Trimethylsilyl Triflate Catalysed Diels-Alder Reaction of TMS Ethers of Conjugated Dienols with Cyclic Enones: Evidence for an Endo Transition State, and First Application to Synthesis of Enantiopure Octalins

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Although the Diels-Alder (DA) reaction of 2-cyclohexenones and 1,3-dienes is in principle an elegant method of synthesizing decalin systems, the thermal reaction proceeds poorly. In 1960, it was noted that Lewis acid catalysts increase the rate, and enhance yield and stereoselectivity of the reaction [1]. It is generally accepted that the concerted [4+2] cycloaddition mechanism still applies [2]. When the π -faces of either reactant are diastereotopic, diastereoisomers arising via addition syn or anti to the group that renders the face diastereotopic are formed. Syn selectivity is particularly prevalent in 6-alkyl cyclohexenones [3].

Gassman and coworkers discovered a cationic variant of the DA reaction involving *in situ* generation of allyl cations. Both inter- and intramolecular cycloaddition reactions of allyl cations to 1,3-dienes were accomplished at low temperature [4]. Based on the stereochemical outcome, the authors proposed a stepwise process. We reported a new variant of this reaction in which (3*E*)-3,5-hexadien-1-ol **2** reacts with 6-methylcyclohexenone **1** with AlCl_3 catalyst in dichloromethane below 0 °C to give hemiacetal adduct **3** as the major product, acetal **4** and enol diene **5** [5]:

It was proposed that these cycloadditions proceeded through an oxy-allylic cation. Thus, the Lewis acid mediates addition of the hydroxyl group of the dienyl alcohol to the enone to form hemiacetal **6**. This collapses to oxy-allylic cation **7**, which drives ring closure via the exocyclic allylic cation **8** to provide the trans-fused precursor cation **9** of the final products. The highly stereoselective outcome of the reaction is noteworthy.

We have now examined this reaction in more detail. The rationalization of hemiacetal intermediates and their collapse to cationic intermediates caused us to focus on catalysts which induce acetal formation between ketones and alcohols. Based on the Noyori method for the preparation of

acetals from ketones and TMS ethers of alcohols with TMSOTf as catalyst,¹⁷¹ we examined reactions of the TMS dienyl ether **10** with enone **1** in presence of 2 mol% of TMSOTf at -78 °C. The major product was the cycloadduct **11** and a diastereomeric mixture of conjugate addition products **12**. Optimum yields (to 64%) of cycloadduct are obtained in acetonitrile.

The acetal **11** was hydrolyzed to the hemiacetal **13** in aqueous tetrahydrofuran (1:3 H₂O:THF) containing *p*-TsOH which is shown by X-ray crystallography to have an axial methyl group. Treatment of **13** with AlCl₃ under nitrogen atmosphere slowly converted it into hemiacetal **3**.

A 4:1 mixture of the 3*E*:3*Z* isomers of each of the (*R*)- and (*S*)-2-methyl-3,5-heptadienol TMS ethers **14** and **15** with enone **1** in the presence of 10 mol% TMSOTf in acetonitrile at -20 °C during 1 day gave acetals, acid hydrolysis of which gave the crystalline hemiacetals **16** ([α]_D²¹ = -100°, *c* = 0.60) and **17** ([α]_D²¹ = +102°, *c* = 0.61, CHCl₃) as *single enantiomers respectively*. Configuration of the products, secured by X-ray crystallography, indicates an endo transition state in their formation.

The observation is thus made that the chiral centre at C-2 in the starting TMS ether controls *in an absolute sense* the stereochemistry in the tricyclic product obtained via the ionic Diels-Alder reaction.

The full results, including a rationalisation of the stereochemical outcome of these remarkable reactions, will be presented.

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