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Lewis Acid Catalysts Stable in Water. Correlation between Catalytic Activity in Water and Hydrolysis Constants and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands

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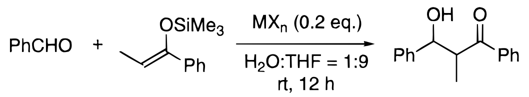
Today's environmental concerns demand clean reaction processes that do not use harmful organic solvents.[1] Water is no doubt the most environmentally friendly solvent; however, its use in organic reaction processes is rather limited because many organic materials do not dissolve in water, and therefore in most cases reactions proceed sluggishly.[2] In addition, many reactive intermediates and catalysts are decomposed by water. This is the case for Lewis acid catalyzed reactions, which are of great current interest because of the unique reactivities and selectivities they can achieve and for the mild conditions used.[3] Lewis acids have been believed to be unstable in water and therefore unusable in aqueous solution. On the other hand, we have recently found water-stable Lewis acids, lanthanide trifluoromethanesulfonates (lanthanide triflates), which can be used in several carbon−carbon bond-forming reactions in aqueous media.[4] The stability and catalytic activity of lanthanide triflates in water were ascribed to their large ionic radii and an equilibrium between the Lewis acids and water. We have now clarified that some metal salts other than lanthanides are also stable Lewis acids in water and work as catalysts.[5] In addition, common characteristics, a certain range of hydrolysis constants, and a high order of exchange rate constants for substitution of inner-sphere water ligands (water exchange rate constant (WERC)) have been found among these water-stable Lewis acids.

We screened group 1−15 metal chlorides in a model reaction of benzaldehyde with (*Z*)-1-phenyl-1-(trimethylsiloxy)propene (the Mukaiyama aldol reaction) (Table 1).[6] The reaction is suitable for testing catalytic ability of the metal chlorides as Lewis acid catalysts in aqueous media, because the silyl enol ether is water-sensitive (especially under acidic conditions) and if the Lewis acids hydrolyze in water, the enol ether decomposes rapidly and the desired reaction proceeds no further. In the first screening, the chloride salts of Fe(II), Cu(II), Zn(II), Cd(II), In(III), and Pb(II) as well as the rare earths (Sc(III), Y(III), Ln(III)) gave promising yields. When the chloride salts of B(III), Si(IV), P(III), P(IV), Ti(IV), V(III), Ge(IV), Zr(IV), Nb(V), Mo(V), Sn(IV), Sb(V), Hf(IV), Ta(V), W(VI), Re(V), and Tl(III) were used, decomposition of the silyl enol ether occurred rapidly and no aldol adduct was obtained. This is because hydrolysis of such metal chlorides is very fast and the silyl enol ethers were protonated then hydrolyzed to afford the corresponding ketone. On the other hand, no product or only a trace amount of the product was detected using the metal chloride salts of Li(I), Na(I), Mg(II), Al(III), K(I), Ca(II), Cr(III), Mn(II), Co(II), Ni(II), Ga(III), Ru(III), Rh(III), Pd(II), Ag(I), Ba(II), Os(III), Ir(III), Pt(II), Au(I), Hg(II), and Bi(III). Some of these salts are stable in water, but have low catalytic ability. After the first screening, a second test was performed for the more promising metals. This test was carried out using the same aldol reaction and the corresponding metal perchlorates or trifluoromethanesulfonates (triflates) (Table 1).[7] It was found that Lewis acids based on Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II) as well as the rare earths (Sc(III), Y(III), Ln(III)) were both stable and active in water.[8,9] Mn(II) and Ag(I) perchlorates gave moderate yields of the aldol adduct.

Table 1. Effect of Metal Salts in the Aldol Reaction[a]



