

# Ti-amide Catalyzed Synthesis of Cyclic Guanidines from Di-/Triamines and Carbodiimides

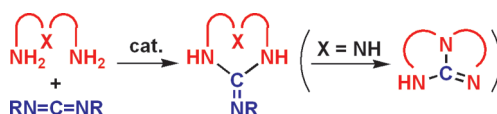
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## ABSTRACT



A titanacarborane monoamide catalyzed, one-step synthesis of mono/bicyclic guanidines from commercially available di/triamines and carbodiimides is reported. The reaction mechanism is also proposed.

A growing number of biologically and pharmaceutically relevant compounds incorporate the cyclic guanidine functionality.<sup>1</sup> Cyclic guanidines are also capable of

catalyzing organic reactions<sup>2</sup> and exhibiting a variety of coordination modes and a range of donor properties leading to compatibility with a wide range of metal ions.<sup>3</sup> Therefore, their synthesis has been extensively explored. Generally, the known methods include (1) the reactions<sup>4</sup> of

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amines with *S,S*-dimethyl-*N*-tosyliminodithiocarbonimides,<sup>4a</sup> dimethyl cyanoimido-dithiocarbonates,<sup>4b</sup> isothiocyanates,<sup>4c–e</sup> or carbon disulfide;<sup>4f</sup> (2) cyclization of guanidino-alkynes;<sup>5</sup> (3) intramolecular alkylation of guanidines;<sup>6</sup> (4) reactions of unsaturated molecules with azridines,<sup>7</sup> and so forth.<sup>8</sup> Very recently, oxidative amination and radical cascade cyclization methods were also successfully applied to the synthesis of cyclic guanidines.<sup>9</sup> However, most of these routes require multistep operations or functionalization of precursors. Herein, we report a novel and direct method for the catalytic synthesis of cyclic guanidines from commercially available di/triamines and carbodiimides in one step.

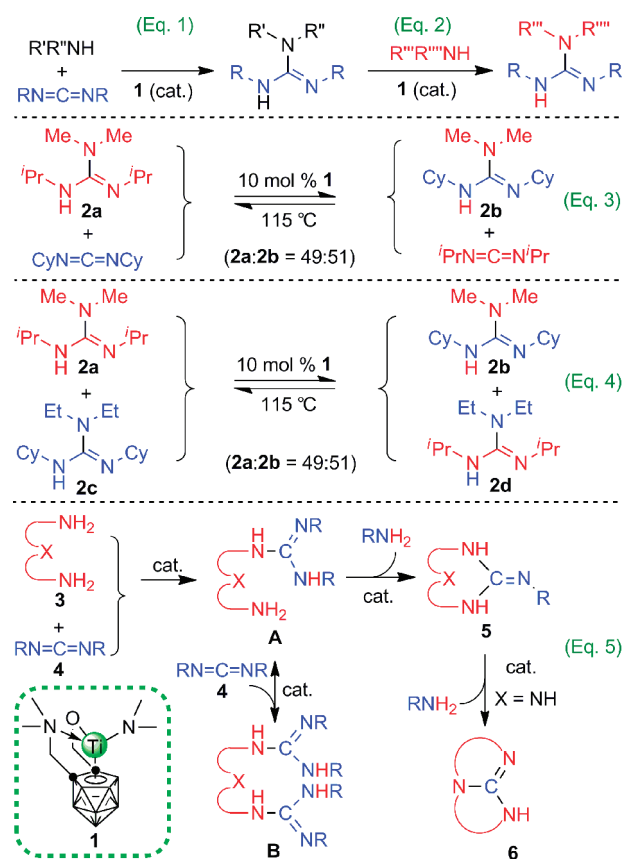
Recently, we reported a highly reactive titanacarborane monoamide [ $\sigma\eta^1\eta^5$ -(OCH<sub>2</sub>)(Me<sub>2</sub>NCH<sub>2</sub>)C<sub>2</sub>B<sub>9</sub>H<sub>9</sub>]*Ti*-(NMe<sub>2</sub>) (**1**),<sup>10</sup> which can be viewed as an isoelectronic/isostrucutral analogue of constrained-geometry lanthanide amide or a cationic group 4 metal amide.<sup>11</sup> This complex efficiently catalyzes the cascade hydroamination of cyanoalkynes to give isoindoles and isoquinolines,<sup>12</sup> the sequential C–N bond-forming reaction of propargylamines with nitriles to yield imidazoles,<sup>12</sup> and the [3 + 2] annulation of propargylamines with carbodiimides to produce 2-amino-imidazoles.<sup>5d</sup>

