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Homogeneous Catalysis. Transition Metal Based Lewis Acid Catalysts.

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Abstract: *Transition metal based Lewis acids provide catalysts for the Diels-Alder and Mukaiyama reactions. These catalysts must possess an electron deficient oxophilic metal center and a labile coordination position. Unlike traditional Lewis acids, those derived from transition metals can function in the presence of water and have well defined structures. It is shown how a normally electron rich ruthenium atom can be converted to a Lewis acid by incorporation of electron withdrawing ligands and ligands with hard donor atoms. This ruthenium complex,* $[Ru(salen)(NO)(H_2O)]^+$*, is an efficient catalyst for the Diels-Alder reaction, but in the Mukaiyama reaction, it tends to be reduced and thereby deactivated by the silyl enol ether. It is shown that the complex* $[TiCp^*_2(H_2O)_2]^{2+}$ *(*Cp^* *is pentamethylcyclopentadienyl) is an efficient catalyst for the Diels-Alder reaction even when water is present. Similarly, the triflato complexes* $[TiCp_2(CF_3SO_3)_2]$ *and* $[ZrCp_2(CF_3SO_3)_2]$ *(Cp is cyclopentadienyl) are efficient catalysts for both the Diels-Alder and Mukaiyama reactions. All of these catalysts are effective at very low loadings of ~ 1 mol%. Catalysis has been shown to occur via substrate-catalyst adducts and moreover these adducts are formed rapidly and reversibly as required for efficient catalysis.*

Lewis acids serve as promoters for a variety of reactions where one of the reactants, a Lewis base, is activated by binding to the Lewis acid. The Lewis acid activation can lead to rate accelerations of 10^6 or greater over the corresponding thermal path. Lewis acids allow the transformations to occur at low temperatures, which in addition to convenience, serves to increase the selectivities.

The most powerful traditional Lewis acids are the halides of B(III), Al(III) and Ti(IV); less potent Lewis acids include species derived from Sn(IV), Fe(III), Si(IV) and the lanthanide elements. Although not always used in catalytic amounts for practical reasons, traditional Lewis acids can act as genuine catalysts giving convenient rates at moderate catalyst loadings. All of these species rely on their oxophilicity in promoting reaction and as such are highly water sensitive. To act as catalysts, however, these Lewis acids demand that strictly anhydrous reaction conditions prevail, in fact even small amounts of water can lead to deactivation of the catalyst by formation of unreactive hydroxides. This is one of the reasons that large amounts of the traditional Lewis acids are used to promote reaction.

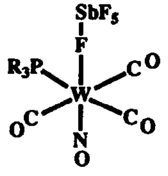
When these Lewis acids are modified by incorporation of ligands additional problems arise. Such ligand incorporated species remain very water sensitive and are generally less active catalysts than the parent halides. Consequently, unless great care is taken in the synthesis of the ligand incorporated Lewis acids, a major portion of catalysis can occur via the more reactive parent halide which would obviate the purpose of ligand incorporation. In addition, ligated Lewis acids are known to rapidly exchange their ligands and have a high tendency to oligomerize. Thus it is not always clear if more than one species is responsible for catalysis. Although some excellent results have been reported for enantioselective traditional Lewis acid catalysis,[1] the identification of the species responsible for the selectivity has been difficult to ascertain because of the complexity of the systems used. We sought to overcome some of these difficulties by developing new classes of transition metal based Lewis acids with specific properties. Our first objective was to determine the factors which a transition metal complex must possess in order to be a catalytically effective Lewis acid. At the same time the selection of the Lewis acid was guided by our long term objective of developing enantioselective Lewis acid catalysts. This latter consideration led to the restriction that the Lewis acid complexes could be readily modified into chiral catalysts.

Ideally, a Lewis acid should have the following properties. First, the catalyst should accelerate the reactions by at least 100-fold so that the contribution of any achiral thermal path is effectively suppressed. Second, it should perform this acceleration at low catalyst loadings. Third, for convenience the catalyst should not be destroyed or strongly inhibited by the presence of water. Fourth, a single, well-defined species should control all of the catalysis. Fifth, the incorporated chiral ligands should have a fixed and stable geometry. Sixth, in order to assess the steric origins of the stereoselectivity and to allow for the tuning of the Lewis acidity, the ligands should be easily modified. Seventh, the binding of the substrate to the catalyst should be rapid and reversible, and the equilibrium should lie strongly toward adduct formation. The rate of catalysis will depend on the binding constant, and the rate of catalysis will be impeded if the rate of formation and exchange is comparable to or slower than the rate of reaction of the adduct. Eighth, the binding of the catalyst with the product should also be rapid and reversible, and the binding constant should be less than that for the substrate. Were the rates of exchange of the product adduct slow and its stability high, the catalysis would experience product inhibition because the product would diminish the effective concentration of the catalyst and eventually the catalysis would become inconveniently slow at high turnover numbers. Ninth, side reactions such as polymerization should not be competitive with the desired reaction.

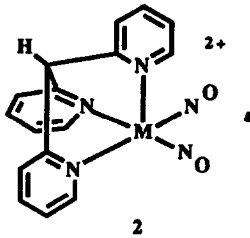
It is very difficult, if not impossible, to meet all of these criteria with the traditional Lewis acids. It is for these reasons that we searched for transition metal based catalysts. This is a largely uncharted area with few guiding principles, but it is an area which we believe holds great promise for tuning Lewis acid activity and for controlling stereoselectivity.

