

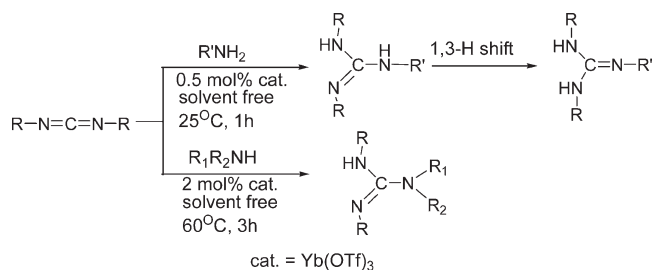
## Ytterbium Triflate: A Highly Active Catalyst for Addition of Amines to Carbodiimides to $N,N',N''$ -Trisubstituted Guanidines

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Ytterbium triflate was found to be efficient catalyst for addition of amines to carbodiimides to  $N,N',N''$ -trisubstituted guanidines with a wide scope of amines under solvent-free condition.

Guanidines can be used not only as base catalysts in organic synthesis,<sup>1</sup> but also as ancillary ligands in a variety

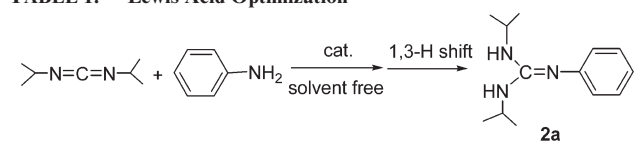
of complexes of main, transition, and lanthanide metals.<sup>2</sup> Moreover, the guanidines groups are the structural units in many biologically relevant compounds.<sup>3</sup> As a result, the synthesis of guanidines has attracted much attention in organic synthesis. Various methods have been explored for the synthesis of guanidines,<sup>4–9</sup> among them, addition of amines to carbodiimides provides a convenient and atom-economic approach. However, addition of amines to carbodiimides without a catalyst requires harsh conditions.<sup>9</sup> So, development of an efficient catalyst for this transformation under mild conditions has become one of the active areas both in organic chemistry and organometallic chemistry of main,<sup>10</sup> transition,<sup>11</sup> and lanthanide<sup>12</sup> metals.

Various lanthanide complexes have recently been found to be efficient catalysts. Hou's group reported the catalytic addition of various primary and secondary amines to carbodiimides by half-sandwich lanthanide alkyl complexes, especially the yttrium complex yielding a series of guanidine derivatives.<sup>12a</sup> Wang's group described the guanylation of both aromatic and secondary amines with carbodiimides catalyzed by simple lanthanide amides<sup>12b</sup> and by [ethylenebis(indenyl)]lanthanide amides, respectively.<sup>12c</sup> Very recently we reported the catalytic addition of amines to carbodiimides by divalent lanthanide complexes.<sup>13</sup> It is worth noting that all of these catalytic systems need to use the lanthanide complexes which are very sensitive to air and moisture. Exploring another class of lanthanide catalysts, which are stable, easy to handle, and readily prepared, is still in demand.

Although lanthanide triflates, as a novel class of Lewis acid, have been widely used in carbon–carbon and

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TABLE 1. Lewis Acid Optimization<sup>a</sup>

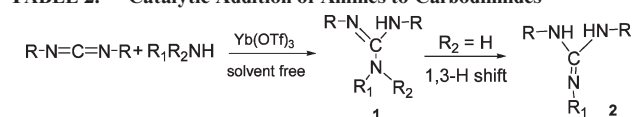
entry	catalyst	catalyst loading (mol %)	temp (°C)	time	yield (%)
1	Yb(OTf) <sub>3</sub>	0.5	60	5 min	90
2	Yb(OTf) <sub>3</sub>	0.5	25	1 h	97
3	Yb(OTf) <sub>3</sub>	0.2	25	4 h	80
4	La(OTf) <sub>3</sub>	0.5	60	2.5 h	trace
5	La(OTf) <sub>3</sub>	0.5	60	24 h	30
6	Nd(OTf) <sub>3</sub>	0.5	60	2.5 h	24
7	Sm(OTf) <sub>3</sub>	0.5	60	2.5 h	76
8	Eu(OTf) <sub>3</sub>	0.5	60	50 min	84
9	Er(OTf) <sub>3</sub>	0.5	60	12 min	86
10			60	5 min	n.r.

<sup>a</sup>The reaction was performed by treating 1 equiv of amines with 1 equiv of carbodiimides.

carbon–heteroatom bond formation,<sup>14</sup> further exploring their application in organic synthesis has still attracted increasing attention, as they are water-tolerant, reusable, and environmentally friendly catalysts. Here we wish to report the addition of amines to carbodiimides catalyzed by Yb(OTf)<sub>3</sub> and the possible mechanism.

