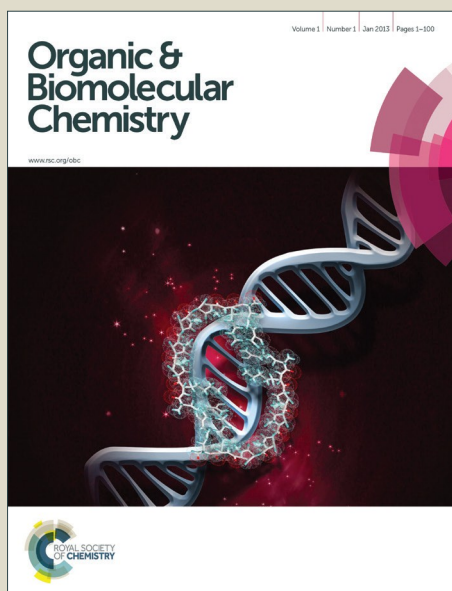


# Organic & Biomolecular Chemistry

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ARTICLE

## Triggering the approach of an Arene or Heteroarene towards an aldehyde *via* Lewis acid-aldehyde communication

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The present work involves a combined experimental/computational study on the Lewis acid promoted hydroxyalkylation reaction involving aldehyde and arene/heteroarene and reveals a mechanism in which rate determining aldehyde to alcohol formation *via* four member cyclic transition state (TS) involves a transfer of hydrogen from arene/heteroarene C-H to aldehyde oxygen with breaking of C-H bond and formation of C-C and O-H bond. The effect of different Sn(IV) derivatives in the hydroxyalkylation reaction from different in-situ NMR and computational studies unveil that the exergonic formation of the intermediate and its gained electrophilicity at the carbonyl carbon even if drives the reaction in SnCl<sub>4</sub> compared to other Sn(IV) derivatives, but overall reaction is low yielding because of its stable intermediate. With respect to different aldehyde, LA promoted hydroxylation is found to be more feasible in case of electron withdrawing aldehyde compared to electron rich aldehyde because of lower stability, enhanced electrophilicity gained at the aldehyde center, and lower activation barrier between its intermediate and TS in former as compared to latter. The relative stability of LA-aldehyde adduct decreases in the order SnCl<sub>4</sub> > AlCl<sub>3</sub> > InCl<sub>3</sub> > BF<sub>3</sub> > ZnCl<sub>2</sub> > TiCl<sub>4</sub> > SiCl<sub>4</sub>, while activation barrier ( $\Delta G^\ddagger$ ) between intermediate and transition state increases in the order AlCl<sub>3</sub> < SnCl<sub>4</sub> < InCl<sub>3</sub> < BF<sub>3</sub> < TiCl<sub>4</sub> < ZnCl<sub>2</sub> < SiCl<sub>4</sub>. On the other hand, activation barrier in case of different arenes/heteroarenes are in the order of indole < furan < anisole < thiophene < toluene < benzene < chlorobenzene < cyanobenzene, which suggest facile reaction in case of indole, while most difficult reaction in case of cyanobenzene. The ease of formation of corresponding diaryl methyl carbocation from alcohol-LA intermediate is responsible for the determination of undesired product and found to be more viable in case of strong LA like AlCl<sub>3</sub>, InCl<sub>3</sub> and SnCl<sub>4</sub> because they have negative free energy of formation ( $\Delta G$ ) for alcohol to corresponding diaryl methyl carbocation.

### Introduction

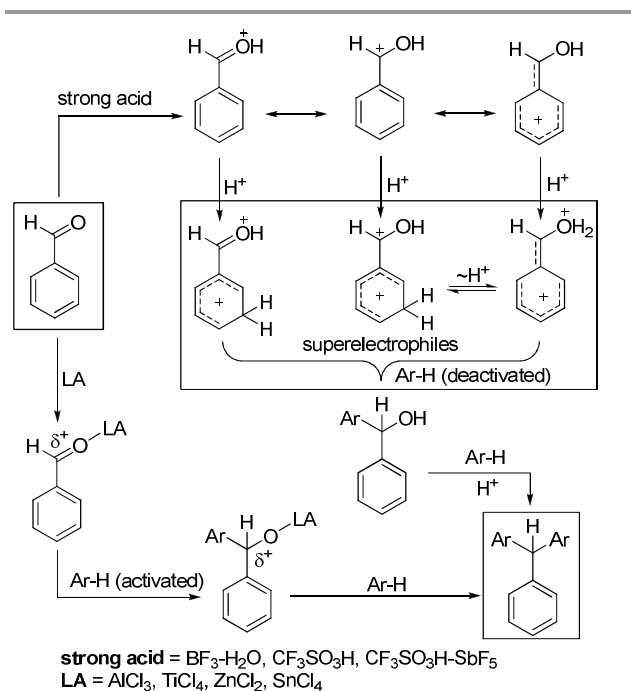
Dating back to 1887, Charles Friedel and James Mason Crafts isolated amylbenzene following the treatment of amyl chloride with AlCl<sub>3</sub> in benzene.<sup>1</sup> "This was not only one of the first descriptions of a Lewis acid used in organic synthesis but also the first example of what was soon after to be called Friedel-Crafts alkylation (FCA) after its inventors."<sup>2</sup> Over the past 125 years, various Lewis acids including BF<sub>3</sub>, BeCl<sub>2</sub>, TiCl<sub>4</sub>, SbCl<sub>5</sub>, or SnCl<sub>4</sub> and along with various strong Brønsted-acids like sulfuric acid, hydrofluoric acid or super acids such as HF•SbF<sub>5</sub> and HSO<sub>3</sub>F•SbF<sub>5</sub> have been described as catalysts for the FCA.<sup>3</sup> Indeed transition metal halides are long established as FCA catalysts. Among various reactions, Lewis acid (hereafter, LA) catalyzed electrophilic reactions of carbonyl compounds are among the most fundamental and important reactions in modern organic synthesis.<sup>4</sup> The electrophilicity of the carbonyl carbon is the main character controlling the reactivity of several important classes of organic compounds, such as aldehydes,

ketones, or carboxylic acid derivatives and substituents in the reacting molecule still strongly adjust its reactivity. The LA or Brønsted acid-catalyzed condensation of aromatic aldehydes and ketones with aromatics or heteroaromatics is often called hydroxyalkylation reaction.<sup>5</sup> Initial step of hydroxyalkylation produces a diarylmethanol which further reacts with another molecule of an arene or heteroarene to give the corresponding triarylmethane. The acidity dependence and the effect of basicity of carbonyl compounds on this reaction has been studied and reported earlier.<sup>6</sup> All the studies on hydroxyalkylation reaction may be categorized into two broad class; (i) superacid catalyzed condensation *via* highly electron-deficient species under strong protosolvolytic conditions,<sup>7</sup> and (ii) LA catalyzed condensation through relatively less electron-deficient species (Scheme 1).<sup>8</sup> In Lewis acid catalyzed reaction, LA weakens the C=O bond of aldehydes *via* coordination with oxygen lone pair of carbonyl and make it more susceptible for nucleophilic attack by enhancing the electrophilicity at the carbonyl carbon.<sup>9</sup> In most of the LA catalyzed hydroxyalkylation reaction of aldehyde, deactivated aromatics failed to condense with aldehyde to produce desired triarylmethane derivatives.<sup>10,11</sup> Earlier report shown that in presence of excess AlCl<sub>3</sub>, benzaldehyde reacts with benzene to give a number of products such as triphenylmethane,

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† Procedural, spectral, and bond order data in Electronic Supporting Information ESI-1 and optimized geometries including frequency data in Electronic Supporting Information ESI-2. See DOI: 10.1039/x0xx00000x

diphenylmethane, triphenylmethanol, and anthracene.<sup>12</sup> The LA-aldehyde complex plays a decisive role in both the progress and stereo chemical preference of the corresponding product. In this regard, Gladysz *et al.* provides a detail and comprehensive analysis on structural aspect of various transition metal Lewis acid-aldehyde complex and shows the relationships between binding equilibria, reactivity, and product configurations in various asymmetric reaction.<sup>13</sup> On the other hand, from spectroscopic and structural studies of various aldehyde-LA complexes, Denmark *et al.* presented fundamental information about their reactivity and selectivity in various catalytic reaction of aldehyde.<sup>14</sup> A major objective of the present work is to generate an insight on how does a Lewis acid-aldehyde coordination trigger the reactivity of aldehyde towards nucleophile like activated or deactivated aromatics in LA promoted hydroxyalkylation reaction? Towards this goal, hydroxyalkylation reaction catalyzed by various Lewis acid in general and Sn(IV) reagents in particular was chosen for the study. The effect of various LA, aldehyde, and arene in the hydroxyalkylation was done based on the theoretical and experimental evidences.