TRANSITION METAL LEWIS ACIDS

Before and during our development of new transition metal based Lewis acid catalysts there appeared a number of reports which described such catalysts. The first and most successful of these[2] was the moisture sensitive species $[W(CO)_3PR_3(NO)SbF_6]$ 1 which was used for catalyzing the Diels-Alder reaction. Although this catalyst operated at low catalyst loadings, it suffered from its tendency to polymerize the diene for slow Diels-Alder reactions. Even so, the discovery was important because it demonstrated how normally electron rich W(0) complexes could be converted to Lewis acids. The characteristics of this species which serve to promote Lewis acidity are the following. First the SbF_6^- ligand is readily displaced by the carbonyl group of a dienophile giving the positively charged intermediate, $[W(CO)_3PR_3(NO)(\text{dienophile})]^+$. The overall positive charge is expected to enhance Lewis acidity. The overall charge, however, is unlikely to be sufficient in itself to produce effective Lewis acid catalysis. A second crucial feature appears to be necessary, namely, the presence of the trans-disposed electron withdrawing NO^+ ligand. In addition to withdrawing electron density from the metal, the NO^+ ligand will labilize trans disposed ligands such as a dienophile. Third, the three electron withdrawing



1



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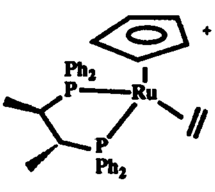
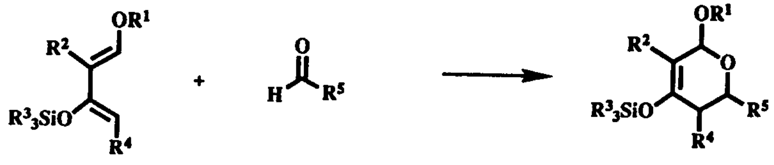


3

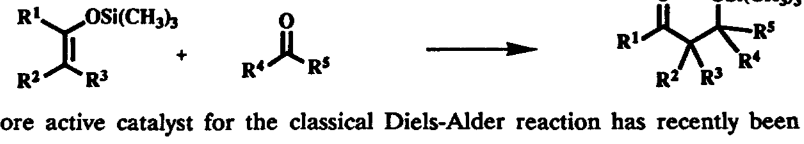
CO ligands also enhance the Lewis acidity. As the number of electron donating phosphine groups is increased[2] by replacement of the CO ligands, the Lewis acidity decreases. Thus it appears that for this catalyst the Lewis acidity depends on the positive charge, the presence of the trans NO^+ ligand and the incorporation of the CO ligands. The addition of electron donating groups can switch off the Lewis acidity even when the positive charge and the NO^+ ligand remain.

Given this prescription for Lewis acidity it is not surprising to find that the species $[M(HC(py_3))(NO)_2]^{2+}$ 2 M = Mo, W act as Lewis acids.[3] They, however, cause polymerization of the diene in the Diels-Alder reaction. The stable adducts formed by aldehydes and ketones have been studied with these complexes.

A much milder Lewis acid has been developed[4] using the chiral precursor $[RuCp(S,S\text{-chiraphos})(C_2H_4)]^+$ 3 Although this species carries a positive charge which promotes Lewis acidity, the ruthenium center remains basic because of the presence of the cyclopentadienyl ligand and phosphine ligands. Consequently, the virtual coordination site can bind olefins, particularly those with electron withdrawing groups.[5] Because of this, the classical Diels-Alder reaction is not promoted by this catalyst since the dienophile forms a strong π-olefin complex which is inert to reaction with the diene. This feature represents one more consideration in designing transition metal based Lewis acid catalysts, namely, binding should occur via the carbonyl oxygen atom and not via the olefin. Despite this, complex 3 can act as a mild catalyst for the hetero-Diels-Alder (Danishefsky) reaction which employs electron-rich dienes and aldehydes (eq 1). When $R^1 = CH_3$; $R^2 = H$; $R^3 = CH_3$; $R^4 = H$; $R^5 = Ph$, catalysis gives the pyrone in good chemical and optical yield. For this catalysis it was demonstrated that benzaldehyde displaced the bound ethylene to form an activated aldehyde adduct.



(1)



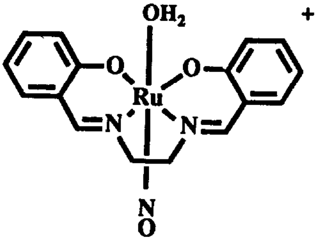
(2)

A more active catalyst for the classical Diels-Alder reaction has recently been reported.[6] The catalyst precursor is $[Zr(Cp)_2(O\text{-}t\text{-}Bu)THF]^+$ which is useful for the reaction of methyl acrylate with isoprene and cyclopentadiene.

In addition to these reports, there is the observation[7] that species of the type $[Rh(diphosphine)(solvent)_2]^+$ catalyze the Mukaiyama reaction (eq 2). Since the rhodium center of this catalyst is electron rich, the observation of catalysis indicates that very mild Lewis acids are capable of promoting the Mukaiyama reaction. This is also likely to be the case for the hetero-Diels-Alder reaction which in some respects is a variation of the Mukaiyama reaction. The classical Diels-Alder reaction, however, requires more potent Lewis acids but if the Lewis acid is made too "hot" polymerization of the substrates can accompany the reaction. Tuning the Lewis acidity for the classical Diels-Alder reaction is therefore not a simple task. A review by Beck[8] lists many potential Lewis acids derived from transition metals. We now describe our work in this area.

1. Diels-Alder Catalysis

1.1 Ruthenium Catalyst. Guided by some of the results previously described together with the general principles of organometallic chemistry, we were drawn to the easily prepared complex, $[Ru(salen)(NO)(H_2O)]SbF_6$ **4** as a possible Lewis acid catalyst[9]. A crystal structure reveals the expected geometry, **5** an essentially linear Ru-N-O angle is observed and the water molecule is trans to the NO. The linear angle indicates a NO^+ ligand[10] which is confirmed by the NO stretching frequency of 1889 cm,$^{-1}$ which among NO^+ complexes is exceptionally high.



