Enhancement of Lewis Acidity by Ligand-Defined Metal Geometry: A Catalytic Allylation of Aldehydes with Allyltrimethylsilane

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Dedicated to Professor Dieter Seebach on the occasion of his retirement.

Abstract: A highly Lewis acidic aluminum complex was produced using a tridentate ligand **1**. The enhanced Lewis acidity of **1**–Al was attributed to the combination of a stereoelectronic effect and an electrostatic effect. Comparison with an unstrained complex **4**–Al indicated that the ligand-defined sp^3 geometry of the aluminum in **1**–Al led to the lower LUMO level and the larger LUMO coefficient on the aluminum. **1**–Al promotes a catalytic allylation of aromatic aldehydes using allyltrimethylsilane. A catalytic amount of excess ligand added to the aluminum was important for high chemical yield. The excess ligand might act as a proton source to facilitate ligand exchange on the highly Lewis acidic aluminum.

Key words: Lewis acid, metal, ligand, allylation, aluminum

Lewis acid catalysis is one of the most important and powerful concepts in synthetic organic chemistry.[1] Lewis acids catalyze a broad range of important reactions such as the Mukaiyama aldol reaction, Diels–Alder reactions, and the Sakurai reaction. The current focus in this field is to further broaden the scope of Lewis acid-catalyzed reactions to less reactive (thus, more stable) substrates with minimum amounts of catalyst using highly active Lewis acids. One obvious and quite successful approach toward this goal is increasing the cationic character of the metal employing strong electron-withdrawing counterions such as triflate (OTf) or bis(trifluoromethansulfonyl)amide (NTf$_2$).[2,3] Another less well established approach is the ligand-defined preorganization of a Lewis acid metal geometry to readily accommodate substrate donor atoms, such as carbonyl-oxygen atoms. This type of ligand effect should lower the metal-centered LUMO energy, the ground state destabilization of the Lewis acid and the transition state stabilization of the substrate coordination step. All of these effects decrease the activation energy of the substrate coordination to the Lewis acid, resulting in Lewis acidity enhancement.[4] We are interested in this approach because a rational ligand design could produce a highly active Lewis acid complex that might be extended to an enantioselective catalyst. Herein we describe our preliminary results of enhanced Lewis acidity of an aluminum complex by controlling the geometry using a tridentate ligand 1 (Figure 1).

The basic ideas behind the design of ligand **1** were as follows. (1) Upon complex formation with a trivalent metal (elements from group 3 or 13), the ligand would geometrically induce an sp^3 hybridization (i.e., tetrahedral geometry) of the metal, thus preorganizing vacant orbital orientation (a stereoelectronic effect). (2) The strongly electron-withdrawing trifluoromethanesulfonyl group would increase the positive charge on the metal (an electrostatic effect). Ligand **1** was easily synthesized from commercially available triol **3** through trifluoromethanesulfonylation of the known triamine[5] (Tf_2O, Et_3N, CH_2Cl_2, –40–0 °C, 50% yield). Similarly, tosyl amide ligand **2** was synthesized through tosylation (TsCl, Et_3N, CH_2Cl_2, 4 °C, 92% yield).[6]

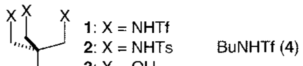

Figure 1

We targeted a catalytic allylation of aldehydes with allyltrimethylsilane (the Sakurai reaction) because a catalytic amount of conventional Lewis acids cannot promote this reaction. Using **1** as a ligand, Lewis acid metals were first screened for allylation of benzaldehyde **5a**. The aluminum complex prepared from Me_3Al and **1** in a 1:1 ratio (**1**–Al: 10 mol%) promoted the reaction smoothly at room temperature in dichloromethane and the desired product **6a** was obtained in 59% yield, together with byproduct **7a** in 5% yield (Scheme 1). Complexes with other metals [$B(OMe)_3$, Ga(*i*-PrO)$_3$, In(*i*-PrO)$_3$, La(*i*-PrO)$_3$, Ti(*i*-PrO)$_4$, and Zr(*t*-BuO)$_4$] did not give any product even after a prolonged reaction time. Aluminum complexes containing less electron-withdrawing ligands (**2** and **3**) than **1** did not promote the reaction at all. More importantly, no reaction proceeded with a catalyst prepared from Me_3Al and **4** in a 1:3 ratio (**4**–Al). This sharp contrast in catalyst activity between **1**–Al and **4**–Al must be due to the ligand-defined geometry of the aluminum, as these complexes should contain a similar positive charge on the aluminum. Molecular modeling studies support this as they show that the aluminum geometry is completely different in these two complexes (Figure 2).[7] The most stable conformation of **1**–Al contains a pyramidized sp^3 hybridized aluminum with a large LUMO, predominantly on the aluminum.