Scheme 1. Superacid and Lewis acid catalyzed hydroxyalkylation reaction.

## Results and Discussion

### NMR evidences of Lewis acid-Aldehyde adduct

Various studies on LA promoted hydroxyalkylation reaction showed that control in the selective product formation and their conversion will be achieved by suitably tuning the LA, aldehyde, or nucleophile.<sup>15</sup> In this regard, the coordination ability of different aldehyde to a particular Lewis acidic acceptor was done from the in-situ  $^{119}\text{Sn}$  NMR analysis.<sup>16</sup> For this, phenyl tintrichloride ( $\text{PhSnCl}_3$ ) was chosen as a Lewis

acidic acceptor and its corresponding  $^{119}\text{Sn}$  NMR shift,<sup>17</sup> after the coordination with particular aldehyde, was measured to check the binding affinity of six different *para* substituted aldehyde.<sup>18</sup> The  $^{119}\text{Sn}$  NMR shifts decreases in the order -OMe > -Me > -H > -Cl > -CF<sub>3</sub> > -CN, which signify stronger coordination between electron rich aldehyde and  $\text{PhSnCl}_3$  compared to electron deficient aldehyde (Fig. 1). The ease of formation of Sn(IV)-aldehyde adduct for different Sn(IV) compounds to a particular aldehyde was judged from the  $^{13}\text{C}$  NMR shift of 4-methyl benzaldehyde after the coordination with corresponding Sn(IV) compounds.<sup>19</sup> In all the cases, downfield shifting of all the carbon of 4-methyl benzaldehyde except C-2 was observed (Table 1). The  $^{13}\text{C}$  NMR shift of aldehyde carbon decreases in the order of  $\text{SnCl}_4 > \text{PhSnCl}_3 > \text{Me}_2\text{SnCl}_2 > \text{Ph}_3\text{SnCl}$ , which indicates the strongest coordination of aldehyde in most Lewis acidic  $\text{SnCl}_4$ . Ensuring the effect of Sn(IV)-aldehyde adduct on the reactivity of aldehyde towards a particular nucleophile, Sn(IV) compounds catalyzed reaction between 4-methyl benzaldehyde and indole to desired bis(indolyl) methane product (**1a**) was achieved.

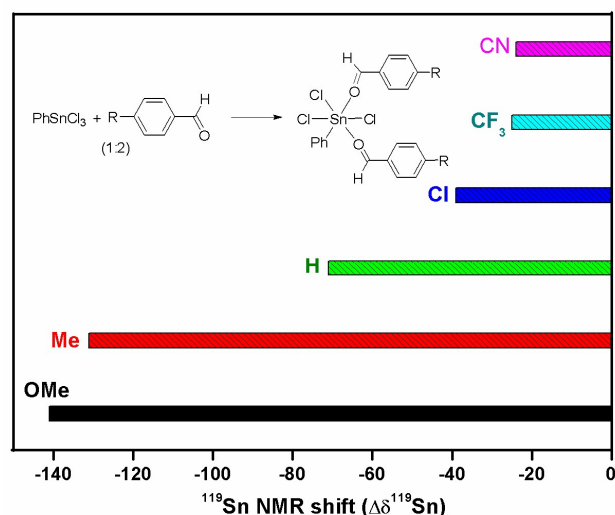
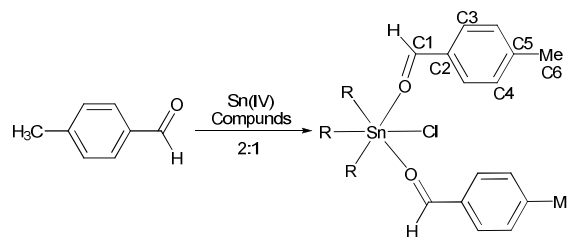


Fig. 1  $^{119}\text{Sn}$  NMR shifts of  $\text{PhSnCl}_3$  with six different *para* substituted benzaldehydes.

Table 1.  $^{13}\text{C}$  NMR shift of 4-methyl benzaldehyde after coordination with different Sn(IV) Compounds.

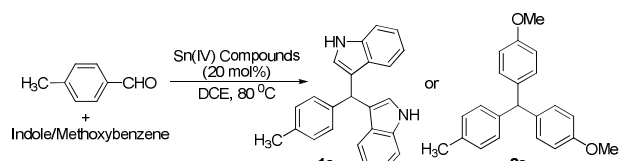


#	$\Delta\delta C1$	$\Delta\delta C2$	$\Delta\delta C3$	$\Delta\delta C4$	$\Delta\delta C5$	$\Delta\delta C6$
SnCl <sub>4</sub> <sup>a</sup>	6.95	-1.65	0.65	0.60	6.0	0.37
PhSnCl <sub>3</sub>	1.7	-0.5	0.56	0.42	1.35	0.43
Me <sub>2</sub> SnCl <sub>2</sub>	0.94	-0.35	0.37	0.18	0.65	0.2
nBu <sub>2</sub> SnCl <sub>2</sub>	0.85	-0.13	0.41	0.27	0.64	0.3
Ph <sub>3</sub> SnCl	0.34	0.13	0.25	0.22	0.37	0.28

$\Delta\delta$  (ppm) = (<sup>13</sup>C NMR of coordinated aldehyde - <sup>13</sup>C NMR of free aldehyde). <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> at 298K.

Interestingly, only SnCl<sub>4</sub> and PhSnCl<sub>3</sub> are found to be active amongst all other tested Sn(IV) compounds as other compounds failed to produce any desired bis(indolyl) methane (Table 2). The Sn(IV) compounds catalyzed hydroxyalkylation reaction was tested with other arene like 4-methoxybenzene. Noticeably, only SnCl<sub>4</sub> is active towards desired triaryl methanes (TRAMs, **2c**) at elevated temperature while, other Sn(IV) compounds are failed to produce any desired TRAM. This indicates that not only the formation of aldehyde-LA adduct is important, but also the reactivity of arene plays a decisive role in the LA catalyzed hydroxyalkylation reaction. To define the possible intermediate of the hydroxyalkylation reaction, the reaction of 4-cyanobenzaldehyde (1 mmol), with a mixture of two arenes namely 1,3,5-trimethoxybenzene (1 mmol), and anisole (1 mmol) in the presence of 20 mol% of SnCl<sub>4</sub> has been chosen as a model reaction.

