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Triarylcarbenium Ions as Catalysts in the Mukaiyama Aldol Addition: A Mechanistic Investigation.

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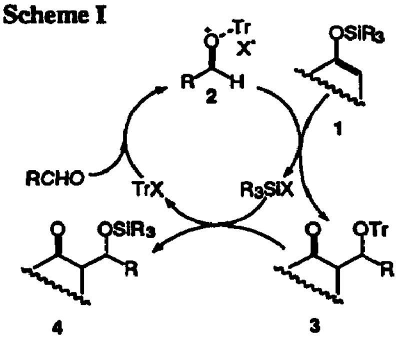
Key Words *: Aldol Condensation ; Triarylcarbenium ions ; Diastereoselective*

Abstract: *1-Phenyl-2:3,6:7-dibenzosuberyl salts* 5^+ *efficiently catalyze the aldol reaction between silyl enol ethers and benzaldehyde with moderate diastereoselectivity. Crossover experiments with doubly labeled silyl enol ethers, kinetic and stereochemical studies identify* 5^+ *as the catalyst rather than a Lewis acidic* R_3SiX *species in this transformation.*

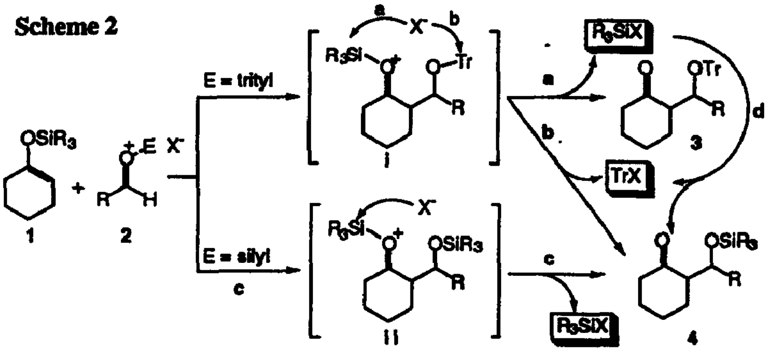
The Mukaiyama aldol reaction between enolsilane derivatives and aldehydes is one of the most versatile synthetic methods for carbon-carbon bond formation.[1] For the last two decades the scope and utility of this transformation has been extended by the employment of various Lewis acids, such as $BF_3 \cdot OEt_2$, $SnCl_4$, $Sn(OTf)_2$, fluoride ions, derivatives of Ti(IV) and Zr(IV), derivatives of Yb(III), various lanthanide salts, ruthenium, and rhodium complexes. In addition, Mukaiyama, et al. have reported that triphenylcarbenium ions (trityl salts) are efficient catalysts for this process.[2] An important preparative and mechanistic feature of the trityl salt-mediated aldol reaction is that it proceeds readily at -78 °C in a *catalytic fashion.* A proposed catalytic cycle is shown in Scheme I. Addition of a silyl enol ether 1 to a trityl-activated aldehyde 2 produces trityl aldolate 3 with release of R_3SiX. Subsequent exchange between the 3 and R_3SiX is required to produce the silyl aldolate 4 and to regenerate the trityl catalyst. While this cycle is plausible, the precise nature of the catalytic species in these reactions has never been established. In particular, we were cognizant that the generation of R_3SiX may provide a shunt to a purely silyl-mediated pathway that does not involve trityl-ion catalysis.[3,4] Since our interest in his reaction is the design of *chiral* trityl salts as novel asymmetric catalysts, we sought to clarify the mechanistic details of this transformation.

Scheme I

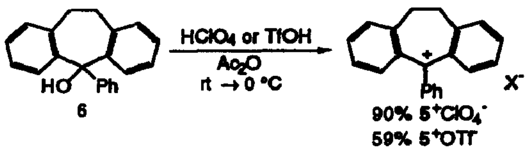


To explain the production of silyl ether products in a trityl salt-mediated reaction, three plausible reaction pathways were considered, paths **a**-**c**, Scheme II. In the trityl-ion-catalyzed process, initial addition of **1** to **2** generates silyloxocarbenium ion intermediate **i**. In the first route (path **a**) the R_3SiX released into the reaction medium undergoes exchange (path **d**) with **3** to give **4**. If the exchange process **d** is slow, then the R_3SiX-catalyzed reaction (path **c**), may compete effectively with the trityl salt catalysis. The third route (path **b**) involves formation of a zwitterion (not shown) that may collapse to **4** by either direct intramolecular or intermolecular silyl group transfer without the intermediacy of R_3SiX. Three sets of experiments were carried out to distinguish these mechanistic scenarios: (1) double-label crossover experiments to establish the intermediacy of R_3SiX, (2) rate and (3) stereochemical studies to establish whether, if present, the R_3SiX is kinetically significant.[5]

Scheme 2



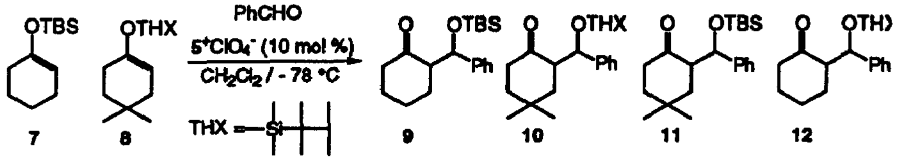
For the test catalysts, two 1-phenyl-2:3,6:7-dibenzosuberyl salts, $5^+ClO_4^-$ and 5^+OTf^-, were prepared by treatment of the corresponding dibenzosuberol 6[6] with perchloric acid and triflic acid in acetic anhydride, resp.[7,8] The dark-red salts could be obtained in analytically pure form by crystallization and must be stored at -20 °C in a dry box. The ^{13}C NMR spectrum of $5^+ClO_4^-$ showed an upfield shift of the carbenium carbon ($\delta = 204.4$ ppm) relative to those of trityl bisulfate ($\delta = 211$ ppm) and 9-phenyl-9-fluorenyl fluorosulfonate ($\delta = 224.2$ ppm).[9] Despite the apparently reduced positive charge (electrophilicity) at the carbenium center, 5^+ salts served as a powerful catalysts for the aldol reaction.



