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Homogeneous Catalysis. $[TiCp_2(CF_3SO_3)_2]$ and $[ZrCp_2(CF_3SO_3)_2THF]$, Fast and Efficient Catalysts for the Mukaiyama Cross-Aldol Reaction

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Key Words: cross-aldol catalysis; titanium and zirconium catalysts; adduct formation.

Abstract: *The catalysts* $[TiCp_2(CF_3SO_3)_2]$ *and* $[ZrCp_2(CF_3SO_3)_2THF]$ *are fast and efficient catalysts for the Mukaiyama cross-aldol reaction involving both ketones and aldehydes and the catalysis is promoted by binding of the carbonyl group to the metal after dissociation of triflato ligands.*

The Mukaiyama cross-aldol reaction involving the coupling of aldehydes and ketones with enol silanes is catalyzed by a variety of Lewis acids.[1] Among these are BF_3, $AlCl_3$, $SnCl_4$, and $TiCl_4$,[2] trityl salts,[3] trimethylsilyl triflate,[4] fluoride ions,[5] derivatives of bis-cyclopentadienyl ytterbium chlorides,[6] various lanthanide salts,[7,8] and rhodium complexes.[9] Many have high turnover frequencies and, in some cases, high enantioselection has been observed.[10-17] In contrast to silyl ketene acetals, silyl enol ethers generally react poorly or not at all with ketones using these catalysts. Further, in most cases the chiral catalysts were prepared *in situ* and consequently, the exact nature of the chiral catalytic species was not defined. We report here two catalysts which are readily transformed into structurally defined chiral catalysts and which catalyze rapidly the cross-aldol reaction between aldehydes and most ketones with silyl ketene acetals and silyl enol ethers. The two catalysts are the structurally characterized complexes $[TiCp_2(CF_3SO_3)_2]$[18] and $[ZrCp_2(CF_3SO_3)_2THF]$[19] (Cp is cyclopentadienyl and THF is tetrahydrofuran) which are readily prepared from commercially available $[MCp_2Cl_2]$ complexes by reaction with $AgCF_3SO_3$.[18,19] Both complexes are moderately moisture sensitive and are best handled in a dry box but the use of the dry box can be avoided by preparing the catalysts *in situ* under standard organic procedures.[20]

The results using 0.5 mol % catalysts loadings and 1M in each substrate in CD_3NO_2 at 25 ° C, are collected in Table 1. Catalysis was followed by ^1H NMR spectroscopy and except for entries 8 and 17 the products are produced in >95% yield. A number of these catalyses were performed on a preparative scale and, after desilylation, the purified products were isolated in yields ranging from 75 to 90%.[20] The rate of catalysis follows the degree of steric hindrance of the ketone or aldehyde to the point where pinacolone (entries 8 and 17) is either catalyzed poorly or not at all. The two catalysts have similar but different rates, and as a practical matter, either can be used. It is conceivable that small amounts of trimethylsilyl triflate are formed during the reaction, and that at least some of the catalysis proceeds by this route. This is an unlikely possibility, because first, the Ti and Zr catalysts have somewhat different rates for corresponding substrates in some cases, second, tetra-n-butylammonium triflate does not catalyze the reaction, third, a chiral bridged metallocene bistriflate complex[21] analogous to those described here gives enantioselection (ee's ~20%), and fourth, no induction period is observed for entry 16 or any other entry with a measurable rate.

Using the substrates in entry 10, we find for the Zr catalyst a linear dependence of rate on catalyst concentration; for 0.1, 0.05, and 0.02 mol% catalyst loadings, 90% reaction was achieved in 40, 80, and 200 min, respectively, in CD_3NO_2 at 25 ° C. The rate of the thermal reaction of these substrates (entry 10) have been measured at 150 ° C.[22] Assuming a 2-fold reduction in rate for every 10 ° C decrease in temperature, we estimate that the present catalysts accelerate the Mukaiyama reaction by $>10^8$ over the uncatalyzed thermal path. The reactions of the silyl enol ether of cyclohexanone with benzaldehyde or isobutyraldehyde show poor diastereoselectivity with either catalyst giving nearly equal amounts of erythro and threo isomers at 25 ° C.