**Table 2.** Sn(IV) Compounds promoted hydroxyalkylation reaction of indole and anisole with 4-methyl benzaldehyde.

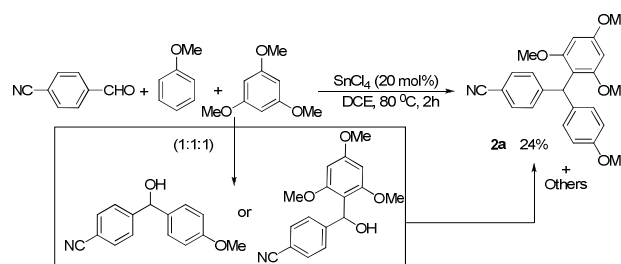


#	Time(h)	Yield ( <b>1a</b> , %)	Yield ( <b>2c</b> , %)
SnCl <sub>4</sub>	1	90	18 <sup>a</sup>
PhSnCl <sub>3</sub>	2	73	0 <sup>a</sup>
Me <sub>2</sub> SnCl <sub>2</sub>	6	0	0
nBu <sub>2</sub> SnCl <sub>2</sub>	6	0	0
Ph <sub>3</sub> SnCl	6	0	0

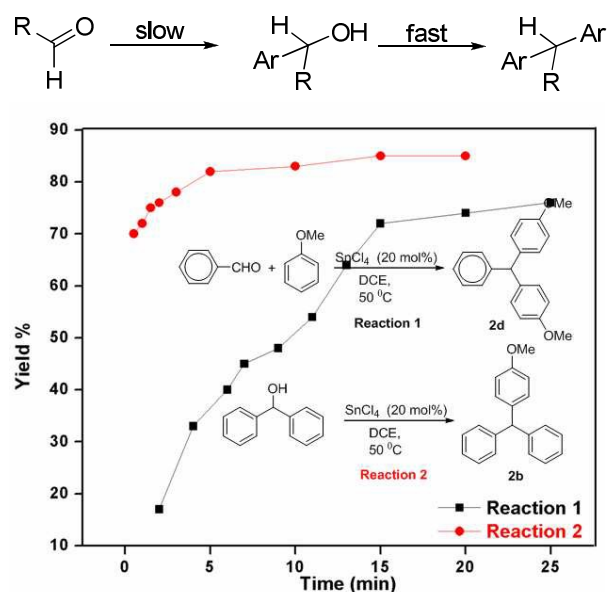
Reaction Condition: Sn(IV) compounds (20 mol%), 0.5 mmol of aldehyde, 1.1 mmol of indole/methoxybenzene, 1,2-dichloroethane (3 mL), temperature 80 °C. <sup>a</sup> reaction was proceeded for 6 h.

Gratifyingly, besides the self coupled product, cross-coupled TRAM product **2a** has been isolated in 24% yield, which suggest the presence of possible secondary alcohol intermediate in the reaction (Scheme 2). Further, to confirm the slowest step of the Sn(IV) promoted hydroxyalkylation reaction, SnCl<sub>4</sub> promoted two separate reaction involving benzaldehyde and anisole, diphenyl methanol and anisole were separately analyzed (Scheme 3).<sup>20</sup> The SnCl<sub>4</sub> promoted reaction between diphenyl methanol and anisole to its corresponding diphenylanisylmethane (**2b**) walk off in a faster rate and reaches steady state within 30 seconds. Whereas, SnCl<sub>4</sub> promoted reaction between benzaldehyde and anisole to its corresponding dianisylphenylmethane (**2b**) slowly proceeds to

steady state. The above two experiment conclude that aldehyde to secondary alcohol formation is the slowest step in the reaction (Scheme 3). So, the reactivity as well as stability of Sn(IV)-aldehyde adduct will play an important role in the hydroxyalkylation reaction as conversion of aldehyde to secondary benzyl alcohol is the slowest step of the reaction. For this, theoretical study was done on the Sn(IV)-aldehyde adduct.



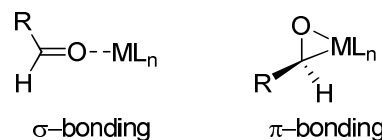
**Scheme 2.** Control experiments on the intermediacy of secondary alcohol.



**Scheme 3.** Aldehyde to triaryl methane through alcohol intermediate.

### Effect of Aldehyde-Sn(IV) Adduct:

The local environment of the reactive carbonyl carbon in Lewis acid-aldehyde complex may be tune through the coordination mode of carbonyl, location of Lewis acid and conformational preferences for the groups adjacent to the carbonyls. The complexation of Carbonyl group with LA may occur either using  $\sigma$ -type or  $\pi$ -type of coordination mode (Figure 2).<sup>21</sup>

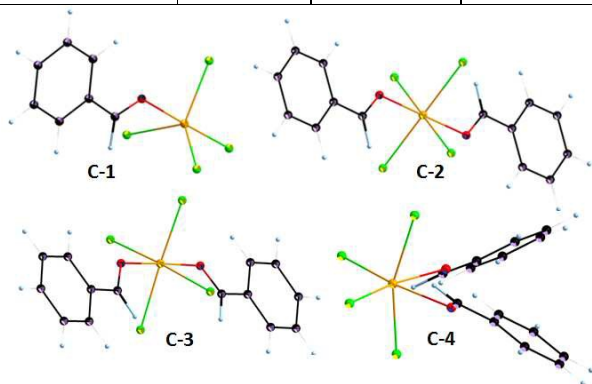


**Fig. 2** Two different binding mode of aldehyde to Lewis acidic metal salt.

In general  $\pi$ -type complexation between aldehyde and metal is governed with electron rich transition metal complexes, where  $\sigma$ - $\pi$  equilibrium is mostly influenced on the electronic nature of the aldehyde. On the other hand, most main group, early transition, and lanthanide-based Lewis acids are believed to coordinate through  $\sigma$ -type bonding, in which location of LA depends on the vacant sites and geometrical preferences of the Lewis acidic metal center.<sup>22</sup> The spectroscopic and structural studies on the structure and conformation of aldehyde-Sn(IV) complexes by Denmark *et al.* suggested that however the 1:1 complex is in equilibrium with the 1:2 complex at high SnCl<sub>4</sub> and aldehyde ratios and is detectable at -80 °C in significant concentration but 1:2 complexation is preferred in solution.<sup>23</sup> To know the stable conformation of aldehyde-SnCl<sub>4</sub> adduct, all the probable structures were optimized at B3LYP level of theory using effective core potential (ECP) along with valence basis sets (LANL2DZ) for tin and 6-31G\* basic set for other atoms. The energetically most stable structure was determined from free energy difference ( $\Delta G$ ) between product and reactant with zero-point energies (ZPE) and thermal corrections at 298 K. Although  $\Delta G$  in both the gas phase and solvent phase (in dichloromethane and toluene) showed slightly higher stability of 1:1 SnCl<sub>4</sub>(aldehyde) adduct, C-1 compared to 1:2 SnCl<sub>4</sub>(aldehyde)<sub>2</sub>, C-2, but in solid state C-2 is more stable and is isolable (Table 3).<sup>23(d)</sup>

**Table 3.** All the probable structure of SnCl<sub>4</sub>-benzaldehyde adduct and their enthalpy of formation ( $\Delta H$ ) and free energy of formation ( $\Delta G$ ) data in gas phase and toluene.

Product <sup>a</sup>	PhCHO + SnCl <sub>4</sub> $\xrightarrow{1:1/1:2}$ (PhCHO)SnCl <sub>4</sub> or (PhCHO) <sub>2</sub> SnCl <sub>4</sub>		
	$\Delta G_{\text{gas}}$	$\Delta G_{\text{DCM}}$	$\Delta G_{\text{toluene}}$
C-1	-37.8	-30.2	-33.4
C-2	-31.2	-27.2	-28.5
C-3	-31.1	-27.3	-28.6
C-4	-33.3	-27.5	-29.5



<sup>a</sup> $\Delta H$  and  $\Delta G$  is the enthalpy and free energy difference between product and reactant with zero-point energies (ZPE) and thermal corrections at 298 K in Kcal/mol.