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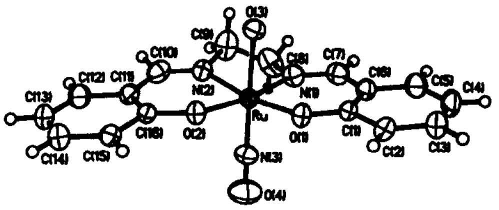


5

The choice of **4** was based on the following considerations. First, the complex has an overall positive charge. Second, the salen contains hard donor atoms which are poorly electron donating. Third, the NO^+ ligand serves to withdraw electron density from the metal. Fourth, the NO^+ ligand is trans to the aquo group, an arrangement which is expected to labilize this coordination position.

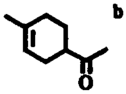
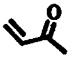
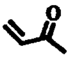
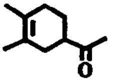
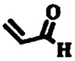
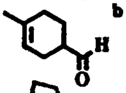
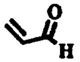
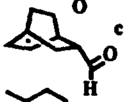
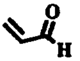
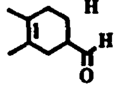
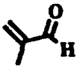
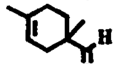
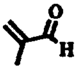
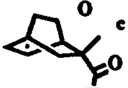
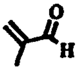
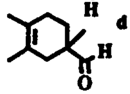
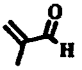
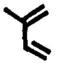
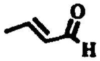
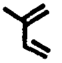
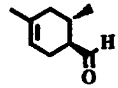
This last characteristic is confirmed by studies of **4** in nitromethane solution. It was found that the equilibrium depicted in eq 3 exists, and in dry CD_3NO_2 solution at 25°C, approximately equal amounts

$$[Ru(salen)(NO)(H_2O)]^+ + CD_3NO_2 \rightleftharpoons [Ru(salen)(NO)(CD_3NO_2)]^+ + H_2O \quad (3)$$

of the aquo and nitromethane complexes are formed. Addition of $^{17}OH_2$ causes the equilibrium to shift to the left, but even at -25°C, exchange between free and coordinated water is extremely rapid on an NMR time scale. Thus **4** possesses ideal characteristics for a catalyst.

Using the $[Ru(salen)(NO)(H_2O)]SbF_6$ catalyst the results for the Diels-Alder reactions are collected in Table 1. Included in this table are the rates and selectivities for the corresponding thermal reactions. The rate comparisons are made for 90% completion of the reactions. In all catalytic cases, only the Diels-Alder products were observed. Aside from entries 1 and 3, the catalytic rate is many orders of magnitude faster than the corresponding thermal rate, even at these very low catalyst loadings. As expected, the selectivities of the catalytic reactions are greater than those of the corresponding thermal

Table 1
Diels - Alder catalysis by [Ru(salen)(NO)(H_2O)]SbF_6 in CD_3NO_2 solutions at 25 °C.

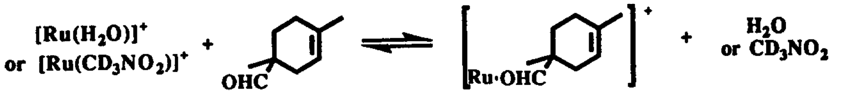
			Catalysis			Thermal	
	Dienophile	Diene	Time for 90% Yield (h)	Isomer Ratio	Major Product	Time for 90% Yield[g] (h)	Isomer Ratio
1			71	91 : 9	 [b]	3000	70 : 30
2			22	99 : 1	ND	> 10^5	93 : 7 [h]
3		 [a]	40	—		2000	—
4			5	99 : 1	 [b]	2700	70 : 30
5			4.4	98 : 2	 [c]	> 10^5	89 : 11 [h]
6		 [a]	3.3	—		2000	—
7			3	93 : 7	 [d]	> 10^5	72 : 28 [h]
8			48	70 : 30	 [c]	> 10^5	ND
9		 [a]	3.2	—	 [d]	14000	—
10			2	90 : 10	 [e]	300	86 : 14
11			718	92 : 8	ND	> 10^5	ND
12			70	92 : 8	 [f]	> 10^5	ND

Unless indicated otherwise all initial substrate concentrations are 2.8 M in each substrate using 1 mol% catalyst. [a] Initial substrate concentration is 1.4 M in each substrate using 2 mol % catalyst. Assignment (^1H NMR) of the major product : [b] Bonneson, P.V.; Pukett, C.L.; Honeychuck, R.V.; Hersh, W.H. J. Am. Chem. Soc. 1989, 111, 6070.; ND = Not Determined; [c] Geibel, K. Chem. Ber. 1970, 103, 1637.; [d] Balwin, J. E.; Lusch, M. J. J. Org. Chem. 1979, 44, 1923.; [e] Kaufmann, D.; Boese, R. Angew. Chem. Int. Ed. Engl. 1990, 29, 545.; [f] Brun, C; Jenner, G.; Deluzarche, A. Bull. Soc. Chim. Fr. 1972, 2332.
[g] Time calculated by extrapolation of a second-order plot of the thermal reaction under the same concentrations of substrate used in catalysis at 25 °C. [h] Ratios obtained by heating substrates either neat or in CD_3NO_2 solution.

reactions. The [Ru(salen)(NO)(H_2O)]$^+$ is a mild catalyst having the advantage of suppressing polymerization even with the most sensitive substrates, but it has the disadvantage of not catalyzing the Diels-Alder reaction with less active dienophiles such as methyl acrylate at these low catalyst loadings. An inspection of Table 1 indicates that aldehyde bearing dienophiles react faster than the ketonic analogues and that steric and electronic factors also control the rate in the expected manner. Kinetic studies of the rate of catalysis using 1 mol% catalyst up to 95% of reaction indicate that there is only slight product inhibition, suggesting that product binding is comparatively weak.

