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Aluminum chloride: A highly efficient catalyst for addition of amines to carbodiimides to synthesize substituted guanidines

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A catalytic addition of amine N–H bonds to carbodiimides using aluminum chloride as a Lewis acid catalyst is developed. The reaction proceeds under mild conditions without solvent to afford a series of substituted guanidines in good to excellent yields using a wide range of amines as substrates. Evidence of the proposed mechanism is provided by *in situ* infrared spectroscopy.

aluminum chloride, catalysis, guanidine

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Guanidines can serve as building blocks for many biologically relevant compounds [1] and are also useful as catalysts in organic synthesis [2–7]. Among the reported routes to multisubstituted guanidines, addition of amines to carbodiimides is undoubtedly the most straightforward and atom-economical one. However, harsh reaction conditions are necessary for the reaction to progress in the absence of catalyst [8]. Some highly active catalysts for this reaction have been developed in recent years, and several organometallic complexes have been found to be effective for this transformation [9–18]. Titanium and vanadium imido complexes are reported to be efficient precatalysts for the addition of primary aromatic amines to carbodiimides to afford the corresponding guanidines. However, secondary amines could not be applied in these reactions because a metal-imido complex is the active species in the catalytic process [9,10]. For the addition of secondary amines to carbodiimides, lithium silylamide [11], lanthanide amides [12,13], carboranyl-alkoxy-ligated titanium amido complexes [14], half-sandwich lanthanide metal alkyl complexes [15–17], and $ZnEt_2$, $MgBu_2$, *n*-BuLi [18], and $Zn(OTf)_2$ [19] have been found to be highly active catalysts. Recently, it was also shown that alkyl aluminum exhibits high activity for the catalytic addition of amines to carbodiimides [20]. In these catalytic processes, an amine reacts with an organometallic catalyst to form a metal amido species, which quickly attacks the central carbon of a carbodiimide. More recently, the Lewis acid $Yb(OTf)_3$ was reported by our group to serve as another efficient catalyst for the addition of both primary and secondary amines to carbodiimides [21]. In this case, $Yb(OTf)_3$ may behave as an electrophile to generate an adduct with carbodiimide, and subsequent nucleophilic addition of an amine to the adduct leads to the formation of a guanidine. As part of our continued work in this field, $AlCl_3$, a cheap and readily available Lewis acid, was investigated as a catalyst for the addition of amines to carbodiimides. Herein we report our results using $AlCl_3$ as a catalyst.

It is known that *N*,*N*′-diisopropylcarbodiimide (^{i}PrN=C=N^{i}Pr) does not react with aniline at 60°C in the absence of catalyst (Table 1, entry 1). However, addition of 0.5 mol% of $AlCl_3$ led to efficient guanylation and the corresponding *N*,*N*′,*N*″-trisubstituted guanidine **1** was obtained in 97% yield at room temperature after just 5 min under solvent-

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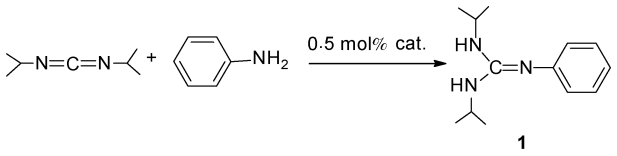
free conditions (entry 2). Several metal chlorides were then tested to assess the influence of the central metal ion on catalytic activity. As shown in Table 1, inferior results compared to those for $AlCl_3$ were obtained when the Lewis acids $FeCl_3$, $SnCl_2$, $ZnCl_2$ and $YbCl_3$ were used.

To examine the scope and generality of guanylation catalyzed by $AlCl_3$, the process was extended to various aromatic amines and carbodiimides. As summarized in Table 2, the method was effective for a wide range of substrates and the corresponding guanidines were obtained in excellent yields. The reaction was general for aromatic amines bearing substitutions at *ortho*- and *para*-positions, and tolerated both electron deficient and electron rich amines. It is noteworthy that the reaction involving *m*-aminophenylacetylene progressed smoothly to form the corresponding guanidine while the terminal alkyne unit remained unchanged. *o*-Aminopyridine was less active than aniline, which may be attributed to the competitive coordination of the pyridyl group with the aluminum cation. In the case of 2,6-diisopropylaniline, the reaction afforded the corresponding guanidine in relatively low yield even with prolonged time, raised reaction temperature and 2 mol% $AlCl_3$, indicating an obvious steric effect.