However in 1:2 SnCl<sub>4</sub>(aldehyde)<sub>2</sub> octahedral adduct, aldehyde may attain either cis or trans position around octahedron. Amongst all the structure, C-4 (in which two aldehyde are cis to each other) is more stable because it has more negative gas/solvent phase  $\Delta G$  compare to C-2 or C-3 (in which two

aldehyde are trans to each other). The optimized structure of C-4 gave good agreement with experimentally observed octahedral structure of SnCl<sub>4</sub>(4-t-BuC<sub>6</sub>H<sub>4</sub>CHO)<sub>2</sub> by Denmark *et al.*<sup>23(d)</sup> Now to know the effect of aldehyde on the stability of aldehyde-Sn(IV) adduct, free energy of formation ( $\Delta G$ ) was calculated with six different *para* substituted aldehydes. The more negative calculated gas/solvent phase  $\Delta G$  in case of electron rich aldehyde compare to electron deficient aldehyde suggest favourable formation of Sn(IV)-aldehyde adduct in former as compare to latter (Table 4).<sup>24</sup> For further understanding the actual bond strength in aldehyde-Sn(IV) complexes, bond order of all the aldehyde along with their corresponding SnCl<sub>4</sub>-adduct was done with AOMIX package.<sup>25</sup> The strength of O-Sn bond increases in the order -CN<-CF<sub>3</sub><-Cl<-H<-Me<-OMe, whereas difference in bond order of C=O between free aldehyde and its corresponding adduct decreases from electron rich to electron deficient aldehyde.<sup>26</sup> So one would expect difference in reactivity between electron rich and electron deficient aldehydes, as their coordination ability towards the Lewis acid are different.

**Table 4.** Free energy of formation ( $\Delta G$ ) data of SnCl<sub>4</sub>(aldehyde)<sub>2</sub> intermediate with six different *para* substituted benzaldehydes in gas phase, toluene, and dichloromethane.

R	$\Delta G_{\text{gas}}$	$\Delta G_{\text{DCM}}$	$\Delta G_{\text{toluene}}$
OMe	-34.5	-28.0	-31.4
Me	-35.6	-28.7	-32.4
H	-33.1	-26.0	-32.1
Cl	-27.6	-20.1	-26.0
CF <sub>3</sub>	-28.7	-23.1	-27.5
CN	-25.3	-17.2	-23.9

<sup>a</sup>  $\Delta G$  values are calculated from the corresponding free energy difference between product and reactant in Kcal/mol with zero-point energies (ZPE) and thermal corrections at 298 K.

For this, SnCl<sub>4</sub> catalyzed alkylation of anisole with five different aldehydes were done. Reactions of anisole with aldehyde such as 4-methyl benzaldehyde or benzaldehyde were sluggish and produced the corresponding TRAM in low yield. However, when benzaldehyde was replaced by an electron deficient aldehyde, such as 4-chloro or 4-cyano benzaldehyde, the reaction became faster and produced desired triarymethanes in moderate to good yield (Table 5). The SnCl<sub>4</sub> promoted reaction between ethyl glyoxalate and anisole also afforded the corresponding TRAM (2g) in 68% yield. So, not only formation of aldehyde-Sn(IV) adduct is important, but also electrophilicity gained at the carbonyl centre after coordination and the activation barrier between aldehyde-Sn(IV) adduct and its transition state after the approach of anisole is also important. The 1:1 Aldehyde-Sn(IV) adduct was used for theoretical calculation. Improved electrophilicity at the aldehyde carbon after the coordination in aldehyde-Sn(IV)

intermediate (*Int.*) will facilitate the approach of anisole. The close proximity between anisole and the *Int.* in transition state (TS) would facilitate the interaction between coordinated oxygen and C-H bond of anisole and thus significantly elongated C-H bond in TS is observed (1.27 Å vs 1.08 Å in the ground state of anisole). So, the rate determining step involves the transfer of hydrogen from anisole C-H to aldehyde oxygen with breaking of C-H bond and formation of one new C-C and O-H bond (Fig. 5).

Table 5. SnCl<sub>4</sub> promoted hydroxyalkylation reaction of anisole with different aldehydes.

Aldehyde	Time (h)	Product	Yield (%)
4-Methyl Benzaldehyde	5		18
Benzaldehyde	5		36
4-chloro benzaldehyde	2		48
4-cyano benzaldehyde	2		52
Ethylglyoxalate	4		68
4-methoxy benzaldehyde	12		0

Reaction Condition: SnCl<sub>4</sub> (0.1 mmol), 0.5 mmol of aldehyde, 1.1 mmol of methoxybenzene, 1,2-dichloroethane (3 mL), temperature 80 °C.

Further to know the effect of aldehyde, transition state (TS) model for SnCl<sub>4</sub> promoted hydroxyalkylation reaction of methoxybenzene with seven different aldehydes have been analyzed.<sup>27</sup> All the geometries of probable TS and intermediate were optimized by using the Gaussian09 suite of quantum chemical programs.<sup>28</sup> Effective core potential (ECP) along with

valence basis sets (LANL2DZ) for tin, while for other atoms 6-31G\* basic set was used. The calculated free energy of formation of aldehyde-SnCl<sub>4</sub> adduct increases from electron rich aldehyde to electron deficient aldehyde, which suggest the ease of adduct formation in case of electron rich aldehyde (Table 6). The computed gas/solvent phase free energy of activation ( $\Delta G^\ddagger$ ) between intermediate and TS for electron deficient aldehyde is found to be lower compared to electron rich aldehyde (Table 6). Thus facile alkylation of anisole in electron withdrawing aldehyde like; 4-chloro benzaldehyde, 4-cyano benzaldehyde, or ethyl glyoxalate is expected and also found in SnCl<sub>4</sub> promoted reaction between those aldehyde and anisole (Table 5). Whereas, inactivity of 4-methoxy benzaldehyde towards the formation of corresponding TRAM is well justified with its higher gas/solvent phase  $\Delta G^\ddagger$ .

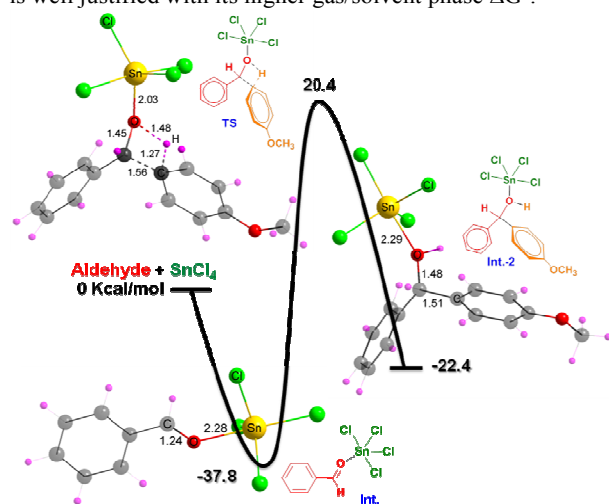


Fig. 5 Gas phase Gibbs Free Energy Profile (in Kcal/mol) for SnCl<sub>4</sub> Promoted hydroxyalkylation reaction between benzaldehyde and anisole.

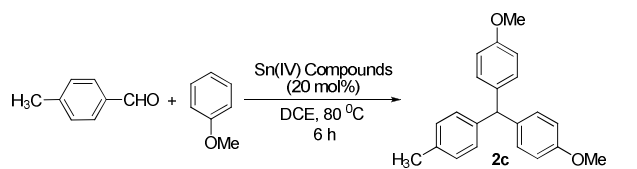
Table 6. Energetic details (in Kcal/mol) for SnCl<sub>4</sub> promoted aldehyde to alcohol formation with various aldehyde.

#	$\Delta G$ (Int.-React.)			$\Delta G^\ddagger$ (Ts-Int.)		
	$\Delta G_{\text{gas}}$	$\Delta G_{\text{Tot}}$	$\Delta G_{\text{DCM}}$	$\Delta G_{\text{gas}}^\ddagger$	$\Delta G_{\text{Tot}}^\ddagger$	$\Delta G_{\text{DC}}^\ddagger$
4-methoxy benzaldehyde	-38.9	1.9	-30.5	61.1	59.4	57.6
4-methyl benzaldehyde	-39.7	2.4	-30.8	59.5	56.3	53.2
Benzaldehyde	-37.8	2.8	-28.9	58.2	57.4	53.1
4-chloro benzaldehyde	-34.9	5.7	-26.2	57.8	53.8	51.1
4-cyano benzaldehyde	-34.1	7.0	-24.4	55.9	53.1	49.5
4-(trifluoromethyl) benzaldehyde	-33.7	6.3	-26.7	54.1	54.5	50.7
Ethyl glyoxalate	-33.3	-2.5	-33.1	42.9	37.0	34.6

## Effect of Sn(IV) compounds on Hydroxyalkylation Reaction:

Further to check the effect of Sn(IV) compounds on hydroxyalkylation reaction, the reaction between 4-methyl benzaldehyde and anisole was chosen as a model reaction. Interestingly, amongst all the tested Sn(IV) compounds, only SnCl<sub>4</sub> was found to be active for the synthesis of corresponding TRAM (**2c**) (Table 7).