The reaction of aniline PhNH<sub>2</sub> with *N,N'*-diisopropylcarbodiimide *i*Pr<sub>2</sub>N=C=N*i*Pr<sub>2</sub> was first tried with Yb(OTf)<sub>3</sub> as a catalyst. The reaction went smoothly at 60 °C even with 0.5% mol of Yb(OTf)<sub>3</sub> under solvent-free condition to afford the *N,N,N'*-trisubstituted guanidine **2a** via 1,3-H shift in 90% yield after 5 min (Table 1 entry 1). However, the same reaction without a catalyst does not occur (Table 1 entry 10). The positive results suggest that Ln(OTf)<sub>3</sub> may serve as the catalyst. Therefore, we examined several lanthanide complexes for this reaction to further assess the effect of lanthanide metals on activity. It was found that the metals have great influence on the activity and the active sequence is La < Nd < Sm < Eu < Er < Yb (Table 1, entries 1 and 4–9), which is consistent with the trend in a decreasing of Ln<sup>3+</sup> ionic radius. The highest activity for the Yb metal may be attributed to the strongest Lewis acidity of the Yb metal among these metals. The reaction can also be carried out at room temperature and the product **2a** in 97% yield was obtained after 1 h (Table 1, entry 2).

With the optimized conditions (Table 1, entry 2) we first examined the reactions of various primary aromatic amines with carbodiimides to explore the generality and scope of Yb(OTf)<sub>3</sub>-catalyzed addition of amines to carbodiimides. As shown in Table 2, Yb(OTf)<sub>3</sub> is a very robust and efficient catalyst, which is compatible with a wide range of substituents at the phenyl ring, regardless of the electron-withdrawing or electron-donating groups. In most cases the reactions with

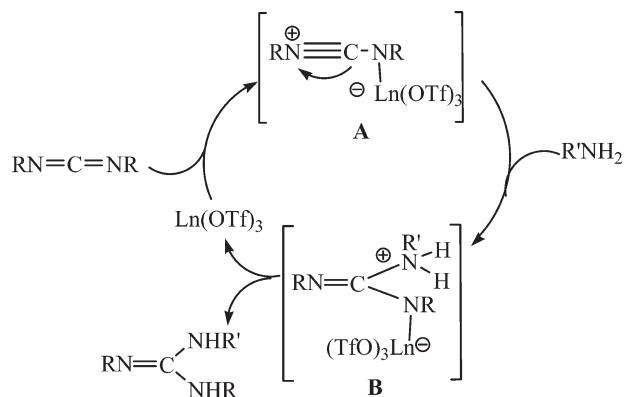
TABLE 2. Catalytic Addition of Amines to Carbodiimides<sup>a</sup>

entry	R	R <sub>1</sub> R <sub>2</sub> NH	product	yield (%) <sup>b</sup>
1	Cy		<b>2b</b>	98 <sup>c</sup>
2	<i>i</i> -Pr		<b>2c</b>	95 <sup>c</sup>
3	Cy		<b>2d</b>	95 <sup>c</sup>
4	<i>i</i> -Pr		<b>2e</b>	93 <sup>c</sup>
5	Cy		<b>2f</b>	94 <sup>c</sup>
6	<i>i</i> -Pr		<b>2g</b>	91 <sup>c</sup>
7	Cy		<b>2h</b>	94 <sup>c</sup>
8	<i>i</i> -Pr		<b>2i</b>	90 <sup>c</sup>
9	Cy		<b>2j</b>	91 <sup>c</sup>
10	<i>i</i> -Pr		<b>2k</b>	97 <sup>c</sup>
11	Cy		<b>2l</b>	94 <sup>c</sup>
12	<i>i</i> -Pr		<b>2m</b>	95 <sup>c</sup>
13	<i>i</i> -Pr		<b>2n</b>	95 <sup>c</sup>
14	<i>i</i> -Pr		<b>2o</b>	92 <sup>c</sup>
15	<i>i</i> -Pr		<b>2p</b>	52 <sup>d</sup>
16	<i>i</i> -Pr	<i>n</i> -BuNH <sub>2</sub>	<b>2q</b>	79 <sup>e</sup>
17	<i>i</i> -Pr		<b>1a</b>	91 <sup>e</sup>
18	Cy		<b>1b</b>	92 <sup>e</sup>
19	<i>i</i> -Pr		<b>1c</b>	88 <sup>e</sup>
20	Cy		<b>1d</b>	85 <sup>e</sup>
21	<i>i</i> -Pr		<b>1e</b>	94 <sup>e</sup>
22	Cy		<b>1f</b>	95 <sup>e</sup>
23	<i>i</i> -Pr		<b>1g</b>	85 <sup>e</sup>
24	Cy		<b>1h</b>	83 <sup>e</sup>
25	<i>i</i> -Pr		<b>1i</b>	76 <sup>f</sup>

