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Homogeneous Catalysis. A Transition Metal Based Catalyst for the Mukaiyama Crossed-Aldol Reaction and Catalyst Deactivation by Electron Transfer.

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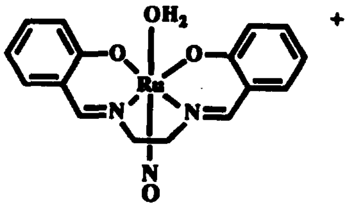
Abstract: *The cationic complex [Ru(salen)(NO)H₂O]SbF₆ is intrinsically a powerful catalyst for the Mukaiyama crossed-aldol reaction at 25°C in nitromethane solutions and at very low catalyst loadings but, for some reactions, electron transfer from the silyl enol ether to the ruthenium catalyst can occur which leads to catalyst deactivation.*

The Mukaiyama crossed-aldol reaction, involving the coupling of silyl enol ethers with aldehydes and ketones, is catalysed by a variety of Lewis acids.[1] Among these catalysts are, $TiCl_4$,[2] halides of boron,[3] aluminum and tin,[4] lanthanum chloride,[5] trityl salts,[6] fluoride ions[7] and a variety of lanthanide triflates.[8] Of relevance to the present work is the use of the bis(1,3-trimethylsilyl)cyclopentadienyl ytterbium(III)chloride[9] and rhodium complexes.[10] Transition metal complexes provide potentially attractive Lewis acid catalysts because it should be possible to devise systems which are both air and water insensitive, which can be electronically tuned by ligand substitution and which have stable, defined geometries for stereochemical control. We report on the use of the transition metal complex, $[Ru(salen)(NO)H_2O]SbF_6$ as a catalyst for the Mukaiyama reaction. The purpose of this communication is two-fold. First, we wish to demonstrate how a normally electron-rich metal such as ruthenium(II) can be converted into a Lewis acid by the appropriate choice of ligands. Second, we draw attention to a key element in the design of such Lewis acids, namely, the capacity of silyl enol ethers to cause catalyst deactivation by electron transfer. The species $[Ru(salen)(NO)H_2O]^+$ possesses a strongly electron withdrawing NO^+ ligand ($\nu_{str} = 1889\ cm^{-1}$), a net positive charge and "hard" donor atoms of the salen ligand. All of these elements will contribute to converting an intrinsically electron-rich



$[Ru(salen)(NO)H_2O]^+$

ruthenium atom into a Lewis acid. Moreover, since the NO^+ and H_2O ligands are trans to each other,[11] the strong trans influence of the NO^+ ligand will labilize the H_2O ligand and allow for labile coordination of the aldehydes and ketones which, upon coordination, become activated for the Mukaiyama reaction. The preparation and characterization of this air stable complex is described elsewhere.[11] In nitromethane solutions the aquo group is found to exchange rapidly with weak ligands such as aldehydes and ketones.[11]

Low catalyst loadings, ranging from 0.05 to 2 mol% in CD_3NO_2 solutions at 25°C, convert many Mukaiyama partners cleanly to the crossed-aldol products.[12] Some of the results are collected in Table 1 where, in all cases, the initial concentration of each substrate was 1 M. The catalysis of benzaldehyde with silyl enol ether 1 proceeds even when the ratio of catalyst to substrate is 1 : 2000 and many of the reactions listed in Table 1 are complete within 3 min of mixing. Although these catalyst loadings are at least an order of magnitude less than are commonly used for other catalysts and indicate that the present ruthenium complex is intrinsically a powerful catalyst, it is prone to deactivation by silyl enol ethers. This deactivation is generally observed when catalysis is slow. Thus, for example, using 2 mol% catalyst loading with the silyl enol ethers 1 or 2 and the substrates trimethylacetaldehyde, cyclopentanone or methyl ethyl ketone leads to about 50% conversion within 5 min. Thereafter catalysis ceased and was accompanied by an intensification of color of the catalysis solution and extensive desilylation of the silyl enol ethers was observed. At very low catalyst loadings (< 1 mol%) this catalyst inhibition is observed for all of the ketone substrates listed in Table 1. We find that neither aldehydes nor ketones are the cause of the catalyst deactivation since allowing the catalyst to stand for days in the presence of aldehydes or ketones does not inhibit catalysis.

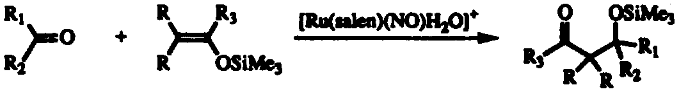
Addition of 15 equivalents of the silyl enol ether 1 to the catalyst in CD_3NO_2 at 25°C in the absence of ketone or aldehyde leads to an intensification of the color of the solution and the appearance of new signals in the ^1H NMR spectrum of the catalyst within 10 min of mixing. Over several hours the ^1H NMR signals of the catalyst continue to change and eventually a constant spectrum, indicating a variety of species, is observed. Because of the instability of the initially formed catalyst product and its conversion to a number of different species we have been unable to establish its exact composition. The deactivation of the catalyst, however, is accompanied by extensive desilylation of the silyl enol ether which is consistent with the formation of silyl enol ether radical cations[13] and, by implication, the reduction of the catalyst. Thus it is probable that catalyst deactivation is caused by electron transfer from the silyl enol ether to the catalyst which we find is thermodynamically possible.

