistry of formation of carbon-carbon bonds are of utmost importance to synthetic organic chemistry. These results show the dramatic effect that a metal-ligand interaction can have in determining the reactive conformation of the transition state for the Claisen rearrangement. This reaction, which forms Z trisubstituted alkenes, complements the results obtained from the SeO₂ catalyzed allylic oxidation¹⁴ which gives rise to the analogous E-allylic alcohol. Further work is in progress and the results will be reported in due course.¹⁵

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- 9. One diastereomer was formed in the rearrangement of 13 to acid 14. The resulting *syn* stereochemistry was determined by ¹H noe studies on lactone 18 and the lactones prepared via bromolactonization of acid 14.
- 10. The geometry of the alkene was determined by NOE difference spectroscopy. The ratios were determined by integration of signals in the ¹H NMR spectrum.
- 11. Typical experimental procedures: Claisen Rearrangement of Esters.

A. As the Bromomagnesium Enolate: A solution of diethylamine (0.077 g, 1.05 mmol) in ether (5 mL) was cooled to 0-5 °C. Methylmagnesium bromide (0.35 mL of a 3 M solution in ether, 1.05 mmol) was added and the mixture was then heated at reflux for 15 min. After cooling to room temperature, HMPA (63 mg, 0.35 mmol) was added and the mixture further cooled to -10 °C. A cooled solution of the appropriate ester (0.35mmol) in THF (2.8 mL) was then added. After 15 -20 min at -10 °C, the mixture was warmed to 0 °C and maintained at that temperature for 18 h. An acid quench (10% hydrochloric acid) followed by a sodium bicarbonate workup afforded the $\gamma_i \delta$ -unsaturated acid.

B. As the Trimethylsilylketene Acetal: A solution of diisopropylamine (106 mg, 1.05 mmol) in THF (5 mL) was cooled to -5 °C. *n*-Butyllithium (0.68 mL of a 1.6 M solution, 1.05 mmol) was added and after 15 min at -5 °C, the solution was further cooled to -78 °C and a solution of the appropriate ester (0.35 mmol) in THF (2mL) was added. The solution was stirred at -78 °C for 15 min then NEt₃ (106 mg, 1.05 mmol) followed by chlorotrimethylsilane (0.114 g, 1.05 mmol) were added. The cooling bath was then removed and the reaction mixture was allowed to warm to room temperature over 30 min. The mixture was then heated at reflux for 4h. An acid quench (10% HCl) followed by a bicarbonate workup furnished the acid.

- 12. These reactions are still under investigation and the results will be discussed in a full account of our work in this area.
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- 15. Representative procedure for the preparation of the allyl esters: The allylic alcohols were prepared by addition of a vinyl lithium to the corresponding ketone. The yields for these reactions were generally between 75-90%. Preparation of 13: To a solution of Z-4-hydroxy-4-methoxymethoxymethyl-2-hexene (790 mg, 4.55 mmol) in 7 mL of THF at ambient temperature was added a solution of ethylmagnesium bromide in THF (5 mL, 5 mmol). The mixture was stirred for 20 min. A solution of propionyl chloride (0.84 g, 9.1 mmol) in 9 mL of THF was then added to the reaction mixture at RT. After stirring for 2 h at RT, the reaction was quenched with saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the organic layers were dried over sodium sulfate and condensed. Purification of the residue by flash chromatography using a 10/1 mixture of hexane and EtOAc gave the ester (13) as a colorless oil (950 mg, 90%). Yields typically ranged from 75-90%.