Table 7. Sn(IV) compound promoted hydroxyalkylation reaction between 4-methyl benzaldehyde and anisole.



Sn(IV) Compounds	Yield (%)
SnCl <sub>4</sub>	18
PhSnCl <sub>3</sub>	0
Bz <sub>2</sub> SnCl <sub>2</sub>	0
Me <sub>2</sub> SnCl <sub>2</sub>	0

The effect of Sn(IV) compounds on the hydroxyalkylation reaction was further checked from the transition state analysis of SnCl<sub>4</sub> and PhSnCl<sub>3</sub> promoted reaction between 4-methyl benzaldehyde and anisole. The intermediate of SnCl<sub>4</sub> was found to be more stable compared to corresponding PhSnCl<sub>3</sub> intermediate because former has negative free energy of formation (Figure 6).

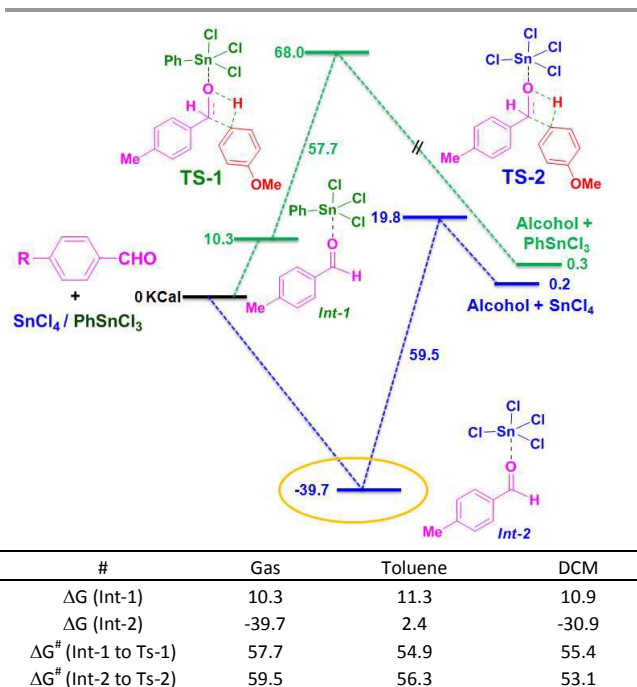


Fig. 6 Gibbs Free Energy Profile (in Kcal/mol) for SnCl<sub>4</sub> and PhSnCl<sub>3</sub> Promoted hydroxyalkylation reaction between 4-methyl benzaldehyde and anisole in both gas phase and solvent continuum (Toluene and DCM).

Both the reaction proceeds through a four member cyclic transition state (TS), in which one hydrogen transfer from anisole C-H to coordinated oxygen with simultaneous bond breaking and forming between aldehyde C=O and anisole C-H. Although the calculated activation barrier for SnCl<sub>4</sub> promoted reaction slightly higher compared to PhSnCl<sub>3</sub> promoted reaction, but the reaction is feasible in former case because of its exergonic formation of intermediate and gained electrophilicity at carbonyl carbon after strong coordination of aldehyde with SnCl<sub>4</sub>. At the same time, lower yield of TRAM product in SnCl<sub>4</sub> promoted reaction may be explained from its strong affinity to form stable adduct with aldehyde, which hold back the stable intermediate to reach its transition state (TS).

## Effect of various Lewis acids on Hydroxyalkylation Reaction:

The interaction between LA and aldehyde results the corresponding aldehyde-LA adduct in which most of the main group and early transition metals are believed to coordinate in a σ-fashion to aldehyde by accepting electron from aldehyde. So, one would expect stronger interaction between LA and aldehyde to form its stable adduct in case of strong LA and electron rich aldehyde. In this study, the 1:1 adduct of 4-methyl benzaldehyde with six different LA was chosen as a model and optimized at B3LYP/LANL2DZ, 6-31G(d) level of theory. The free energy of formation (ΔG) of all the 1:1 adduct was determined from the free energy difference between product and reactant with zero-point energies (ZPE) and thermal corrections at 298 K. The calculated ΔG shows the exergonic formation of LA-aldehyde adduct in all the cases except SiCl<sub>4</sub> and TiCl<sub>4</sub> (Fig. 7). The relative stability of the LA-aldehyde adduct decreases in the order AlCl<sub>3</sub> > InCl<sub>3</sub> > ZnCl<sub>2</sub> > BF<sub>3</sub> > TiCl<sub>4</sub> > SiCl<sub>4</sub>. The trends as well as the conclusions are found to remain more or less similar with the Gibbs free energies as well, in both the gas phase and the solvent continuum (in toluene and DCM). So, aldehyde binding to a transition or main group Lewis acidic metal center is crucial as it activates the aldehyde center and facilitates the approach of arene/heteroarene in the transition state and controls the activation barrier in the aldehyde to diaryl methanol conversion. For this, transition state of all the six LA promoted reaction between 4-methyl benzaldehyde and anisole were optimized. All the six optimized transition state along with some of the important bond lengths were provided in Fig. 8.

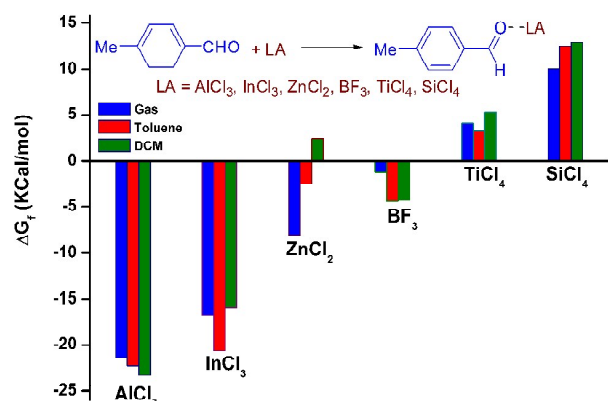


Fig. 7 Free energy of formation plot for Lewis acid-aldehyde intermediate with six different Lewis acid.

The four member cyclic transition state of all the LA involves the simultaneous breaking of anisole C-H bond and the formation of one new C-C and O-H bond. The calculated activation barrier ( $\Delta G^\ddagger$ ) between intermediate and TS increases in the order  $\text{AlCl}_3 < \text{SnCl}_4 < \text{InCl}_3 < \text{BF}_3 < \text{TiCl}_4 < \text{ZnCl}_2 < \text{SiCl}_4$  (Table 8) and trends remain more or less similar both in gas phase and the solvent continuum (in toluene and DCM). So, one might expect that the hydroxyalkylation reaction will be most favorable in case of  $\text{AlCl}_3$ , while most difficult in  $\text{SiCl}_4$  or  $\text{ZnCl}_2$ . Further to check the effect of arene or heteroarene on the LA promoted hydroxyalkylation reaction theoretical studies were done with eight different arene/heteroarene, discussed in the next section.