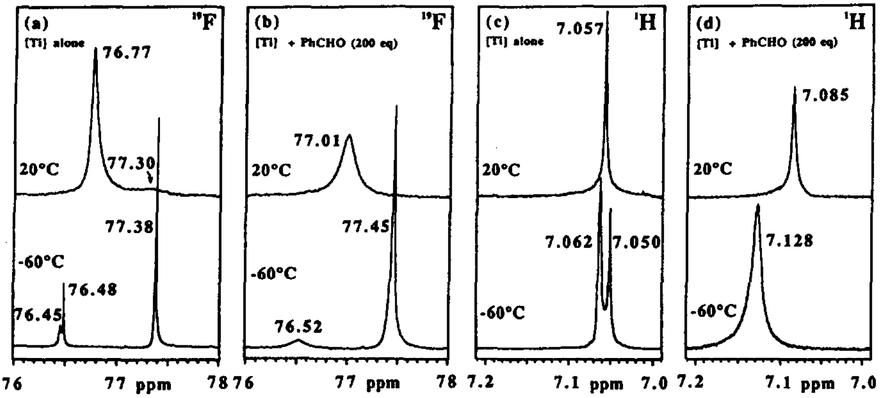
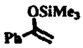
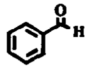
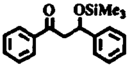
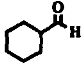
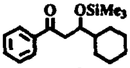
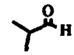
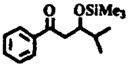
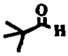
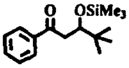
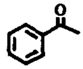
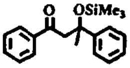
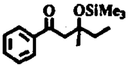
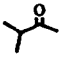
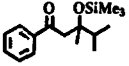
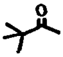
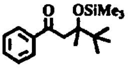
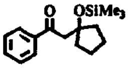
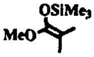
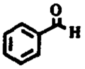
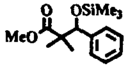
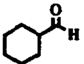
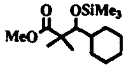
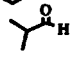
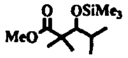
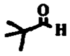
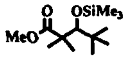
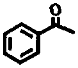
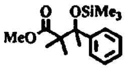
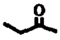
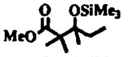
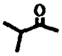
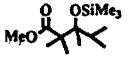
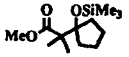


Figure 1. 400 MHz ^{19}F NMR (a and b) and ^{1}H NMR (c and d) spectra of the Ti catalyst alone (a and c) and in the presence of 200 equivs of benzaldehyde (b and d) at 20 and -60°C. The solution did not freeze at -60°C.

In 1×10^{-3} M CH_3NO_2 solutions at 25 ° C, the Ti and Zr catalysts have conductivities of $\Lambda_M = 128$ and 88 mol^{-1} ohm^{-1} cm^2, respectively, indicating that the former is between a 1:1 and 2:1 electrolyte and the latter is close to a 1:1 electrolyte.[23] These results attest to the lability of the triflato ligands, which in these cases, are presumably replaced by coordination of the CH_3NO_2 solvent to give species of the type $[MCp_2(CF_3SO_3)(CH_3NO_2)](CF_3SO_3)$ and $[MCp_2(CH_3NO_2)_2](CF_3SO_3)_2$. Given the weak coordinating ability of CH_3NO_2 we anticipate that aldehyde and ketone substrates would also displace the triflato ligands or the solvent ligands to form adducts which cause the substrates to be activated toward reaction. These expectations are confirmed by a temperature dependent ^{19}F and ^{1}H NMR study of the Ti catalyst under catalytic concentrations in CD_3NO_2 solution (Figure 1). ^{19}F NMR signals corresponding to free triflate were observed at 77.38 ppm (-60 ° C) for the catalyst alone and at 77.45 ppm for catalyst in the presence of 200 equivalents of benzaldehyde. That free triflate was present was confirmed by the signal of tetra-n-butylammonium triflate. The signals at 76.45 and 76.48 ppm of the catalyst alone, by inference, represent bound triflate in the complexes $[TiCp_2(CF_3SO_3)_2]$ and $[TiCp_2(CF_3SO_3)(CD_3NO_2)]^+$. Upon the addition of benzaldehyde a single broad ^{19}F NMR signal is observed at 25 ° C which separates into two signals at -60 ° C where the bound triflato signal appears at 76.52 ppm. The ^{1}H NMR signals show similar but less defined behavior. Integration of the ^{19}F and ^{1}H NMR signals of the catalyst alone at -60 ° C suggest that the proton signal at 7.062 ppm represents $[TiCp_2(CD_3NO_2)_2]^{2+}$ and the proton signal at 7.050 ppm represents, coincidentally, the $[TiCp_2(CF_3SO_3)_2]$ and $[TiCp_2(CF_3SO_3)(CD_3NO_2)]^+$ species. These data allow us to draw the following conclusions. First, in CD_3NO_2 solutions extensive dissociation of the triflato ligands occurs and their exchange with solvent is rapid and reversible at 20 ° C. Second, exchange between bound and free benzaldehyde is also rapid and reversible. These circumstances are ideal for catalysis since the catalytic frequency will depend only on the concentration of the substrate adduct and not on the rates of exchange of the various species in solution.