Compared to traditional Lewis acids the present catalyst is not destroyed by water and, even more important, catalysis proceeds in the presence of water. Thus, for example, the partners in entry 7 react only at half the rate when the nitromethane solvent is saturated (2% w/w) with water (100 mol%) due to competitive binding of water to the catalyst. For practical purposes neither the reagents nor the solvent need to be dried in order to carry out the Diels-Alder catalysis. Binding of methacrolein and of its Diels-Alder product with isoprene (entry 7) to the catalyst has been established by ^{1}H NMR studies in CD_3NO_2 solutions. It was found that under catalytic concentrations about 30% of the catalyst is bound to methacrolein and that under similar concentration conditions, the Diels-Alder products (entry 7) bind about one third as strongly. Further, in both cases the adduct equilibria are established upon mixing. The rapid equilibration of both adducts confirms that the catalytic rate depends only on the stabilities of the adducts and not on their rates of formation. It is interesting to note that methacrolein adduct formation is endothermic, in other words the adduct concentration increases with increasing temperature. This net endothermicity probably arises from the participation of a variety of equilibria in solution involving binding of water, nitromethane and the dienophile. During catalysis three equilibria have been demonstrated and are shown in eqs 3, 4, 5.

(4)



(5)

Thus the present ruthenium based catalyst has a number of desirable characteristics for the Diels-Alder reaction. It is not destroyed by water, catalysis proceeds in the presence of water, adduct formation is established rapidly, the dienophile binds more strongly than the product, very low catalyst loadings can be employed, no olefin binding occurs and no polymerization of substrates is observed. A summary of the catalytic mechanism is illustrated in Figure 1.

1.2 Titanium and Zirconium Catalysts. Titanium(IV) and zirconium(IV) halides are effective Lewis acid catalysts but they suffer from all of the problems associated with traditional Lewis acids. We considered the possibility of exploiting this inherent Lewis acidity and converting these metals into complexes which were tolerant of water, which were structurally defined and which eventually could be modified into chiral catalysts. Perhaps the most obvious complexes of this type are the bent metallocenes, [MCp_2X_2], which are readily prepared, and the firmly held Cp ligands provide a structural framework for chiral elaboration. In order to convert these complexes into Lewis acids we require labile X ligands which can be displaced by the carbonyl functionalities of dienophiles. These species are very

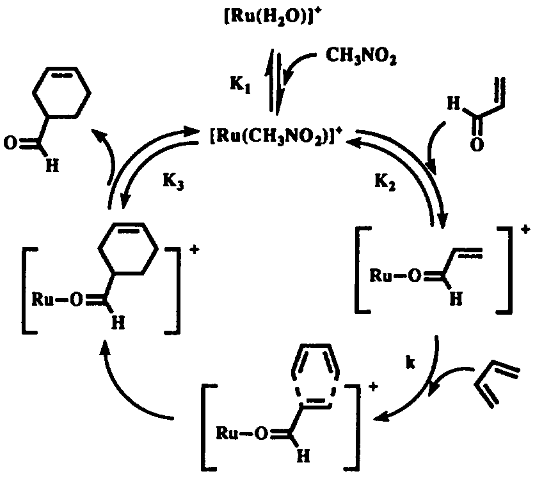


Fig. 1. An outline of the catalytic cycle for the Diels-Alder reaction using the $[Ru(salen)(NO)(H_2O)]^+$ catalyst in CH_3NO_2 solution. The dienophile adduct formation is shown as deriving from the CH_3NO_2 adduct, $[Ru(CH_3NO_2)]^+$; it could equally well form from the H_2O complex, $[Ru(H_2O)]^+$.

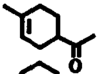
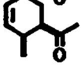
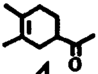
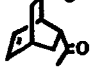
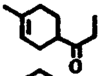
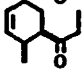
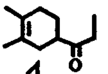
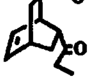
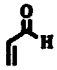
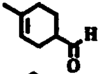
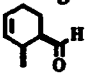
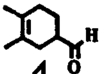
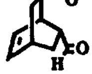
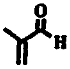
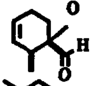
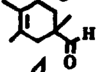
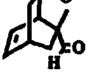
oxophilic and we expected that at low catalyst loadings small amounts of adventitious water could lead to the formation of the diaquo cations, $[MCp_2(H_2O)_2]^{2+}$. Thus our first concern in the development of these catalysts was to investigate the catalytic behavior of the diaquo complexes.

The complex, $[TiCp^*_2(H_2O)_2](CF_3SO_3)_2$, has been prepared and structurally characterized.[11] It is a crystalline compound which can be handled in air and is soluble in CH_2Cl_2 and CH_3NO_2 solvents. Using 1 mol% catalyst loadings Diels-Alder catalysis is observed for the substrates listed in Table 2.[12] As will be noted, even at these low catalyst loadings rate accelerations of between 10^2 and $>10^5$ are observed and, as expected, the selectivity is greatly improved. The substrates depicted in entry 1 (Table 2) have similar catalytic rates in either CH_2Cl_2 or CH_3NO_2 solutions. The catalysis is remarkably insensitive to the presence of water. Addition of 100 equiv of H_2O (1M) in CD_3NO_2 solution slows the catalytic rate by only a factor of three. Addition of 10 equiv of H_2O has no detectable effect on the rate. As a practical matter neither the solvents nor the substrates need to be dried in order to obtain acceptable catalytic rates.

In addition, this catalyst does not display significant product inhibition. We find, for example, that the substrates (entry 1, Table 2) are catalyzed at the same rate in either the presence or absence of 100 equiv of the product. Although this catalyst has these desirable features, it does suffer from its ability to polymerize dienes. The rate of polymerization is very slow so that the entries in Table 2 are not affected by this competing reaction. The slow catalysis of the Diels-Alder reaction between crotonaldehyde and isoprene, for example, gave 40% Diels-Alder product, before all of the remaining diene was consumed as polymer. Of course, the reaction can be driven to completion by the addition of excess of diene. As in the case of the ruthenium catalyst, this titanium catalyst does not effectively promote Diels-Alder reactions with α, β-unsaturated esters.