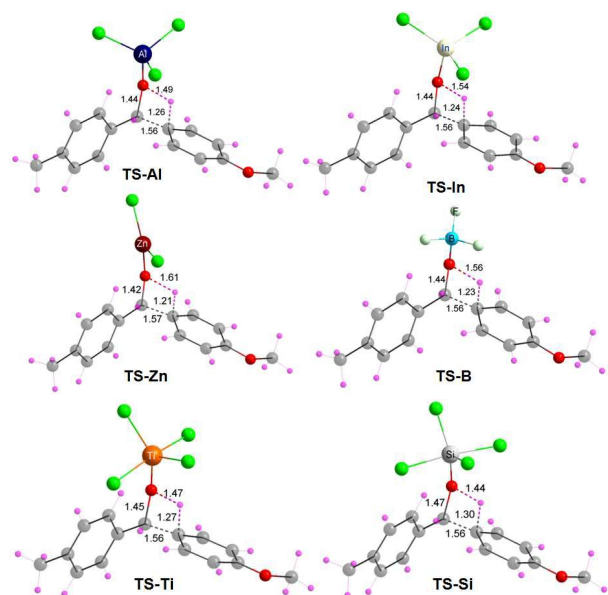


Fig. 8 Optimized structure of six transition state (TS) with six different Lewis acid.

Table 8. Energetic details (in Kcal/mol) for LA promoted 4-methyl benzaldehyde to (4-methoxyphenyl)(p-tolyl)methanol formation with six different Lewis acid.

Lewis acid	$\Delta G^\ddagger(\text{TS-Int.})$		
	$\Delta G^\ddagger_{\text{Gas}}$	$\Delta G^\ddagger_{\text{Tol}}$	$\Delta G^\ddagger_{\text{DCM}}$
$\text{AlCl}_3$	53.5	51.7	51.6
$\text{SnCl}_4$	59.5	56.3	53.2
$\text{InCl}_3$	56.5	56.9	52.9
$\text{BF}_3$	58.0	56.6	52.1
$\text{TiCl}_4$	59.6	58.4	54.6
$\text{ZnCl}_2$	59.8	58.9	60.2
$\text{SiCl}_4$	67.1	58.5	56.3

### Effect of various Arene or Heteroarene in Hydroxyalkylation Reaction

As an important contribution, Roberts and co-workers showed  $\text{AlCl}_3$  promoted transformation of benzaldehyde to corresponding dianisylphenyl-methane in 27% yield from the reaction between benzaldehyde and anisole. Whereas, they got 3% of ditolylphenylmethane from the  $\text{AlCl}_3$  promoted reaction between benzaldehyde and toluene.<sup>9a</sup> So, the reactivity of arene/heteroarene is also a decisive factor in hydroxyalkylation reaction. Thus, theoretical study on both  $\text{AlCl}_3$  and  $\text{SnCl}_4$  promoted transformation of 4-methyl benzaldehyde to its corresponding diarylmethanol derivatives with eight different arene/heteroarene was chosen as a model reaction. All the probable TS and intermediate were optimized at B3LYp level of theory using effective core potential (ECP) along with valence basis sets (LANL2DZ) for Lewis acidic metal, while 6-31G\* basic set for other atoms. Five representative optimized transition state with five different arene/heteroarene have been provided in Fig. 9.<sup>28</sup> The gas/solvent phase activation barrier ( $\Delta G^\ddagger$ ) of all the  $\text{AlCl}_3$  and  $\text{SnCl}_4$  promoted 16 reactions were calculated with Gibbs free energies in both the gas phase and the solvent continuum (in toluene and DCM). The trends as well as the conclusions are found to remain more or less similar in both the  $\text{AlCl}_3$  and  $\text{SnCl}_4$  promoted reactions. The  $\text{AlCl}_3$  promoted reactions are found to be slightly more facile compared to  $\text{SnCl}_4$  promoted reactions because of lower  $\Delta G^\ddagger$  in the former case favours the reaction. The gas/solvent phase  $\Delta G^\ddagger$  in both the  $\text{AlCl}_3$  and  $\text{SnCl}_4$  promoted reactions increases in the order indole < furan < anisole < thiophene < toluene < benzene < chlorobenzene < cyanobenzene (Table 9-10), which suggest most facile reaction in indole while; most difficult reaction in cyanobenzene. Gratifyingly, the above reactivity order of arene and heteroarene obtained from the activation barrier ( $\Delta G^\ddagger$ ) of two reactions are found to be in good agreement with the previously reported experimental observations.<sup>29</sup>



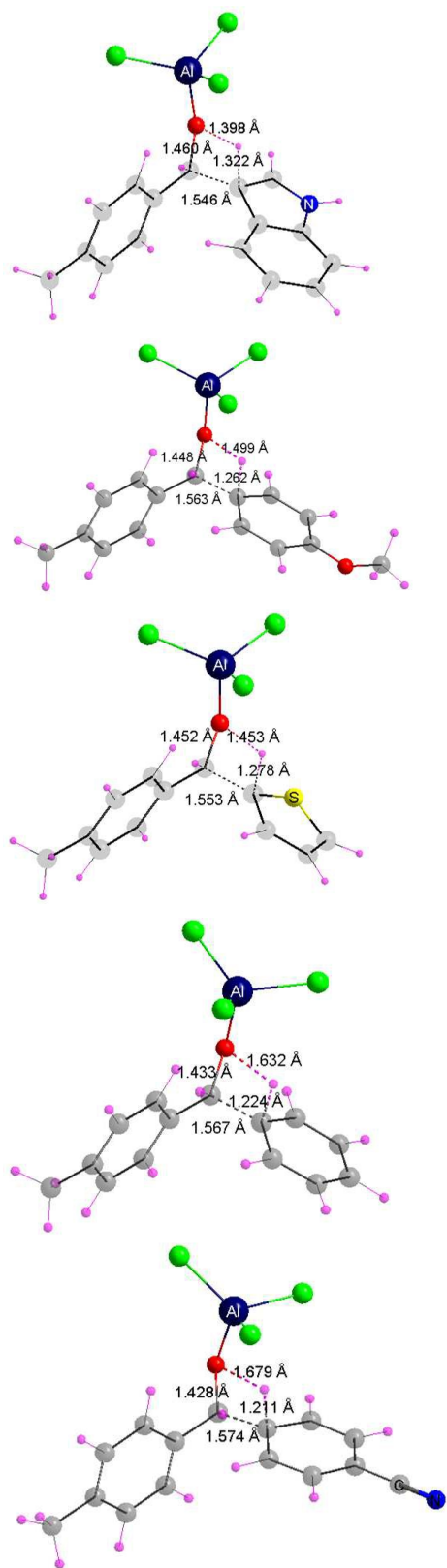


Fig. 9 The optimized transition state of five representative arene/heteroarene.

Table 9. Energetic details (in Kcal/mol) for SnCl<sub>4</sub> promoted hydroxyalkylation reaction of 4-methyl benzaldehyde with eight different arene/heteroarene.

Arene/Heteroarene	$\Delta G^{\ddagger}_{\text{Gas}}$	$\Delta G^{\ddagger}_{\text{ToI}}$	$\Delta G^{\ddagger}_{\text{DCM}}$
Cyanobenzene	79.5	76.0	75.6
Chlorobenzene	73.3	69.5	66.3
Benzene	70.0	64.5	61.5
Toluene	67.1	60.9	59.2
Thiophene	60.6	57.6	55.3
Methoxybenzene	59.5	56.0	53.1
Furan	58.7	47.9	52.6
Indole	53.6	49.1	49.2

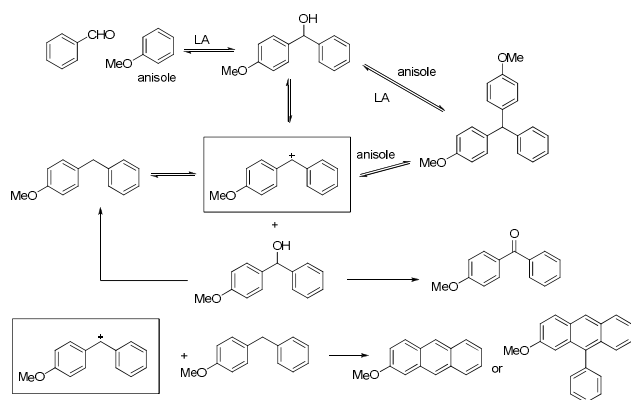
Table 10. Energetic details (in Kcal/mol) for AlCl<sub>3</sub> promoted hydroxyalkylation reaction of 4-methyl benzaldehyde with eight different arene/heteroarene.