$AlCl_3$ can also be used to catalyze the guanylation of ^{i}PrN=C=N^{i}Pr with a primary aliphatic amine such as *n*-$BuNH_2$ to afford the corresponding *N*,*N*′,*N*″-trisubstituted guanidine in good yield (Table 3, entry 1). Secondary amines are generally less reactive than primary amines toward carbodiimides. However, the reactions involving a series of cyclic secondary amines proceeded smoothly at 60°C in the presence of 2 mol% $AlCl_3$ to produce the corresponding *N*,*N*′,*N*″,*N*″-tetrasubstituted guanidines in good to excellent yields. This indicates that the activity of secondary amines can compete with that of primary amines under the present catalytic conditions. In addition, the reaction

Table 1 Catalyst screening for the addition of aniline to ^{i}PrN=C=N^{i}Pr[a)]

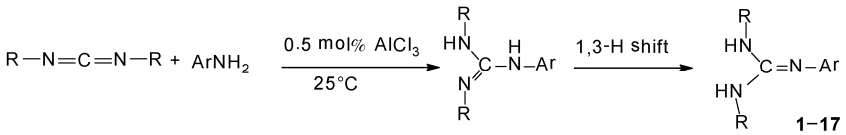


1

Entry	Catalyst	*T* (°C)	Time	Yield (%)
1	–	60	5 min	n.r.
2	$AlCl_3$	25	5 min	97
3	$FeCl_3$	25	1.5 h	21
4	$SnCl_2$	25	1.5 h	35
5	$ZnCl_2$	25	1.5 h	Trace
6	$YbCl_3$	25	1.5 h	20

a) The reaction was performed by treating 1 equiv. of aniline with 1 equiv. of ^{i}PrN=C=N^{i}Pr.

Table 2 $AlCl_3$-catalyzed addition of primary aromatic amines to carbodiimides[a)]

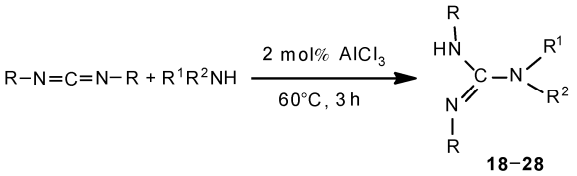


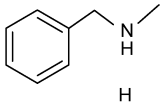
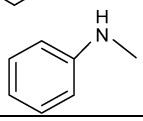
1–17

Entry	R	Ar	Time	Product	Yield (%)[b)]
1	*i*-Pr	Ph	5 min	**1**	97
2		*p*-F-C_6H_4	5 min	**2**	96
3		*p*-Cl-C_6H_4	10 min	**3**	95
4		*o*-Cl-C_6H_4	2 min	**4**	97
5		*p*-Me-C_6H_4	5 min	**5**	93
6		*p*-MeO-C_6H_4	2 min	**6**	96
7		*o*-Me-C_6H_4	5 min	**7**	95
8		*α*-naphthyl	10 min	**8**	93
9		*p*-NO_2-C_6H_4	30 min	**9**	96[c)]
10		*m*-acetylenylphenyl	2 h	**10**	94[d)]
11		*o*-pyridyl	2 h	**11**	93[d)]
12		2,6-*i*-Pr_2-C_6H_3	28 h	**12**	66[e)]
13	Cy	Ph	30 min	**13**	96
14		*p*-F-C_6H_4	30 min	**14**	96
15		*o*-Cl-C_6H_4	30 min	**15**	96
16		*p*-MeO-C_6H_4	30 min	**16**	93
17		*o*-Me-C_6H_4	30 min	**17**	94

a) The reaction was performed by treating 1 equiv. of amine with 1 equiv. of carbodiimide; b) isolated yield; c) 2 mol% of catalyst at 60°C; d) 2 mol% of catalyst; e) 2 mol% of catalyst at 80°C.

Table 3 $AlCl_3$-catalyzed addition of aliphatic amines to carbodiimides[a)]



Entry	R	R^1R^2NH	Product	Yield (%)[b)]
1	*i*-Pr	*n*-$BuNH_2$	**18**	72(86[c)])
2	*i*-Pr		**19**	90
3	Cy		**20**	92
4	*i*-Pr		**21**	85
5	Cy		**22**	87
6	*i*-Pr		**23**	94
7	Cy		**24**	96
8	*i*-Pr		**25**	82
9	Cy		**26**	84
10	*i*-Pr		**27**	93[c)]
11	*i*-Pr		**28**	96[d)]

a) The reaction was performed by treating 1 equiv. of amine with 1 equiv. of carbodiimides at 60°C for 3 h; b) isolated yields; c) 80°C; d) 60°C for 12 h.

of ^{i}PrN=C=N^{i}Pr with *N*-methylpiperazine, a linear secondary amine, afforded the desired product in 93% yield at 80°C (Table 3, entry 10), revealing the activity of $AlCl_3$ is higher than that of $Yb(OTf)_3$.