The observation of Diels-Alder catalysis by aquo complexes provides for a possible alternative origin of the catalysis. Aquo complexes are known to be weak acids and it could be argued that some or all of the catalysis proceeds by a proton catalyzed path. This is highly improbable because we find that 1

Table 2
Diels - Alder catalysis by $[Ti(Cp^*)_2(H_2O)_2](CF_3SO_3)_2$ in CD_2Cl_2 solutions at 25 °C.

	Dienophile[a]	Diene[a]	Catalysis			Thermal	
			Time for 90% Yield (h)	Isomer Ratio	Major Product	Time for 90% Yield (h)	Isomer Ratio
1			13	94:6		6×10^3	70:30
2			3.6	94:4:2:0[f]		7×10^3	72:16:9:3
3			3.2	—		4×10^3	—
4			2.1	95:5		$>10^5$	93:7
5			6.7[b]	89:11		4×10^3	66:34
6			13	ND[c,d]		$>10^5$	ND
7			11	—		3×10^3	—
8			10	100:0		$>10^5$	ND
9			6.7	95:5		5×10^3	70:30
10			5.0	93:4:3:0[f]		4×10^3	86:9:5:0
11			1.3	—		3×10^3	—
12			3.2	94:6		$>10^5$	89:11
13			32	91:9		$>10^5$	70:30
14			7.8	95:4:1:0[f]		$>10^5$	ND
15			4.4	—		$>10^5$	—
16			76[e]	75:25		$>10^5$	ND

[a] Catalysis was carried out at 1M concentration in each substrate and 1 mol% catalyst except as noted. [b] 2 mol% catalyst. [c] ND=not determined. [d] Overlapping signals prevented determination of isomeric ratios. [e] Polymerization observed during the catalysis. [f] The isomer ratio sequence is *cis*-1,2:*trans*-1,2:*cis*-1,3:*trans*-1,3.

mol% trifluoroacetic acid does not catalyse the Diels-Alder reactions to any extent after 24 h under the conditions used. Trifluoroacetic acid is a very strong acid and is likely to have a proton activity many orders of magnitude greater than the aquo complexes.[13]

Finally, it should be noted that neither the $[TiCp^*_2Cl_2]$ nor the $[TiCp^*_2(CF_3CO_2)_2]$ complex acts as a catalyst whereas $[TiCp^*_2(DMF)_2]^{2+}$ is a slow catalyst. This indicates that in order to obtain catalysis weakly coordinating ligands($CF_3SO_3^-$, SbF_6^-, AsF_6^-) which can be displaced by the dienophile are required.

The complexes, $[TiCp_2(CF_3SO_3)_2]$ and $[ZrCp_2(CF_3SO_3)_2THF]$ are readily prepared from the corresponding chlorides and both complexes have been structurally characterized.[14] The species containing SbF_6^- and AsF_6^- ligands have also been prepared[15] but by less convenient routes.

The triflato complexes are soluble in CH_2Cl_2 and CH_3NO_2 but not in non-polar solvents. The Diels-Alder catalysis was carried out using 1 mol% $[ZrCp_2(CF_3SO_3)_2THF]$ and 0.5 mol% $[TiCp_2(CF_3SO_3)_2]$ catalyst loadings(Table 3).[16] The results are similar to those observed for the $[TiCp^*_2(H_2O)_2]^{2+}$ catalyst. As before, the triflato complexes are efficient catalysts for the more reactive Diels-Alder partners but for intrinsically slower pairs, polymerization of the diene is competitive with Diels-Alder catalysis. The rate of Diels-Alder catalysis is the same whether or not the reagents or the solvent are dried. Slight product inhibition is observed but catalysis continues indefinitely.

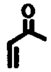
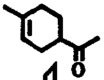
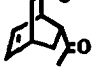
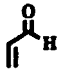
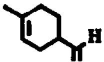
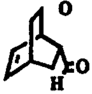
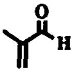
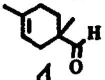
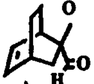
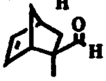
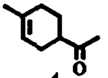
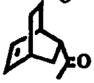
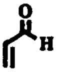
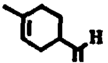
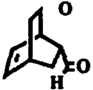
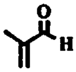
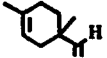
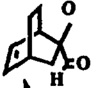
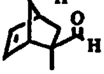
Adduct formation between methyl vinyl ketone (MVK) and $[TiCp_2(CF_3SO_3)_2]$ in CD_2Cl_2 under catalytic concentrations was investigated by ^{19}F and ^1H NMR spectroscopy. The NMR spectra of the $[TiCp_2(CF_3SO_3)_2]$ alone indicate that both triflato ligands are fully bound to the titanium center. This is confirmed by conductivity measurements. Upon the addition of 100 equiv of MVK at 20°C the single ^{19}F and ^1H NMR signals broaden and as the temperature is lowered the single signals split into a number of peaks. These low temperature signals can be ascribed to the presence of $[TiCp_2(CF_3SO_3)_2]$, $[TiCp_2(CF_3SO_3)MVK]^+$ and $[TiCp_2(MVK)_2]^{2+}$ with the latter two predominating. These data indicate, first, that at 20°C exchange between MVK and the catalyst is rapid and that MVK displaces triflato ligands. Second, substantial amounts of these adducts are formed. These are ideal circumstances for Lewis acid catalysis.