MX_n	yield/%	MX_n	yield/%
$AlCl_3$	trace	$InCl_3$	**68**[c]
ScCl_3	**70** (**78**)[b]	$In(ClO_4)_3$	14
Sc$(ClO_4)_3$	**82**	$SnCl_2$	4
$CrCl_3$	trace	**La**$(OTf)_3$	**80**
$MnCl_2$	trace	**Ce**$(OTf)_3$	**81**
$Mn(ClO_4)_2$	18 (40)[b]	**Pr**$(OTf)_3$	**83**
$FeCl_2$	39	**Nd**$(OTf)_3$	**78**
Fe$(ClO_4)_2$	26 (**55**)[b]	**Sm**$(OTf)_3$	**85**
$FeCl_3$	21	**Eu**$(OTf)_3$	**88**
$Fe(ClO_4)_3$	7	**Gd**$(OTf)_3$	**90**
$CoCl_2$	trace	**Tb**$(OTf)_3$	**81**
$Co(ClO_4)_2$	17 (7)[b]	**Dy**$(OTf)_3$	**85**
$NiCl_2$	trace	**Ho**$(OTf)_3$	**89**
$Ni(ClO_4)_2$	17 (7)[b]	**Er**$(OTf)_3$	**86**
$CuCl_2$	25	**Tm**$(OTf)_3$	**85**
Cu$(ClO_4)_2$	47 (**81**)[b]	**Yb**Cl_3	11 (**92**)[b]
$ZnCl_2$	10	**Yb**$(ClO_4)_3$	**84**
Zn$(ClO_4)_2$	46 (**57**)[b]	**Yb**$(OTf)_3$	**92**
$GaCl_3$	trace	**Lu**$(OTf)_3$	**84**
YCl_3	5 (**86**)[b]	$IrCl_3$	trace
Y$(ClO_4)_3$	**90**	$PtCl_2$	trace
$RhCl_3$	trace	AuCl	trace
$PdCl_2$	trace	$HgCl_2$	trace
AgCl	trace	HgCl	trace
$AgClO_4$	42 (36)[b]	$PbCl_2$	15
$CdCl_2$	18	**Pb**$(ClO_4)_2$	**59** (**65**)[b]
Cd$(ClO_4)_2$	49 (**72**)[b]	$BiCl_3$	trace

[a] No adduct was obtained and the starting materials were recovered when LiCl, NaCl, $MgCl_2$, PCl_3, KCl, $CaCl_2$, $GeCl_4$, $RuCl_3$, $SbCl_3$, $BaCl_2$, and $OsCl_3$ were used. No adduct was obtained and the silyl enol ether was decomposed when BCl_3, $SiCl_4$, PCl_5, $TiCl_4$, VCl_3, $ZrCl_4$, $NbCl_5$, $MoCl_5$, $SnCl_4$, $SbCl_5$, $HfCl_4$, $TaCl_5$, WCl_6, $ReCl_6$, and $TlCl_3$ were used. [b] H_2O:EtOH:toluene = 1:7:3. [c] Cf. ref 9.

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(1) For example, see: Anastas, P. T., Williamson, T. C., Eds.; *Green Chemistry*; ACS Symposium Series 626; American Chemical Society: Washington: DC, 1996, and references therein.

(2) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (b) Reissig, H.-U. In *Organic Synthesis Highlights*; Waldmann, H., Ed.; VCH: Weinheim, 1991; p 71. (c) Einhorn, C.; Einhorn, J.; Luche, J. *Synthesis* **1989**, 787.

(3) (a) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1995. (b) Schinzer, D., Ed.; *Selectivities in Lewis Acid Promoted Reactions*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989.

(4) (a) Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S. *Chem. Lett.* **1991**, 2187. (c) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. (d) Kobayashi, S.; Hachiya, I.; Yamanoi, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2342. (e) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.

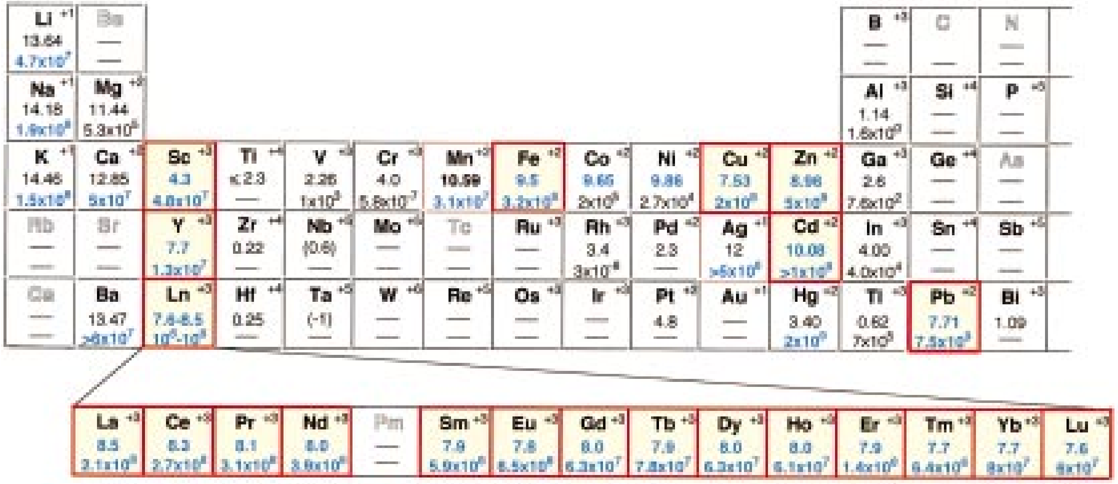
(5) Scandium and yttrium triflates and related compounds were also found to be stable Lewis acids in water. (a) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755. (b) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472. (c) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958. (d) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *38*, 4559. (e) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831.