Arene/Heteroarene	$\Delta G^{\ddagger}_{\text{Gas}}$	$\Delta G^{\ddagger}_{\text{ToI}}$	$\Delta G^{\ddagger}_{\text{DCM}}$
Cyanobenzene	72.7	70.6	69.4
Chlorobenzene	66.8	63.2	62.9
Benzene	63.4	60.1	58.1
Toluene	61.0	58.7	56.3
Thiophene	57.1	52.9	54.1
Methoxybenzene	53.5	51.7	51.6
Furan	54.9	52.58	49.6
Indole	49.2	48.3	46.9

### Effect of Lewis acid on Side Product formation

Although the AlCl<sub>3</sub> promoted reaction between aldehyde and arene to its corresponding alcohol formation is facile in case of activated arene like anisole. But the corresponding yield of dianisylphenylmethane in AlCl<sub>3</sub> promoted reaction between aldehyde and anisole is low.<sup>9a</sup> This may be due to either very stable intermediate of AlCl<sub>3</sub>-aldehyde adduct, which hold back the intermediate to reach its transition state or in presence of AlCl<sub>3</sub>, alcohol get converted into other products. However, experimental observation with Lewis acid like AlCl<sub>3</sub>, SnCl<sub>4</sub> suggests the formation of by-product like anisylphenylmethane, dianisylphenylmethanol. All the by-product may come from the carbocation intermediate of the corresponding anisylphenyl methanol (Scheme 4). Thus, the generation of carbonation from the alcohol relies on the relative strength of the Lewis acidic metals. For this, free energy of formation ( $\Delta G$ ) in terms of free energy change between product and reactant for LA promoted carbocation generation from anisyl phenylmethanol was done at B3LYP level of theory using the same basis set as detailed in computational details with zero-point energies (ZPE) and thermal corrections at 298 K. The  $\Delta G$  of various LA in gas phase and solvent continuum (in toluene and DCM) are plotted in Fig. 10. The  $\Delta G$  trends in both the gas phase and the solvent continuum (in toluene and DCM) are found to remain more or less similar and follows the order AlCl<sub>3</sub> < InCl<sub>3</sub> < SnCl<sub>4</sub> < TiCl<sub>4</sub> < BF<sub>3</sub> < SiCl<sub>4</sub> < ZnCl<sub>2</sub>. The above trend suggest that generation of carbocation from the corresponding anisylphenyl methanol is most facile in AlCl<sub>3</sub> while, most difficult for ZnCl<sub>2</sub>. So, one would expect the formation of side product in AlCl<sub>3</sub> promoted hydroxyalkylation reaction of aldehyde, which actually

observed experimentally.<sup>9a</sup> On the other hand, positive  $\Delta G$  for  $\text{SnCl}_4$ ,  $\text{ZnCl}_2$  and  $\text{BF}_3$  promoted reaction suggest minor chance of side product formation in these cases.



Scheme 4. Probable side product of Lewis acid promoted hydroxyalkylation reaction

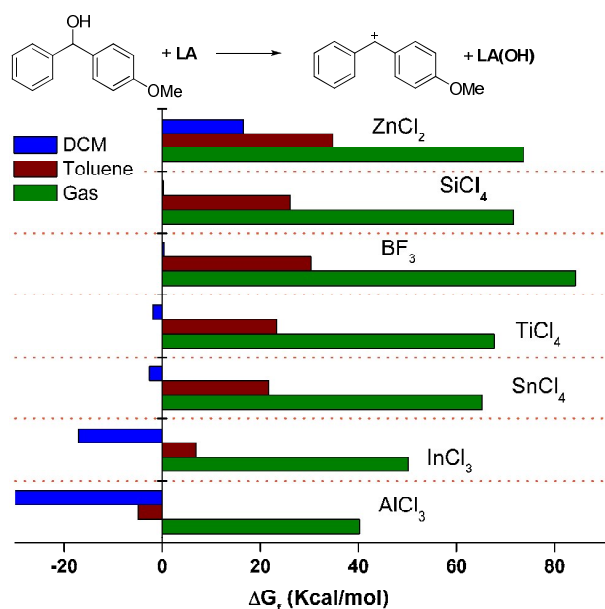


Fig. 10 Free energy of formation ( $\Delta G$ ) plot for Lewis acid promoted carbocation generation from anisyl phenylmethanol.

## Experimental

All the reactions performed under a dry oxygen free argon atmosphere using standard vacuum lines and Schlenk techniques. All the solvents used for the study have been dried and distilled by standard methods and previously deoxygenated in the vacuum line. The commercial  $\text{CDCl}_3$  was dried by passing the solvent with a bed of anhydrous  $\text{MgSO}_4$  and then  $\text{K}_2\text{CO}_3$  to remove  $\text{HCl}$  and stored it over dried  $4\text{\AA}$  molecular sieves and used for NMR experiment.  $^1\text{H}$  (200, 400 MHz) and  $^{13}\text{C}$  NMR (54.6, 100 MHz) spectra (chemical shifts referenced to signals for residual solvent) were recorded on 200 and 400 MHz spectrometer at 298 K.  $^{119}\text{Sn}$  NMR (149.2 MHz) spectra

(chemical shifts referenced to signals for external tetramethyltin) were recorded in 400 MHz spectrometer at 298 K.

## General procedure to study the $\text{SnCl}_4$ promoted hydroxyalkylation reaction of aldehyde

A 10-mL Schlenk flask equipped with a magnetic bar, was charged with  $\text{SnCl}_4$  (0.1 mmol) in dichloroethane (3 mL) under an argon atmosphere. The appropriate aldehyde (0.5 mmol) was added to the latter and the solution was stirred for 5 min. After that the appropriate arene or heteroarene (1.1 mmol) was added to it and placed into a constant temperature bath at  $80\text{ }^\circ\text{C}$  and allowed to continue at  $80\text{ }^\circ\text{C}$ . After completion, the reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{F}$  solution, extracted with ethylacetate (20 mL) and washed with water (10 mL  $\times$  3), brine (10 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After removing the solvent the residue was subjected to silica gel column chromatography (60-120 mesh, ethyl acetate-petroleum ether, gradient elution) to afford pure triarylmethane product.

**1a:** colorless viscous liquid, 150 mg, Yield = 90%,  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.36 (3H, s), 5.87 (1H, s), 6.59 (2H, d,  $J = 2.0$  Hz), 6.99-7.34 (10H, m), 7.43 (2H, d,  $J = 7.8$  Hz), 7.78 (2H, s).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 21.1, 39.8, 111.1, 119.2, 119.8, 120.0, 121.9, 123.6, 127.1, 128.6, 128.9, 135.5, 136.7, 141.1.

**2a:** colorless solid, 45 mg, Yield = 24%,  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 3.57 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 5.96 (1H, s, CH), 6.11 (1H, s), 6.77 (2H, d,  $J = 8.8$  Hz), 7.07 (2H, d,  $J = 8.4$  Hz), 7.14 (2H, d,  $J = 8.0$  Hz), 7.44 (2H, d,  $J = 8.4$  Hz).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 44.6, 55.2, 55.3, 55.5, 55.6, 91.5, 108.7, 112.4, 113.4, 119.5, 129.4, 130.2, 131.2, 134.1, 151.3, 157.9, 158.8, 160.4. HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{23}\text{NO}_4$  [ $\text{M}+\text{H}$ ] $^+$  = 390.1705, found 390.1699. Anal. ( $\text{C}_{24}\text{H}_{23}\text{NO}_4$ ) calcd, C: 74.02; H: 5.95 found, C: 73.92, H: 5.76

**2b:** colorless solid, 110 mg, Yield = 82%,  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 3.79 (3H, s), 5.51 (1H, s, CH), 6.79-6.86 (2H, m), 7.0-7.33 (12H, m).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 55.2, 56.1, 113.7, 126.2, 128.3, 129.4, 130.4, 136.1, 144.3, 158.1.