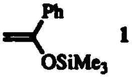
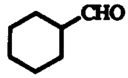
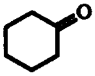
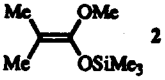
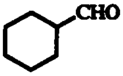
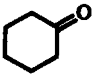
Cyclic voltammetry of 1 in acetonitrile solutions gives a quasi-reversible wave which indicates an oxidation potential of +0.88V versus Ag/AgCl. The oxidation potentials of $CH_2{=}C(OEt)OSiEt_3$ and $(CH_3)_2C{=}C(OEt)OSiEt_3$ were estimated[14] to be +0.87 and +1.27V, respectively versus Ag/AgCl.[15] Cyclic voltammetry of the $[Ru(salen)(NO)H_2O]SbF_6$ species in CH_3CN solutions indicates a reduction potential of -0.83 versus Ag/AgCl. Thus all of the silyl enol ethers are capable of reducing the catalyst.[16]

The ability of silyl enol ethers to reduce Lewis acids has been noted before[14] and it was demonstrated that the $SnCl_4$ catalysed Michael-Mukaiyama reaction proceeds via a radical pathway. It is therefore conceivable that the catalytic reactions listed in Table 1 proceed by a radical coupling rather than by the generally assumed nucleophilic path. In order to resolve this issue we performed the cross experiment using $CH_2{=}C(OMe)OSiMe_3$ and $(Me)_2C{=}C(OMe)OSiMe_3$ to couple with benzaldehyde. Using one equivalent of benzaldehyde, one equivalent of each of the two silyl enol ethers and 0.5 mol% catalyst at 5°C in CD_3NO_2 solution, we found a 1.5 : 1 preference for the coupling of the less sterically hindered substrate $CH_2{=}C(OMe)OSiMe_3$. Were the catalysis a radical process we would expect a preference for the coupling of the more substituted silyl enol ether.

The ability of silyl enol ethers to reduce catalysts has important implications in the design of transition metal based

Table 1. Catalysis of the Mukaiyama Reaction by [Ru(salen)(NO)H$_2$O]SbF$_6$.^{a}



Carbonyl	Silyl enol ether	Catalyst Loading^b	Time^c
PhCHO	 1	0.05	< 6 min
	1	0.1	1 h
	1	0.5	13 min
	1	0.5	< 3 min
PhCOCH$_3$	1	2	30 min
CH$_3$COCH$_3$	1	2	3 h
	1	2	1.3 h
PhCHO	 2	1	< 3 min
	2	1	38 min
	2	0.5	18 min
	2	1	< 3 min
PhCOCH$_3$	2	1	< 3 min
CH$_3$COCH$_3$	2	2	< 15 min
	2	2	< 3 min

a) in CD$_3$NO$_2$ solutions at 25 ° C. b) in mol %. c) for 90 % reaction.

Lewis acid catalysts. Catalysts with reduction potentials more positive than about -1 V versus Ag/AgCl could lead to side reactions and to catalyst deactivation. Many of the traditional Lewis acids are also prone to reduction by silyl enol ethers[14] but it appears that for most of these cases the rate of the crossed-aldol reaction is much faster than the rate of electron transfer. A similar kinetic trade-off obtains for the present catalyst where, for some substrates, the rate of catalysis is much faster than electron transfer and for others it is competitive leading to catalyst deactivation. For the present catalyst the electron transfer deactivation can be circumvented in many cases by increasing the catalyst loading.

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(11) The preparation of [Ru(salen)(NO)H_2O]SbF_6 is described elsewhere, Odenkirk, W.; Rheingold, A.; and Bosnich, B. *J. Am. Chem. Soc.* in press. The structure of the complex was confirmed by X-ray analysis.

(12) The results reported in Table 1 were obtained by following the reactions by ^1H NMR typically as follows. [Ru(salen)(NO)H_2O]SbF_6 (0.16 mg; 0.25 μmol) was weighed in an NMR tube and dissolved in CD_3NO_2 (333 μL). Benzaldehyde (0.50 mmol; 52 μL) and CH_2=C($OSiMe_3$)Ph (0.50 mmol; 102 μL) were sequentially injected into the catalyst solution. The progress of the reaction was followed by the disappearance of the substrate and appearance of product ^1H NMR peaks. At completion of reaction no side products were detected. **Preparative scale.** In a typical procedure the catalyst (0.31 mg; 0.48 μmol) was dissolved in nitromethane (700 μL) and to this solution was added benzaldehyde (1 mmol; 104 μL) and CH_2=C($OSiMe_3$)Ph (1 mmol; 204 μL). The catalysis was complete after 20 min at 25°C whereafter the solution was diluted with nitromethane (2 mL) and was stirred with trifluoroacetic acid (100 μL) for 15 min. To this solution was added water (3 mL) and the mixture was vigorously stirred for 15 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2 and the extract was concentrated under vacuum. The residue was taken up in CH_2Cl_2 and passed through a short column of Florisil® and the eluent solvent was removed under vacuo to give the product, $PhCOCH_2CH(OH)Ph$, (0.21 g; 92% yield) as an oil, pure by ^1H NMR.

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(16) Two quasi-reversible waves are observed for the [Ru(salen)(NO)H_2O]$^+$ species, one at -0.313V and one at -0.830V. We have concluded that the former couple involves one electron oxidation because we find that the ferrocenium ion (+0.43V versus Ag/AgCl) is capable of oxidizing the catalyst by only one electron. It should be noted that in acetonitrile solution the catalyst exists as the [Ru(salen)(NO)CH_3CN]$^+$ species so that the quoted reduction potential refers to this complex. The difference in the redox potential between this species and the catalyst species is likely to be small and will not affect the status of the discussion presented here.

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