<sup>a</sup>The reaction was performed by treating 1 equiv of amines with 1 equiv of carbodiimides. <sup>b</sup>Isolated yields. <sup>c</sup>0.5 mol % of cat., 25 °C, for 1 h. <sup>d</sup>1 mol % of cat., 80 °C, for 24 h. <sup>e</sup>2 mol % of cat., 60 °C, for 3 h. <sup>f</sup>2 mol % of cat. 80 °C, for 3 h.

primary aromatic amines completed at room temperature within 1 h to give the corresponding *N,N,N'*-trisubstituted guanidines in excellent yields (Table 2, entries 1–14).

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**SCHEME 1. Proposed Mechanism for Addition of Amines to Carbodiimides**

The catalyst system showed good functional group tolerance. For example, the groups of F and Cl at the phenyl ring remained unchanged during the reactions (Table 2, entries 2 and 3, and 10, 11, and 13). However, the reaction with a steric bulky amine, diisopropylaniline, went slowly and gave the guanidine in 52% yield, even with 1 mol % of catalyst at 80 °C (entry 15).

The present catalyst can also catalyze the addition of a primary aliphatic amine, such as *n*-BuNH<sub>2</sub>, to a diisopropylcarbodiimide, even the present catalyst is less active than divalent lanthanide amides reported.<sup>13a</sup> As shown in Table 2, the reaction afforded the corresponding *N,N',N''*-trisubstituted guanidine in 79% yield (entry 16).

Secondary cyclic amines are well-known to be less reactive than primary amines toward carbodiimides. Thus, the reactions with several cyclic secondary and acyclic secondary amines were then conducted. In the presence of 2 mol % of Yb(OTf)<sub>3</sub> various cyclic amines could react with diisopropylcarbodiimide and dicyclohexylcarbodiimide at 60 °C affording the guanidines in good to excellent yields (Table 2, entries 17–24). Although 1-methylpiperazine is less active, the reactions with it can still afford the desired products in over 80% yields (Table 2, entries 23 and 24).

The present reactions are scalable. For example, the reaction of 102 mmol of diisopropylcarbodiimide with 1 equiv of aniline afforded **2a** in 98% yield at room temperature after 30 min (Supporting Information).

A possible mechanism for Yb(OTf)<sub>3</sub>-catalyzed addition of amines to carbodiimides is proposed in Scheme 1. Yb(OTf)<sub>3</sub> should react first with a carbodiimide as a Lewis acid catalyst

to generate an intermediate **A**. Nucleophilic addition of an amine to **A** would afford **B**. Intramolecular proton transfer of **B** readily led to regenerate Yb(OTf)<sub>3</sub> and release the guanidine.

In conclusion, Yb(OTf)<sub>3</sub> has been found to be an efficient catalyst for addition of amines to carbodiimides to *N,N',N''*-trisubstituted guanidines in good to excellent yields under solvent-free condition. The system shows a wide range of scope of substrate including primary aromatic amines and secondary cyclic amines. Detailed study on the reaction mechanism is going on in our laboratory.

## Experimental Section

**General Procedure 1: For the Direct Synthesis of Guanidines from Reaction of Aromatic Amines with Carbodiimides Catalyzed by Yb(OTf)<sub>3</sub> (product **2a** as an example).** A 10 mL Schlenk tube under dried argon was charged with Yb(OTf)<sub>3</sub> (0.0035 g, 0.0056 mmol). To the flask were added the *N,N'*-diisopropylcarbodiimide (0.18 mL, 1.13 mmol) and aniline (0.10 mL, 1.13 mmol). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then hydrolyzed with water (0.5 mL), extracted with dichloromethane (3 × 10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and filtered. After the solvent was removed under reduced pressure, the residue was recrystallized in hexane to provide a white solid **2a** (97% yield).

**General Procedure 2: For the Direct Synthesis of Guanidines from Reaction of Secondary Amines with Carbodiimides Catalyzed by Yb(OTf)<sub>3</sub> (product **1a** as an example).** A 10 mL Schlenk tube under dried argon was charged with Yb(OTf)<sub>3</sub> (0.0217 g, 0.035 mmol). To the flask were added the *N,N'*-diisopropylcarbodiimide (0.27 mL, 1.74 mmol) and pyrrolidine (0.15 mL, 1.74 mmol). The resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was then hydrolyzed with water (0.5 mL), extracted with hot hexane (3 × 10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and filtered. After the solvent was removed under vacuum, the final product **1a** was obtained as a white powder in 91% yield.

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**Supporting Information Available:** Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.