(6) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. See also: (b) Lubineau, A.; Meyer, E. *Tetrahedron* **1988**, *44*, 6065.

(7) Metal parts of metal perchlorates or triflates are more cationic than those of metal chlorides, and thus metal perchlorates or triflates are more Lewis acidic than metal chlorides. See also ref 4c.

(8) Some copper salts were reported to be stable Lewis acids in water solution. (a) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702. (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1997**, 959.

Table 2. Hydrolysis Constant[a] and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands[b]



Li +1 13.64 4.7×10^7	Be — —											**B** +3 — —	C — —	N — —
Na +1 14.18 1.9×10^8	**Mg** +2 11.44 5.3×10^5											**Al** +3 1.14 1.6×10^0	**Si** +4 — —	**P** +5 — —
K +1 14.46 1.5×10^8	**Ca** +2 12.85 5×10^7	**Sc** +3 4.3 4.8×10^7	**Ti** +4 ≤2.3 —	**V** +3 2.26 1×10^3	**Cr** +3 4.0 5.8×10^{-7}	**Mn** +2 10.59 3.1×10^7	**Fe** +2 9.5 3.2×10^6	**Co** +2 9.65 2×10^5	**Ni** +2 9.86 2.7×10^4	**Cu** +2 7.53 2×10^8	**Zn** +2 8.96 5×10^8	**Ga** +3 2.6 7.6×10^2	**Ge** +4 — —	As — —
Rb — —	Sr — —	**Y** +3 7.7 1.3×10^7	**Zr** +4 0.22 —	**Nb** +5 (0.6) —	**Mo** +6 — —	Tc — —	**Ru** +3 — —	**Rh** +3 3.4 3×10^{-8}	**Pd** +2 2.3 —	**Ag** +1 12 $>6\times10^6$	**Cd** +2 10.08 $>1\times10^8$	**In** +3 4.00 4.0×10^4	**Sn** +4 — —	**Sb** +5 — —
Cs — —	**Ba** +2 13.47 $>6\times10^7$	**Ln** +3 7.6-8.5 10^6-10^8	**Hf** +4 0.25 —	**Ta** +5 (-1) —	**W** +6 — —	**Re** +5 — —	**Os** +3 — —	**Ir** +3 — —	**Pt** +2 4.8 —	**Au** +1 — —	**Hg** +2 3.40 2×10^9	**Tl** +3 0.62 7×10^5	**Pb** +2 7.71 7.5×10^9	**Bi** +3 1.09 —

La +3 8.5 2.1×10^8	**Ce** +3 8.3 2.7×10^8	**Pr** +3 8.1 3.1×10^8	**Nd** +3 8.0 3.9×10^8	Pm — —	**Sm** +3 7.9 5.9×10^8	**Eu** +3 7.8 6.5×10^8	**Gd** +3 8.0 6.3×10^7	**Tb** +3 7.9 7.8×10^7	**Dy** +3 8.0 6.3×10^7	**Ho** +3 8.0 6.1×10^7	**Er** +3 7.9 1.4×10^8	**Tm** +3 7.7 6.4×10^6	**Yb** +3 7.7 8×10^7	**Lu** +3 7.6 6×10^7

[a] pKh = -log K_{xy} (Ref. 10). $x\,M^{z+} + y\,H_2O \rightleftharpoons M_x(OH)_y^{(xz-y)+} + y\,H^+$

$$K_{xy} = \frac{[M_x(OH)_y^{(xz-y)+}][H^+]^y}{[M^{z+}]^x} \cdot \frac{g_{xy}\, g_{H^+}{}^y}{g_{M^{z+}}{}^x\, a_{H_2O}{}^y}$$

As for Cu^{2+}, Zr^{4+}, Al^{3+}, see Ref. 11.

