The effect of Lewis acidity in carbonyl coupling reactions

Biswajit Purkayastha, Krishna S Deka (née Krishna Sen) & Dibakar C Deka
Department of Chemistry, Gauhati University, Guwahati 781 014, India
Email: decdea@rediffmail.com
Fax: +91 361 2570133

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Relative Lewis acidities of (+)-Pr(hfc)₃, (+)-Eu(hfc)₃ and (+)-Yb(hfc)₃ have been estimated by measuring the induced chemical shift of the aldehydeic proton of benzaldehyde in the presence of these lanthanide complexes. The order has been estimated as Pr(hfc)₃ > Yb(hfc)₃ > Eu(hfc)₃. These lanthanide complexes and a few other non-lanthanide compounds such as BF₃(+)Et₂O, TiCl₄ and SnCl₄ have been used as Lewis acid catalysts in a coupling reaction between an aldehyde and (E)-1-methoxy-1-(trimethylsilyloxy)propane. Results show that the chemical yield of the reaction is in the same order as the Lewis acidity of the catalyst used. The observation is in consonant with the expectation that higher is the Lewis acidity more should be degree of activation of the carbonyl base by the Lewis acid.

Carbonyl coupling reaction is one of the best-known carbon-carbon bond forming reactions. It needs no mention that this reaction has got wide applications in synthetic organic chemistry. Large volume of research works has already been carried out on carbonyl coupling reactions especially when one of the carbonyl compounds used is in the form of enolates. All these reactions are catalysed by Lewis acids and a good number of Lewis acid catalysts have been discovered/developed in recent years. Amongst the prominent Lewis catalysts there are lanthanide complexes, lanthanide and transition metal halides and compounds of p-block elements. Compared to a large number of Lewis acids known, only a few of them have been compared for their relative Lewis acidity and no effort has been made to examine whether there exists any relationship between the Lewis acidity and the reaction velocity and/or stereochemical outcome of the coupling reactions. In this report we are comparing the Lewis acidity of a few lanthanide complexes based on ¹H NMR chemical shifts. Effects of Lewis acidity of these complexes and a few other non-lanthanide compounds of known relative Lewis acidity in carbonyl coupling reactions have also been discussed.

Experimental Section

Materials

Aldehydes: Commercially available benzaldehyde was purified by treatment with saturated sodium bicarbonate solution followed by extraction with diethyl ether. The extract, after dried over anhyd. sodium sulfate and solvent removed by a rotary vacuum evaporator, was fractionally distilled under reduced pressure and the middle fraction at 73-74°C/65 mmHg was collected as pure benzaldehyde. m-Methoxy- and p-methoxybenzaldehyde were of Aldrich-make and were used without further treatment.

(E)-1-Methoxy-1-(trimethylsilyloxy)propane. It was prepared from methyl propionate following the procedures of Chan et al. and was obtained as an isomeric mixture of (E)- and (Z)-isomers (85% and 15% respectively). The isomeric ratio was determined from ¹H NMR.

¹H NMR (300 MHz, CDCl₃) δ: 0.21(s, 9H)[0.19, s], 1.49 (d, 3H, J=6.6 Hz)[1.50, d, J=6.6 Hz], 3.52 (s, 3H)[3.47, s], 3.66 (q, 1H, J=6.6 Hz). Bracketed values are those of the Z-isomer.

¹³C NMR (300 MHz, CDCl₃) δ: -0.05[0.04], 9.14[9.36], 54.56[54.36], 78.69[76.99], 154.09[156.98]. Bracketed values are those of the Z-isomer.

Catalysts. Lewis acid catalysts were procured from commercial sources and used as such. While (+)-Pr(hfc)₃, (+)-Eu(hfc)₃ and (+)-Yb(hfc)₃ were solids (from Aldrich) TiCl₄, SnCl₄, BF₃(+)Et₂O and BBr₃ were obtained as 1.0 M solution in dichloromethane (from Fluka).

Measurement of relative Lewis acidity. Lewis acidities of (+)-Pr(hfc)₃, (+)-Eu(hfc)₃ and (+)-Yb(hfc)₃ were measured with respect to benzaldehyde as the common base. A known amount of benzaldehyde was dissolved in CDCl₃ and the chemical shift of the aldehydeic proton was recorded. After this 5 mol% of the lanthanide complex was now added and the chemical shift of the aldehydeic proton was again recorded. The difference in chemical shift was again recorded. The difference in chemical shift was taken as the measure of relative Lewis acidity. The data are shown in Table I.