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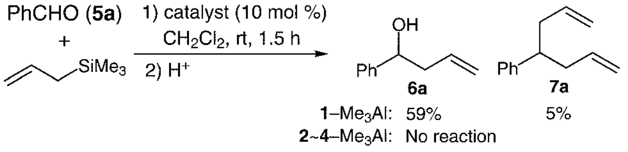
However, **4**–Al contains a planar sp^2 hybridized aluminum. In this case, although the largest LUMO coefficient exists in the p-orbital of the aluminum, the LUMO coefficient was reduced due to a partial orbital diffusion to another part of the molecule. Therefore, in the case of **1**–Al, the ligand-defined geometry of the aluminum should produce a lower LUMO level (sp^3 *vs.* p-orbital) and a larger LUMO coefficient than **4**–Al (Figure 2). This stereoelectronic effect is the key for enhancement of the Lewis acidity and the catalyst activity in the case of **1**–Al.



Scheme 1

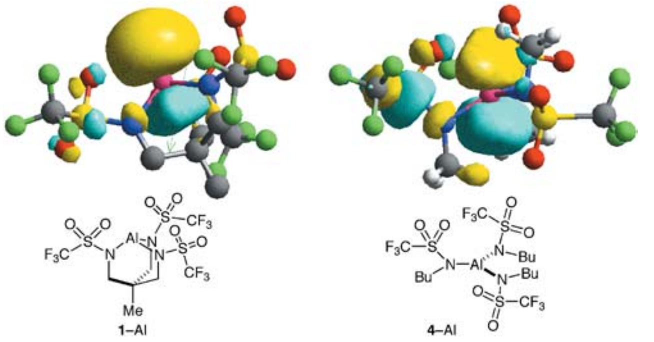


Figure 2 LUMO of Al-complexes in the most stable conformations.

Once preliminary experimental support for the concept was obtained, we began optimization of the reaction conditions using **1**–Al as catalyst. The major byproduct **7a** was produced through a benzylic cation formation from the initial product, by the Lewis acid, and subsequent allylation. To prevent this over-reaction, we performed the reaction at a lower temperature. Thus, the yield of **6a** was improved to 73% at 4 °C with very little formation of **7a**. The yield was further improved to 81% when the amount of catalyst was reduced to 5 mol%.[8] Solvents other than dichloromethane gave less satisfactory results.[9]

During the optimization, the reaction was sometimes unpredictable and in some cases the chemical yield decreased to ca. 50%. Careful investigation revealed that the ligand/Al ratio was very important for a clean conversion (Figure 3). When the ligand/Al ratio was less than 1, many byproducts were produced and the desired **6a** was obtained in only ca. 50% yield. The yield increased as the ligand/Al ratio increased and up to an 84% yield was obtained when ligand/Al = 1:1.1.

The substrate scope was investigated using the optimized reaction conditions and the results are summarized in the Table. Moderate to high chemical yields were obtained from aromatic aldehydes.[10] Previous studies[11] suggested that the excess ligand would work as a proton source to facilitate the dissociation of the product from the highly Lewis acidic aluminum center and the catalyst regeneration. Based on this assumption, a working model of the catalytic cycle was proposed (Scheme 2). After the allyl transfer to the activated aldehyde, the aluminum might exist as an ate-complex **8**, which is inactive as a Lewis acid catalyst. The excess amount of the ligand might protonate the alkoxide and cleave the Al–O bond to regenerate the active catalyst **1**–Al. In the absence of the excess ligand, the lifetime of a highly Lewis acidic silicon of **8** might become long enough to promote side-reactions.[12] Silicon exchange between the resulting **9** and alcohol **6** would give the silylated product **10** and regenerate the proton source **1**.