2. *Mukaiyama Cross-Aldol Catalysis*

2.1 The $[Ru(salen)(NO)(H_2O)]^+$ Catalyst. The Mukaiyama reaction (eq 2) is catalyzed or promoted by a variety of Lewis acids.[17] Among these are $TiCl_4$;[18] halides of boron,[19] aluminum and tin[20]; lanthanum chloride,[21] trityl salts[22] and lanthanide triflates.[23] Of particular interest to the present work is the use of bis(1,3-trimethylsilyl)cyclopentadienyl ytterbium chloride[24] and rhodium salts[7,25] for this catalysis. Generally mild Lewis acids suffice for the Mukaiyama reaction and we expected that the mild ruthenium catalyst 4 would be ideal for this reaction. This expectation was borne out, but the study[26] revealed another important consideration in the design of transition metal based Lewis acid catalysts.

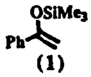
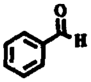
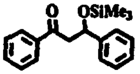
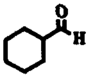
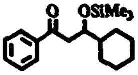
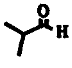
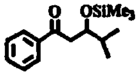
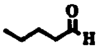
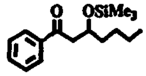
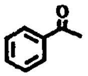
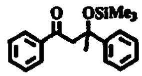
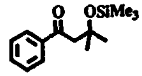
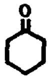
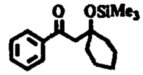
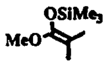
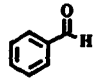
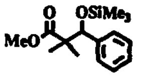
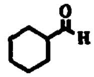
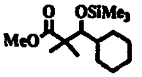
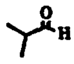
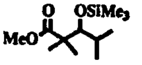
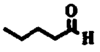
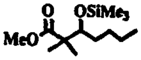
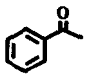
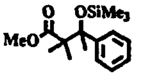
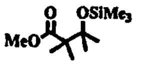
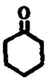
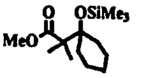
Table 4 collects the results of the catalysis by 4 of a number of Mukaiyama partners. It will be noted that the catalyst causes reaction of benzaldehyde with the silyl enol ether 1 (Table 4) even when the catalyst to substrate ratio is 1:2000 and that many of the catalytic reactions are complete within 3 min of mixing. Although these catalyst loadings are of an order of magnitude less than are commonly used for other catalysts, the catalysis is prone to deactivation when the reaction is slow. At very low catalyst loadings of < 1 mol% all of the reactions with the ketones listed in Table 4 suffer from deactivation. This deactivation can be circumvented by increasing the catalyst loading. The origins of the catalyst

Table 3
Diels-Alder catalysis by [$Zr(Cp)_2(CF_3SO_3)_2THF$] 1mol% and [$Ti(Cp)_2(CF_3SO_3)_2$] 0.5mol% in CD_2Cl_2 solutions at 25 °C.

			Catalysis			Thermal	
	Dienophile[a]	Diene[a]	Time for 90% Yield (h)	Isomer Ratio	Major Product	Time for 90% Yield (h)	Isomer Ratio
				[$Zr(Cp)_2(CF_3SO_3)_2THF$]			
1			13	94:6		$6x10^3$	70:30
2			3.7	95:5		$>10^5$	93:7
3			18	87:13		$5x10^3$	70:30
4			0.4	97:3		$>10^5$	89:11
5			5.7	92:8		$>10^5$	70:30
6			66	80:20		$>10^5$	ND[b]
7			<0.05	85:15		$7x10^2$	82:18
				[$Ti(Cp)_2(CF_3SO_3)_2$]			
8			3.8	92:8		$6x10^3$	70:30
9			4.9	93:7		$>10^5$	93:7
10			22	90:10		$5x10^3$	70:30
11			3.0	91:9		$>10^5$	89:11
12			8.9	88:12		$>10^5$	70:30
13			160	82:18		$>10^5$	ND
14			0.2	85:15		$7x10^2$	82:18

[a] Catalysis was carried out at 1M concentration in each substrate.
[b] ND = not determined.

Table 4
Catalysis of the Mukaiyama Aldol Reaction with [Ru(salen)(NO)(H_2O)]SbF_6 in CD_3NO_2 at 25°C with 1M initial substrate concentration.

Substrates		Catalyst Loading (mol %)	Time for 90% Yield (min)	Product
 (1)		0.05	< 6	
		0.5	< 3	
		0.5	13	
		0.1	60	
		2	30	
		2	180	
		2	78	
 (2)		1	< 3	
		1	< 3	
		0.5	18	
		1	38	
		1	< 3	
		2	< 15	
		2	< 3	

deactivation has been traced to the reducing power of silyl enol ethers.

Addition of 15 equiv of either silyl enol ether (1 or 2; Table 4) to the catalyst 4 in CD_3NO_2 solution in the absence of the other substrates leads to a slow intensification of the color of the solution. This color change is associated with the production of a variety of catalytically inactive species. Catalyst deactivation is also accompanied by extensive desilylation of the silyl enol ether which is consistent with the formation of silyl enol ether radical cations[27] and, by implication, reduction of the catalyst.

Cyclic voltammetry of the silyl enol ether 1 indicates an oxidation potential of +0.88 V versus Ag/AgCl. The oxidation potentials of $CH_2=C(OEt)OSiEt_3$ and $(CH_3)_2C=C(OEt)OSiEt_3$ were estimated[28] as +0.87 and +1.27 V, respectively versus Ag/AgCl. We find that the catalyst 4 has a reduction potential of -0.83 V versus Ag/AgCl. Thus the silyl enol ethers are capable of reducing the catalyst. The high reducing power of silyl enol ethers has been noted before[28] and it was shown that $SnCl_4$ is reduced during the Michael-Mukaiyama reaction.

The ability of silyl enol ethers to reduce transition metal catalysts is an important consideration in the design of such catalysts. The fact that catalyst reduction is possible thermodynamically does not determine the effectiveness of Lewis acids for catalysis with silyl enol ethers. Ultimately, it is the rate of electron transfer versus the rate of catalysis which is decisive. This is demonstrated by the results listed in Table 4 where, in some cases, the catalysis can be carried to completion by raising the catalyst loading to increase the catalytic rate over the electron transfer rate.