For the crossover experiments, two silyl enol ethers 7 and 8 with comparable steric and electronic properties were combined with benzaldehyde, Scheme 3. A 1 : 1 mixture of 7 and 8 (0.56 equiv. of each) in CH_2Cl_2 was added to a solution of benzaldehyde in CH_2Cl_2 in the presence of 10 mol % of $5^+ClO_4^-$ at -78 °C. The reaction was complete in 5 min. and product composition was determined by GC analysis.[8,10] A mixture of scrambled silyl ethers was isolated in a ratio of 2.1 / 1.8 / 1.3 / 1 (9 / 10 / 11 / 12). Control experiments showed that neither the starting silyl enol ethers (7 and 8) nor the silylated aldol products (9 and 10) exchanged under similar reaction conditions. *On the basis of these observations, the reaction pathway b involving intramolecular silyl transfer without release of* R_3SiX *was unambiguously precluded.* In addition, the intermolecular version of this pathway (bimolecular reaction of the zwitterion) is unlikely due to unfavorable entropic and steric factors.

Since the crossover experiment supported an aldolization mechanism that proceeds with intervention of R_3SiX (path a), it was necessary to establish whether an independent catalytic cycle involving this species was operative (path c). The possibility of a trityl-initiated/silyl-catalyzed process can be eliminated if the rate of exchange of 3 and R_3SiX (path d) is faster than the rate of aldoliztion under R_3SiX catalysis. This would remove R_3SiX from the reaction manifold (by forming 4) thereby suppressing secondary catalysis.

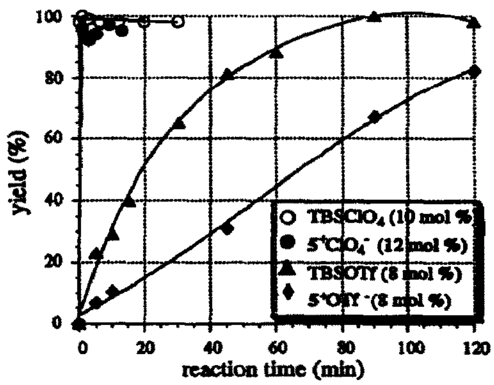
Scheme 3



Three independent lines of evidence lead to the conclusion that metathesis is faster than silyl catalysis. First, neither trityl ether 3 nor desilylated aldol products were detected in the reaction between benzaldehyde and 7 in the presence of 20 mol % each of $5^+ClO_4^-$ and 2,6-di-*tert*-butyl-4-methylpyridine at -78 °C or upon warming to ambient temperature. Second, stereochemical studies revealed that different anti/syn ratios of silyl ether 9 were obtained when the aldol reaction was carried out under $TBSClO_4$[11] (anti/syn-9, 4.2/1) and $5^+ClO_4^-$ (anti/syn-9, 2.1/1) catalysis or under TBSOTf (anti/syn-9, 3.5/1) and 5^+OTf^- (anti/syn-9, 2.4/1) catalysis.

Finally, kinetic experiments, Figure 1, demonstrated a measurably different rate of reaction catalyzed by 5^+OTf^- compared to the corresponding reaction mediated by TBSOTf ($t_{1/2}$ = ~70 min. vs. 20 min.). If the 5^+OTf^- promoted process involved trityl initiation followed by silyl catalysis, the rate would be expected to be the same as for the TBSOTf catalyzed process.[12] Both $TBSClO_4$ and $5^+ClO_4^-$ promoted the aldol reaction at a dramatically faster rate than the corresponding triflates. Unfortunately, these reactions went to completion in <1 min which did not allow discrimination between a silyl and trityl ion-catalyzed process. Therefore, the different diastereomeric composition of the products provides the strongest evidence against a $TBSClO_4$ promoted pathway.

Figure 1. Kinetic Plots of Catalyzed Reaction Between 7 and PhCHO.



The relative rates of TBSOTf and 5^+OTf^- mediated reactions provide an intriguing dichotomy. Even though TBSOTf is generated in the reaction cascade and even though it is a more effective promoter of the aldolization, it does not compete with 5^+OTf^- catalysis! This apparent inconsistency is easily understood by invoking a rapid metathesis reaction (path d) that removes the faster-acting silyl catalyst from the scene to create the final product 4 and regenerate the slower-acting trityl catalyst. Since the silyl-X species investigated here turned out to be very powerful catalysts for the aldol reaction between TBS enol ethers and benzaldehyde, careful survey of silyl group structure and counter ion type will be essential for the rational design of chiral triarylcarbenium ion catalysts for the Mukaiyama aldol reaction. If the silyl-mediated pathway takes over, the opportunity for asymmetric catalysis is lost.

In summary, from this mechanistic investigation a picture emerges that supports the catalytic cycle depicted in Scheme 1. The experiments utilizing doubly-labeled silyl enol ethers together with stereochemical and kinetic studies provide a useful mechanistic tool to distinguish trityl (and related species) from silyl catalysis. The development of chiral triarylcarbenium ions related to 5^+ for an asymmetric variant of the Mukaiyama aldol reaction is currently underway and will be reported in due course.

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(12) We cannot rule out the possibility of simultaneous catalysis by TBSOTf and 5^+OTf^- or slow release of TBSOTf. More precise kinetic measurements are required to locate an inflection point in the curve.

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