**Note**
Procedure for coupling reaction. The Lewis acid catalyst was added to a solution of the aldehyde in dichloromethane (1.0 M, 2 mL) in a 50 mL round bottomed flask under nitrogen atmosphere at 0°C. The mixture was thoroughly stirred, cooled to -83°C (ethyl acetate-liquid nitrogen bath) and (E)-l-monium chloride solution mixture was thoroughly stirred, cooled to -83°C with sodium bicarbonate solution with ethyl acetate followed by brine and sodium sulfate. Solvent removed and the product was purified by a column of silica (60-120 mesh) with a mixture of hexane and ethyl acetate (5:1) as the eluent. In case of benzaldehyde the dielectric constant of the product, methyl 3-hydroxy-3-phenyl-2-methylpropionate, was determined from $^1$H NMR. *Threo* and *erythro* isomers were identified from the coupling constant of the $\alpha$- and $\beta$-hydrogens.\(^{13}\)

Spectral data of methyl 3-hydroxy-3-phenyl-2-methylpropionate: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: [threo 0.99 (d, $J=7$ Hz), erythro 1.13(d, $J=7.2$ Hz), 3H], 2.79 (m, 1H), [erythro 3.66 (s), threo 3.72 (s), 3H], [threo 4.74 (d, $J=8.6$ Hz), erythro 5.09 (d, $J=4.4$ Hz), 1H], 7.34 (aromatic, 5H); $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$: 10.52 (erythro), 14.19 (threo), 46.29 (erythro), 46.99 (threo), 51.79 (erythro), 73.55 (threo), (126.03, 126.77, 127.55, 128.15, 128.32, 128.57, 141.63, 141.70), 176.38 (erythro), 176.53 (threo); IR (neat): 3450, 1750, 1090, 700 cm$^{-1}$.\(^{14}\)

Results and Discussion

Lanthanide complexes are known to act as NMR shift reagents.\(^{16}\) High oxophilicity of lanthanides\(^{11}\) enables them to activate the carbonyl carbon by coordinating with the carbonyl oxygen in a manner as shown with benzaldehyde in Eqn 1. Coordination

$$\text{O} \quad \text{H} \quad + \quad \text{Ln(hfc)}_3 \quad \rightarrow \quad \text{O} \quad \text{H} \quad \text{Ln(hfc)}_3$$

with the carbonyl oxygen results in the induced chemical shifts of all the nuclei in general and the aldehydic proton in particular. Because of the close proximity of the latter to the coordination site the induced chemical shift it undergoes is appreciable. Thus aldehydic proton of benzaldehyde is a nucleus of choice for measurement of induced chemical shift vis-à-vis Lewis acidity of any Lewis acid coordinated to benzaldehyde through the aldehydic oxygen. As shown in Table I the induced chemical shift for the aldehydic proton is highest by Pr(hfc)$_3$ closely followed by Yb(hfc)$_3$ and the same by Eu(hfc)$_3$ is much lower. Thus taking the induced chemical shift as the measure for Lewis acidity, the order of Lewis acidity of the three lanthanide complexes examined can be stated as Pr(hfc)$_3$ $>$ Yb(hfc)$_3$ $>$ Eu(hfc)$_3$. When these lanthanide complexes were used as catalyst in a coupling reaction as shown in Eqn 2 it was observed that a stronger Lewis acid gives better yield. Pr(hfc)$_3$, the strongest Lewis acid amongst the three examined, gives 71% closely followed by Yb(hfc)$_3$ giving 66% (Table II). Eu(hfc)$_3$, being much weaker compared to the other two, yields only 52%.

It is reported\(^{12}\) that BB$_3$ is much stronger Lewis acid than BF$_3$OE$_2$, and this is reflected in the chemical yields of the coupling reaction catalysed by them (59% and 20% respectively). Likewise, Lewis acidity of TiCl$_4$ is reported\(^{12}\) as 1.3 times that of SnCl$_4$, and
the chemical yields produced by these Lewis acids are respectively 42% and 32% giving a ratio of 1.3.

The observation noted above regarding the effect of Lewis acidity in carbonyl coupling reaction has been further confirmed with two more aldehydes namely m- and p-methoxybenzaldehyde as shown in Equation 3 and results in Table III. As with benzaldehyde (Table II), near 1 : 1 diastereomeric ratio was observed on tlc.

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References
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