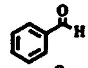
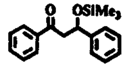
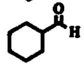
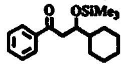
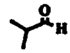
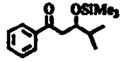
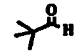
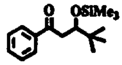
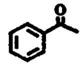
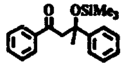
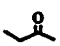
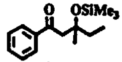
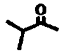
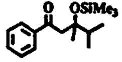
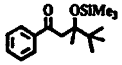
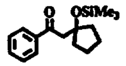
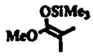
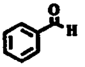
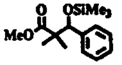
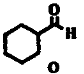
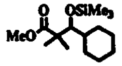
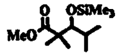
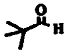
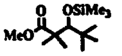
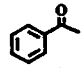
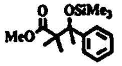
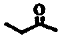
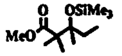
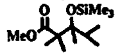
2.2 *Titanium and Zirconium Catalysts.* The reduction potentials for $[TiCp_2Cl_2]$ and $[ZrCp_2Cl_2]$ are found [29] to be approximately -0.76 and -1.76 V versus Ag/AgCl. The corresponding reduction potentials for the triflato complexes have not been reported but assuming that cationic adduct intermediates of the type $[MCp_2(CF_3SO_3)(substrate)]^+$ are formed we would expect that these cationic species would have more positive potentials. Thus it seems reasonable to conclude that silyl enol ethers are thermodynamically capable of reducing the $[TiCp_2(CF_3SO_3)_2]$ catalyst or the corresponding cationic adducts but not the zirconium analogues. Despite this we have, as yet, not observed reduction of the titanium catalysts with silyl enol ethers.

Using the $[TiCp_2(CF_3SO_3)_2]$ and $[ZrCp_2(CF_3SO_3)_2THF]$ catalysts the reaction of a variety of aldehydes and ketones with the two silyl enol ethers are listed in Table 5.[30] The rate of catalysis follows the degree of steric hinderance of the carbonyl compound to the stage where pinacolone (entries 8 and 17) is catalyzed poorly or not at all. The two catalysts have similar rates and, for practical purposes, either can be used. Although these catalysts are among the most effective yet discovered, operating at catalyst to substrate ratios of 1:10,000, they show poor diastereoselectivity at 25°C. Thus the silyl enol ether of cyclohexanone reacts with benzaldehyde and with isobutyraldehyde to give nearly equal amounts of the erythro and threo isomers.

Unlike the cases in dichloromethane solutions where both catalysts are non-electrolytes indicating that the triflato ligands are fully bound, in nitromethane solutions the titanium and zirconium catalysts have conductivities of $\Lambda_M = 128$ and 88 $mol^{-1}ohm^{-1}cm^2$, respectively. This indicates that the former is between a 1:1 and 2:1 electrolyte and that the latter is close to a 1:1 electrolyte in nitromethane solutions. Since the triflato ligands are dissociated to a considerable extent in both cases, we assume the presence of species of the type $[MCp_2(CF_3SO_3)(CH_3NO_2)]^+$ and $[MCp_2(CH_3NO_2)_2]^{2+}$ in nitromethane solutions. Nitromethane is expected to be a poor ligand which should be readily displaced by aldehyde or ketone substrates. These conclusions are confirmed by ^{19}F and ^1H NMR studies of the titanium catalyst in CD_3NO_2 solution at catalytic concentrations. The ^{19}F NMR spectrum at 20°C of the titanium complex alone shows broad signals which sharpen when the temperature is lowered to -60°C, (where the solution did not freeze). At -60°C signals are observed for the $[TiCp_2(CF_3SO_3)_2]$, $[TiCp_2(CF_3SO_3)(CD_3NO_2)]^+$ and $[TiCp_2(CD_3NO_2)_2]^{2+}$ species. When 200 equiv of benzaldehyde are added at 20°C the ^{19}F NMR signal becomes very broad but at -60°C it resolves into two signals, the major

Table 5

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 with 1M initial substrate concentration.

Entry	Substrates		Time for 90% Yield (min)		Product
			[$TiCp_2(CF_3SO_3)_2$]	[$ZrCp_2(CF_3SO_3)_2THF$]	
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	
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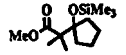
18			46	13	

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 catalyst solution followed by the aldehyde to avoid competitive catalytic cyclic trimerization of the aldehyde. c. 15 min after catalysis is complete, 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.

one representing free triflate. The ^1H NMR signal at -60°C in the presence of benzaldehyde remains broad. These results suggest that exchange of both triflato ligands with solvent and with benzaldehyde is rapid and reversible on an NMR time scale. In addition, substantial amounts of the benzaldehyde-catalyst adduct are probably formed at 25°C. As noted before, both of these characteristics will enhance the rate of catalysis.

EXPERIMENTAL

Preparation of Catalysts.

[Ru(salen)(NO)Cl] NaH (260 mg) in dry DMF (40 mL) was allowed to react with salenH_2 (1.05 g) for 20 min at 25°C, whereafter $[Ru(NO)Cl_3(H_2O)]$ (1.0 g) was added. The mixture was stirred at 110° for 22 h under an inert atmosphere. The DMF was then removed under reduced pressure and the gum was taken up in CH_2Cl_2 and was washed several times with water. The dark red CH_2Cl_2 layer was stirred with $MgSO_4$ (32 g) for 1 h and was filtered, and the CH_2Cl_2 was removed under reduced pressure to 30 mL giving crystals of the product. Addition of Et_2O to this mixture gave [Ru(salen)(NO)Cl]$\cdot$0.6 CH_2Cl_2 as dark well formed crystals (940 mg, 49% yield). [Ru(salen)(NO)Cl] ^1H NMR (300 MHz, CD_3NO_2): δ 8.47 (s, 2H), 7.40-7.50 (m, 4H), 7.04 (d, J=8.4 Hz, 2H), 6.70-6.76 (m, 2H), 4.10-4.40 (m, 4H). IR (mull): ν(NO)1828cm^{-1}.