To gain more information about the mechanism of the present $AlCl_3$-catalyzed guanylation, the reaction of aniline with ^{i}PrN=C=N^{i}Pr in chloroform was monitored by *in situ* infrared (IR) spectroscopy. The spectra and a plot of absorbance *versus* time are shown in Figure 1. The intensity of the band at 2119 cm^{-1}, assigned to carbodiimide (N=C=N), decreased rapidly when $AlCl_3$ was added to the solution of ^{i}PrN=C=N^{i}Pr in chloroform. At the same time, a peak appeared at 2204 cm^{-1}, suggesting the formation of a carbon-nitrogen triple bond (C≡N). When aniline was added, the peak at 2204 cm^{-1} disappeared immediately. The change of absorbance over time indicated that both the formation of an $AlCl_3$-carbodiimide complex and the attack of this complex by aniline are quick.

Based on the analysis of *in situ* IR spectra and previous work [20,22], a possible mechanism for $AlCl_3$-catalyzed guanylation of amine with carbodiimide was proposed, as shown in Scheme 1. $AlCl_3$ may behave as an electron-deficient species and react with a carbodiimide to yield intermediate **A**. Nucleophilic addition of an amine to **A** affords **B**. Intramolecular proton transfer of **B** readily releases the target guanidine and regenerates $AlCl_3$.

In summary, we have demonstrated that the guanylation

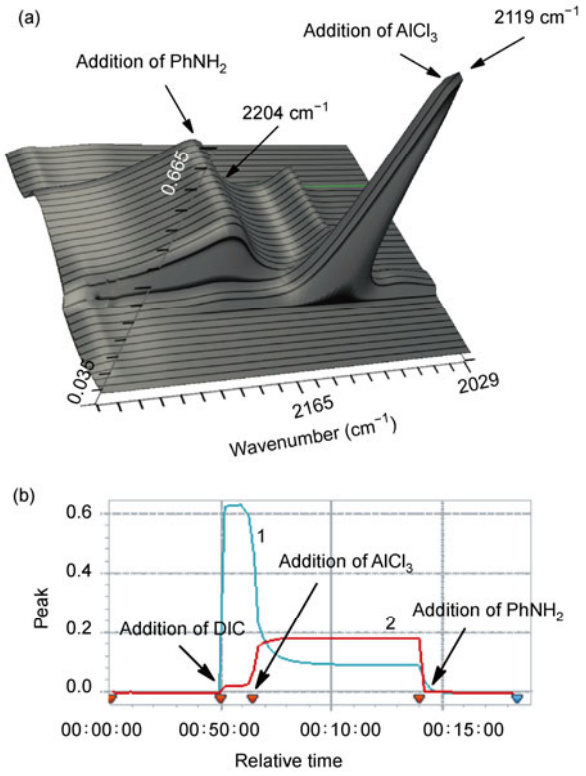
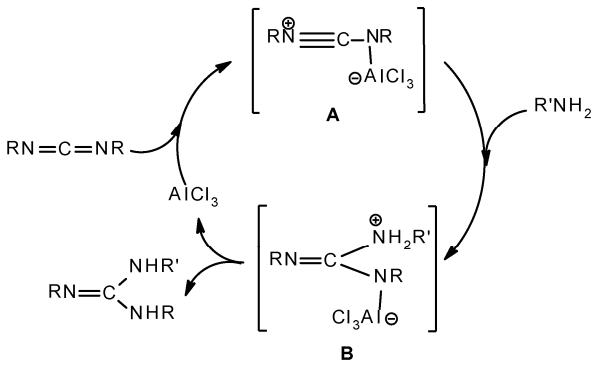


Figure 1 (Color online) (a) Three-dimensional plots of IR spectra collected every 15 s for the reaction of aniline with ^{i}PrN=C=N^{i}Pr in chloroform. (b) Intensities of the bands at 2119 (curve 1) and 2204 cm^{-1} (curve 2) upon sequential addition of ^{i}PrN=C=N^{i}Pr, $AlCl_3$ and aniline to the reaction system.



Scheme 1 Proposed mechanism for $AlCl_3$-catalyzed addition of an amine to a carbodiimide.

of amines with carbodiimides can be effectively achieved under mild reaction conditions using catalytic amount of $AlCl_3$, a simple and readily available reagent, allowing guanidines to be prepared efficiently in high to excellent yields. The system is applicable to a wide range of substrates including primary and secondary cyclic amines. *In situ* IR spectra provided some evidence for the proposed mechanism. A detailed study of the reaction mechanism is in progress in our laboratory.

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