**2c:** colorless viscous liquid, 27 mg, Yield = 18%,  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.33 (3H, s,  $\text{CH}_3$ ), 3.79 (6H, s, 2  $\text{OCH}_3$ ), 5.43 (1H, s, CH), 6.80 (4H, d,  $J = 7.8$  Hz, CH arom.), 6.97-7.12 (8H, m, CH arom.).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 20.9, 54.6, 55.2, 113.6, 128.9, 129.2, 130.2, 135.6, 136.7, 141.6, 157.9. Anal. ( $\text{C}_{22}\text{H}_{22}\text{O}_2$ ) calcd, C: 82.99; H: 6.96 found, C: 82.72, H: 6.72.

**2d:** colorless viscous liquid, 53 mg, Yield = 36%,  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 3.78 (6H, s, 2  $\text{OCH}_3$ ), 5.45 (1H, s, CH), 6.82 (4H, d,  $J = 8.7$  Hz, CH arom.), 7.02 (4H, d,  $J = 8.7$  Hz, CH arom.), 7.08-7.28 (5H, m, CH arom.).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 48.8, 55.2, 113.7, 126.2, 128.3, 129.3, 130.3, 136.5, 144.6, 158.0. Anal. ( $\text{C}_{21}\text{H}_{20}\text{O}_2$ ) calcd, C: 82.86; H: 6.62 found, C: 82.58, H: 6.32.

**2e:** colorless solid, 80 mg, Yield = 48%,  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 3.79 (6H, s, 2  $\text{OCH}_3$ ), 5.42 (1H, s, CH), 6.82 (4H, d,  $J = 8.7$  Hz, CH arom.), 6.99

(4H, d,  $J = 8.7$  Hz, CH arom.), 7.03 (2H, d,  $J = 8.5$  Hz, CH arom.), 7.24 (2H, d,  $J = 8.5$  Hz, CH arom.).  $\delta_C$  (CDCl<sub>3</sub>) 54.5, 55.2, 113.7, 128.3, 130.2, 130.6, 131.9, 135.9, 143.2, 158.1. ESI-MS: for C<sub>21</sub>H<sub>19</sub>ClO<sub>2</sub> [M] [M+H]<sup>+</sup> = 339.1. Anal. (C<sub>21</sub>H<sub>19</sub>ClO<sub>2</sub>) calcd, C: 74.44; H: 5.65 found, C: 74.18, H: 5.38.

**2f**: colorless solid, 85 mg, Yield = 52%,  $\delta_H$  (CDCl<sub>3</sub>) 3.79 (3H, s), 5.49 (1H, s, CH), 6.84 (4H, d,  $J = 8.6$  Hz, CH arom.), 6.99 (4H, d,  $J = 8.8$  Hz, CH arom.), 7.23 (2H, d,  $J = 8.2$  Hz, CH arom.), 7.56 (2H, d,  $J = 8.2$  Hz, CH arom.).  $\delta_C$  (CDCl<sub>3</sub>) 53.3, 110.1, 114.0, 119.0, 130.1, 130.2, 132.1, 134.9, 150.3, 158.4. Anal. (C<sub>22</sub>H<sub>19</sub>NO<sub>2</sub>) calcd, C: 80.22; H: 5.81 found, C: 79.98, H: 5.65. ESI-MS: for C<sub>22</sub>H<sub>19</sub>NO<sub>2</sub> [M] [M+H]<sup>+</sup> = 330.1.

**2g**: colorless viscous oil, 102 mg, Yield = 68%,  $\delta_H$  (CDCl<sub>3</sub>) 1.24 (3H, t,  $J = 7.2$  Hz), 3.77 (3H, s), 4.22 (2H, q,  $J = 4.0$  Hz), 4.90 (1H, s), 6.84 (4H, d,  $J = 8.8$  Hz), 7.25 (4H, d,  $J = 8.8$  Hz).  $\delta_C$  (CDCl<sub>3</sub>) 14.2, 55.2, 55.5, 61.1, 113.9, 129.5, 131.3, 158.7, 173.0. Anal. (C<sub>20</sub>H<sub>18</sub>O<sub>4</sub>) calcd, C: 71.98; H: 6.71 found, C: 71.72, H: 6.62.

### Computational Details

All the calculations were performed using Gaussian09 suite of program.<sup>30</sup> Geometries of all the LA-aldehyde intermediate and transition state were optimized at B3LYP level of theory employing effective core potential (ECP) along with valence basis sets (LANL2DZ) for Lewis acidic transition or main group metal, while 6-31G\* basic set for other atoms. The formation energy of all the LA-aldehyde intermediate was done at same level of theory with zero-point energies (ZPE) and thermal corrections at 298 K. The formation energy and energy of activation in both toluene and dichloromethane (DCM) was done with the frequency calculation in single point run of the optimized gas phase geometry in solution phase using polarized continuum model (PCM)<sup>31</sup> employing toluene and dichloromethane as the solvent. The bond order of all the aldehydes and SnCl<sub>4</sub>(aldehyde)<sub>2</sub> intermediates have been carried out using the single point run on the optimized geometry of all the compounds in AOMix program at B3LYP level of theory employing effective core potential (ECP) along with valence basis sets (LANL2DZ) for Sn, while 6-31G\* basic set for other atoms.

### Conclusions

In summary; the mechanistic study on Lewis acid (LA) promoted hydroxyalkylation reaction involving aldehyde and arene/heteroarene reveals a rate determining aldehyde to secondary alcohol formation via four member cyclic transition state (TS), in which a transfer of hydrogen from arene/heteroarene C-H to aldehyde oxygen occurs with breaking of C-H bond and formation of new C-C and O-H bond. The LA promoted hydroxyalkylation reaction is suggested to be more facile in strong LA like AlCl<sub>3</sub> or SnCl<sub>4</sub> because of more

stable LA-aldehyde intermediate and lower activation barrier ( $\Delta G^\ddagger$ ) between intermediate and transition state and reactivity follows in the order AlCl<sub>3</sub> > SnCl<sub>4</sub> > InCl<sub>3</sub> > BF<sub>3</sub> > TiCl<sub>4</sub> > ZnCl<sub>2</sub> > SiCl<sub>4</sub>. Although the exergonic formation of the intermediate and its gained electrophilicity at the aldehyde center even if drives the reaction in strong LA compare to other, but overall reaction is low yielding because of their stable intermediate. With respect to different aldehyde, the reaction is found to be more feasible in electron withdrawing aldehyde compare to electron rich aldehyde because of lower stability, enhanced electrophilicity gained at the aldehyde center, and lower activation barrier between its intermediate and TS in former as compare to latter. The activation barrier ( $\Delta G^\ddagger$ ) of both AlCl<sub>3</sub> and SnCl<sub>4</sub> promoted hydroxyalkylation reaction of eight different arene/heteroarene increases in the order indole < furan < anisole < thiophene < toluene < benzene < chlorobenzene < cyanobenzene, suggest facile reaction in case of indole, while most difficult reaction in case of cyanobenzene. The formation of undesired product in AlCl<sub>3</sub>, InCl<sub>3</sub> and SnCl<sub>4</sub> promoted hydroxyalkylation reaction is found to be more viable because they have negative free energy of formation ( $\Delta G$ ) towards the generation of corresponding diaryl methyl carbocation from alcohol, which is the key of all undesired product.

### Acknowledgements

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solvents. The author thanks the esteemed reviewer for raising this point.

<sup>17</sup> The corresponding <sup>119</sup>Sn NMR shift was measured from the difference between aldehyde-PhSnCl<sub>3</sub> adduct and free PhSnCl<sub>3</sub>.

<sup>18</sup> The PhSnCl<sub>3</sub> was chosen for the study because of higher solubility of PhSnCl<sub>3</sub>-aldehyde adduct in CDCl<sub>3</sub>.

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