Table 1

Catalysis of the Mukaiyama Aldol Reaction With 0.5mol% [$TiCp_2(CF_3SO_3)_2$] and 0.5mol% [$ZrCp_2(CF_3SO_3)_2THF$] in CD_3NO_2 at 25°C

	Substrates		Time for 90% Reaction (min)		
Entry	Enol Silane	Carbonyl Compound	[$TiCp_2(CF_3SO_3)_2$]	[$ZrCp_2(CF_3SO_3)_2THF$]	Product
1			$<5^{a,d}$	$<5^{a}$	
2			$<5^{b}$	$<5^{b}$	
3			<5	<5	
4			7^{c}	7^{c}	
5			10	7	
6			35	10	
7			160	130	
8			(56%,48h)	(60%,19h)	
9			110	35	
10			<5	<5	
11			$<5^{b}$	$<5^{b}$	
12			<5	<5	
13			370	300	
14			7	<5	
15			7	<5	
16			780	500	
17			—	—	—
18			46	13	

a. Solvent was CD_2Cl_2, because in CD_3NO_2 the product is slowly transformed to the ether Ph(CO)CH_2C(Ph)OC(Ph)CH_2(CO)Ph. b. Silane added to the catalyst solution followed by the aldehyde to avoid competitive catalytic cyclic trimerization of the aldehyde. c. 15 min after the catalysis has begun, catalyst induced product decomposition to unidentified products is observed. d. Those entries with a time of <5 min indicate that the catalysis was complete essentially upon mixing.

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20. **Typical catalytic procedure.** [$ZrCp_2(CF_3SO_3)_2THF$] (0.0015 g, 0.0025 mmol) was weighed into an NMR tube under Ar. A volume of CD_3NO_2 such that the final concentration of each substrate would be 1 M was injected. After dissolution of the catalyst the carbonyl substrate (0.50 mmol) followed by the enol silane (0.50 mmol) were injected. The progress of the reaction was monitored by ^1H NMR integration of the signals due to the substrates and product. **Typical Preparative Procedure**: $AgCF_3SO_3$ (6.8 mg; 0.026 mmol) in CH_3NO_2 (1.0 mL) was injected under Ar into a solution of [$TiCp_2Cl_2$] (3.4 mg; 0.013 mmol) in CH_3NO_2 (0.3 mL) and the resulting bright red mixture was stirred for 20 min. It was filtered under Argon, washed with CH_3NO_2 (0.5 mL) and the filtrate was cooled to 0 ° C and, for example, isobutyraldehyde (245 μL; 2.65 mmol) and 1-phenyl-1-(trimethylsiloxy) ethylene (540 μL; 2.65 mmol) were sequentially injected. The solution was stirred at 0 ° C for 15 min, was then allowed to warm to 25 ° C and then stirred for a further 15 min. Trifluoroacetic acid (120 μL) and water (120 μL) were added and the mixture was stirred for 1 h. The mixture was poured into water (20 mL) and was extracted with benzene (30 mL). The benzene extract was dried (Na_2SO_4) and after evaporation in vacuo gave the pure desilylated product as an oil (0.52 g; 82%).
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