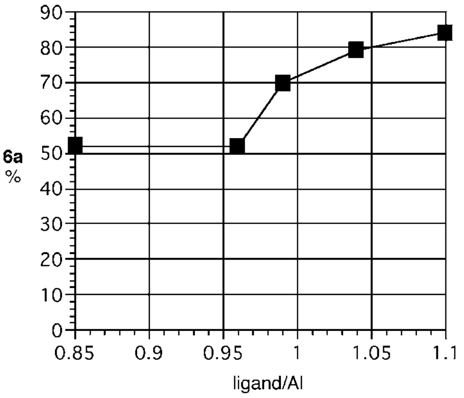
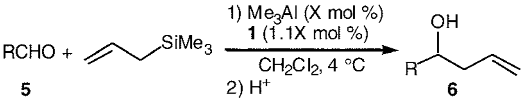
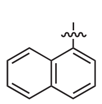
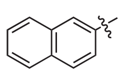


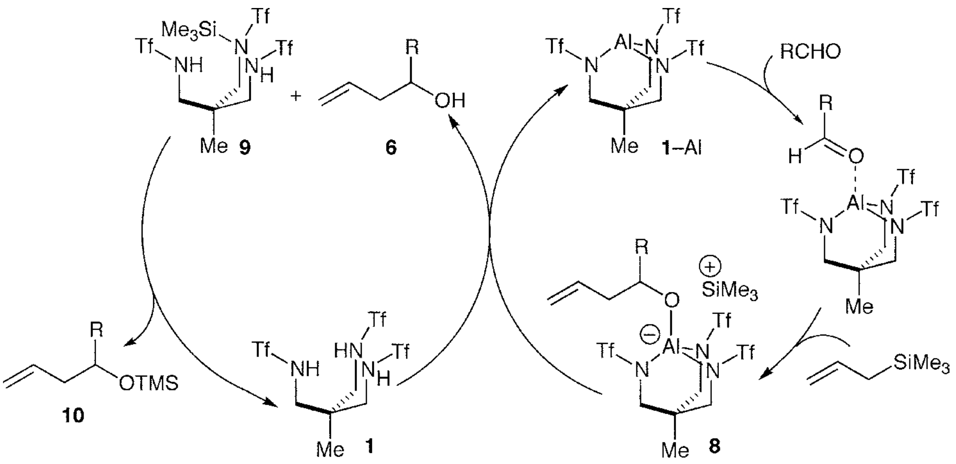
Figure 3 Relationship between yield and ligand/Al ratio.

Table 1 Catalytic Allylation of aldehydes Using Allyltrimethylsilane



Entry	R (aldehyde)		Cat. (X mol%)	Time (h)	Yield (%)
1	C_6H_5	**5a**	5	4	84
2	4-$O_2NC_6H_4$	**5b**	5	4	81
3	4-BrC_6H_4	**5c**	5	4	86
4		**5d**	10	4	75
5		**5e**	10	4	63

In summary, we developed aluminum complex **1**–Al with an enhanced Lewis acidity. The higher activity of **1**–Al was due to the combination of a stereoelectronic effect and an electrostatic effect enhanced by the ligand-defined geometry of the aluminum. **1**–Al can promote catalytic allylation of aromatic aldehydes using allyltrimethylsilane. Further efforts to extend the scope of this type of catalyst



Scheme 2

and to develop an asymmetric catalyst based on this concept are currently ongoing.

Typical Procedure (Table 1, Entry 1)

A hexane solution of Me_3Al (49 μL, 0.05 mmol) was added to a suspension of **1** (28 mg, 0.055 mmol) in CH_2Cl_2 at r.t. and the resulting solution was stirred for 1 h. After the solution was cooled to –20 °C, **5a** (102 μL, 1 mmol) and allyltrimethylsilane (238 μL, 1.5 mmol) were added and the reaction temperature was maintained at –20 °C for 30 min. The reaction temperature was gradually raised to 4 °C and after 4 h, 2 M HCl aq in MeOH (1:1) was added for desilylation. The standard aqueous work-up and purification by silica gel column chromatography (EtOAc–hexane, 1:19) gave **6a** in 84% yield.

Selected spectral data of ligand 1

^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.05$ (s, 3 H), 3.17 (d, $J = 7.0$ Hz, 6 H), 5.61 (t, $J = 7.0$ Hz, 3 H)

^{13}C NMR (DMSO-d_6, 126 MHz): $\delta = 15.89$, 38.4, 46.32, 118.5 (q, $J = 33$ Hz)

^{19}F NMR [$CDCl_3$, 470 MHz, CF_3CO_2H used as the external standard (= 0 ppm)]: $\delta = -76.9$.

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(8) The chemical yield decreased when catalyst loading of less than 5 mol% was used, <50% with 2 mol% and no reaction with 1 mol%.

(9) Trifluorotoluene ($CF_3C_6H_5$), toluene, and acetonitrile gave the product in 10%, 50%, and 0% yield, respectively.

(10) Unfortunately, the desired allylation did not proceed from aliphatic aldehydes or α, β-unsaturated aldehydes. Cyclic trioxanes were the major products from primary and secondary alkyl substituted aldehydes. No reaction occurred from pivalaldehyde and α, β-unsaturated aldehydes.

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