[b] Measured by NMR, sound absorption, or multidentate ligand method (see Ref. 12).

Although at first sight these elements seem to have little in common, we noticed a correlation between their catalytic activity in water and hydrolysis constants[10,11] and WERC.[12] pK_h values (K_h = hydrolysis constant)[13] and WERC of the cations are shown in Table 2.[10−13] Metal compounds, which gave more than 50% yields in the aldol reaction, have pK_h values from 4.3 to 10.08 *and* WERC greater than 3.2×10^6 M^{-1} s^{-1}. There is no exception in all the metal compounds we tested. Cations are generally difficult to hydrolyze when their pK_h values are large. In the case that pK_h values are less than 4.3, cations are easy to hydrolyze and oxonium ions are formed. Under these conditions, silyl enol ethers decompose rapidly. On the other hand, in the case that pK_h values are more than 10.08, the cations are too stable. The pK_h values are closely related to hydration energy and (electron)^2/(ionic radii) values. These values are correlated to the Lewis acidity of the cations. Cations which have pK_h values greater than 10.08 have a small hydration energy as well as a small (electron)^2/(ionic radii) value, and therefore their Lewis acidity is low. Similarly, WERC is also closely related to (electron)^2/(ionic radii) value. In general, a small (electron)^2/(ionic radii) value means a fast WERC. These requirements of pK_h and WERC values for obtaining sufficient activity as Lewis acid catalysts in water are very strict, and if even one of them is not fulfilled, low catalytic activity is observed. For example, several alkali and alkaline earth elements have fast WERC, but their pK_h values are too large; consequently, almost no catalytic activity was observed in the aldol reaction. On the other hand, Co(II) and Ni(II) have suitable pK_h values, but their WERC is smaller than the criteria; therefore less than only 20% of the aldol adducts were obtained even when Co(II) and Ni(II) perchlorate were used in the aldol reaction. "Borderline" elements are Mn(II) and Ag(I). Their pK_h and WERC values are very close to the criteria limits,[14] and the yields obtained in the aldol reaction are 40% and 42%, respectively. Another interesting point is that, excluding the rare earths, the elements fitting the criteria, Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II), are all classified as "soft acids."[15] This may be related to interaction of these elements with water, which is a "hard base."[15]

Judging from these findings, the mechanism of Lewis acid catalysis in water (for example, aldol reactions of aldehydes with silyl enol ethers) can be assumed to be as follows. When metal compounds are added to water, the metals dissociate and hydration occur immediately. At this stage, the intramolecular and intermolecular exchange reactions of water molecules frequently occur. If an aldehyde exists in the system, there is a chance for it to coordinate to the metal cations instead of the water molecules and the aldehyde is then activated. A silyl enol ether attacks this activated aldehyde to produce the aldol adduct. According to this mechanism, it is expected that many Lewis acid catalyzed reactions should be successful in water solution.

This paper has shown the possibility of using several promising metal compounds as Lewis acid catalysts in water. Research work developing new aqueous reactions on the basis of these new findings is in progress in our laboratories.

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(9) Recently, indium(III) chloride-catalyzed Mukaiyama aldol reactions in water were reported. (a) Loh, T.-P.; Pei, J.; Cao, G.-Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819. However, these reactions could not be reproduced in our hands. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* **1998**, 1579.

(10) Baes, C. F., Jr.; Mesmer, R. *The Hydrolysis of Cations*; Wiley: New York, 1976.

(11) Yatsimirksii, K. B.; Vasil'ev, V. P. *Instability Constants of Complex Compounds*; Pergamon: New York, 1960.

(12) Martell, A. E., Ed.; *Coordination Chemistry*; ACS Monograph 168; American Chemical Society: Washington, DC, 1978; Vol. 2.

(13) Most values are −log K_{xy}. See ref 10 and Table 2.

(14) Actually, the hydrolysis constant of Ag(I) is 6.9 according to ref 11.

(15) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.