[Ru(salen)(NO)(H$_2$O)]SbF$_6$ [Ru(salen)(NO)Cl]$\cdot$0.6 CH_2Cl_2 (261 mg) was suspended in CH_2Cl_2 (20 mL) and acetone (15 mL) and to it was added $AgSbF_6$ (180 mg) in acetone (20 mL). The solution was stirred for 1 h and was then filtered through Celite. The solvent was removed and the residue was dissolved in acetone (30 mL) and the solution was again filtered through Celite. The filtered solution was reduced to 10 mL and was cooled at 5°C as hexane was slowly added. Dark red crystals of the product were collected and dried in vacuo to remove acetone of crystallization. The yield is 71% (250 mg). $[Ru(salen)(NO)(H_2O)]SbF_6$ ^1H NMR (300 MHz, CD_3NO_2): δ 8.79 (s, 2H), 7.80-8.30 (br s, 1.4H), 7.49 (dd, J=7.9, 1.6 Hz, 2H), 7.00-7.15 (m, 2H), 6.73-6.85 (m, 2H), 6.47 (d, J=8.4 Hz, 2H), 4.30-4.70 (m, 4H), 2.10 (br s, 0.8H). IR (mull): ν(NO) 1889cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_3O_4SbF_6Ru$: C, 29.51; H, 2.48; N, 6.45. Found: C, 29.82; H, 2.46; N, 6.47.

$[TiCp^*_2(H_2O)_2](CF_3SO_3)_2$ To a solution of $[TiCp^*_2Cl_2]$[12] (400 mg) in CH_2Cl_2 (25 mL) was added a solution of $AgCF_3SO_3$ (528 mg) in acetone (10 mL) and the mixture was stirred for 3 h. It was then filtered, and the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and filtered again. The solvent was removed, the residue was dissolved in CH_2Cl_2 (20 mL), and pentane (100 mL) was slowly added to give dark violet needles of the product (575 mg, 86%). ^1H NMR (CD_3NO_2, TMS) δ 2.21 (s). Conductivity in CD_3NO_2 (1×10^{-3}), $\Lambda_M = 151.8$ mol^{-1}ohm^{-1}cm^2 (2:1 electrolyte). Anal Calc. for $C_{22}H_{34}F_6O_8S_2Ti$. C, 40.5; H, 5.3; F, 17.5. Found C, 40.1; H, 5.1; F, 17.8.

$[TiCp_2(CF_3SO_3)_2]$ To a solution of $[TiCp_2Cl_2]$ (625 mg) in dry THF (40 mL) was added a solution of $AgCF_3SO_3$ (1.415 g) in dry THF (30 mL). The mixture was stirred for 15 min and the solution was filtered, and the red filtrate was carefully layered with hexane (100 mL). After standing for 24 h, the crystals were collected and recrystallized in a similar manner to give red needles of the product (350 mg,

29%). ^{1}H NMR (CD_3NO_2) δ 7.06 (s). Anal Calc. for $C_{12}H_{10}F_6O_6S_{22}Ti$. C, 30.27; H, 2.12. Found: C, 30.28; H, 2.07.

[ZrCp$_2$(CF$_3$SO$_3$)$_2$THF] To a solution of [$ZrCp_2Cl_2$] (645 mg) in dry THF (15 mL) was added a solution of $AgCF_3SO_3$ (1.12 g) in dry THF (10 mL). After the mixture was stirred for 30 min it was filtered. Hexane (100 mL) was carefully layered over the colorless filtrate, and after standing for 24 h the white crystals were collected (684 mg, 53%). ^{1}H NMR ($CDCl_3$) δ 1.89 (m, 4H), 3.78 (m, 4H), 6.52 (s, 10H). Anal Calc. for $C_{16}H_{18}F_6O_7S_2Zr$. C, 32.48; H, 3.07. Found: C, 32.42; H, 3.06.

Typical Preparative Procedures.

Diels-Alder Reaction [Ru(salen)(NO)(H_2O)]SbF_6 (18.4 mg) was dissolved in CH_3NO_2 (625 μL) and then methacrolein (249 mg) followed by isoprene (245 mg) were added at 25°C. The reactions was monitored by ^{1}H NMR; the reaction was complete after 12 h. Benzene (9 mL) was then added and the solution was passed through a plug of Florisil. The solvent was removed under reduced pressure giving the products, 1,4- and 1,3-dimethyl-3-cyclohexene-1-carboxaldehyde (95:5, respectively) as an oil (380 mg, 76%).

Mukaiyama Reaction Catalysis with the titanium or zirconium catalysts can be performed either from the isolated triflato complexes or from triflato complexes prepared in situ. The latter procedure is perhaps more convenient and is described for the titanium catalyst. $AgCF_3SO_3$ (6.8 mg) in CH_3NO_2 (1.0 mL) was added to a solution of [$TiCp_2Cl_2$] (3.4 mg) in CH_3NO_2 (0.3 mL) and the mixture was stirred for 20 min at 25°C. It was then filtered under argon and the residue was washed with CH_3NO_2 (0.5 mL). The filtrate was cooled to 0°C and isobutyraldehyde (245 μL) followed by 1-phenyl-1-(trimethylsiloxy) ethylene (540 μL) was added to the solution of the catalyst. The solution was stirred at 0°C for 15 min and triflouroacetic acid (120 μL) followed by water (120 μL) was added. After stirring for 1 h the solution was diluted with water (20 mL) and was extracted with benzene (30 mL). The benzene was dried (Na_2SO_4) and after evaporation under reduced pressure, the pure desilylated product remained as an oil (520 mg, 82%).

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