In addition, complex **1** acts as an elegant catalyst in the hydroamination of carbodiimides (Scheme 1, eq 1),<sup>13</sup> and it also shows a very high catalytic activity toward the transamination reaction of guanidines (Scheme 1, eq 2).<sup>14</sup>

These results and the group 4 metallocarborane mediated C–N bond cleavage of guanidines<sup>15</sup> promote us to further explore the catalytic metathesis of guanidines with carbodiimides and that of two guanidines. After a C<sub>6</sub>D<sub>6</sub> solution of guanidine **2a** (0.1 mmol), DCC (0.1 mmol), and **1** (0.01 mmol, 10 mol %) was heated at 115 °C for 24 h, the <sup>1</sup>H NMR indicated that an equilibrium between **2a** and **2b** (in a molar ratio of 49:51) was reached (Scheme 1, eq 3). Similarly, the NMR reaction of **2a** with **2c** in the presence of 10 mol % of **1** at 115 °C for 24 h resulted in another equilibrium of **2a:2b** (49:51) (Scheme 1, eq 4). In marked contrast, no metathesis reaction was observed in the absence of catalyst **1**.

On the basis of the prevalence of olefin ring-closing metathesis (RCM) and the fact that **1** catalyzes both the hydroamination of carbodiimides (Scheme 1, eq 1) and the intermolecular metathesis of guanidines with amines/carbodiimides/guanidines (Scheme 1, eq 2/3/4), we envisaged

**Scheme 1.** Construction and Reconstruction of Guanidines Catalyzed by **1**



that a reaction of di/triamines with carbodiimides in the presence of **1** would serve as a new approach for the synthesis of cyclic guanidines (Scheme 1, eq 5), via the

**Table 1.** Effects of Metal Complexes in Reaction of **3a** with **4a**<sup>a</sup>

entry	catalyst	loading (mol %)	temp (°C)	time (h)	yield (%)
1	none	0	110	196	<10
2	<b>1</b>	5	110	196	60
3	<b>1</b>	10	110	196	>95
4	<b>1</b>	5	140	32	63
5	<b>1</b>	10	140	32	>95
6	Ti(NMe <sub>2</sub> ) <sub>4</sub>	10	110	196	70
7	Zr(NMe <sub>2</sub> ) <sub>4</sub>	10	110	196	20
8	Hf(NMe <sub>2</sub> ) <sub>4</sub>	10	110	196	18
9	Cp <sub>2</sub> TiMe <sub>2</sub>	10	110	196	<10
10	Cp <sub>2</sub> ZrMe <sub>2</sub>	10	110	196	<10
11	Cp <sub>2</sub> HfMe <sub>2</sub>	10	110	196	<10

<sup>a</sup> NMR yield using ferrocene as the internal standard.

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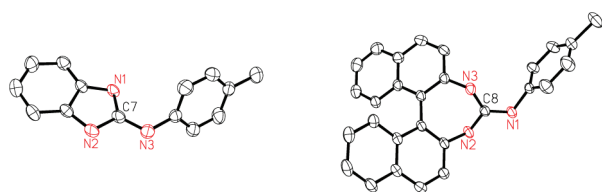
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intermolecular hydroamination (**3+4** to **A**) and the intramolecular metathesis (**A/B** to **5**, **5** to **6**).

The model reaction of *o*-phenylenediamine (**3a**) with diisopropylcarbodiimide (**4a**) was initially examined (Table 1) in the presence of a catalytic amount of **1** or commercially available complexes or commonly used catalysts.<sup>16</sup> In the absence of a catalyst, no expected product **5aa** was observed at 110 °C for 196 h (entry 1). However, addition of 10 mol % of **1** led to the formation of **5aa** in more than 95% NMR yield under the same conditions (entry 3). The reaction could also go to completion in 32 h at 140 °C (entry 5). A lower catalyst loading resulted in a lower yield (entries 2 and 4).

It is documented that carbodiimides react readily with highly nucleophilic cyclic aliphatic amines, in the absence of a catalyst, to generate the corresponding guanidines at high temperatures.<sup>17</sup> Thus, the substrate scope of this reaction was examined to see if the catalyst is necessary for different substrates (Table 2). The reaction of highly nucleophilic *N,N'*-dimethylethylenediamine **3j** proceeded very well in the absence of the catalyst (entry 9 vs 10), whereas reactions of correspondingly less nucleophilic amines (such as aromatic diamine **3a** and primary aliphatic diamine **3f**) do need the catalyst (entries 1–6). The diarylcarbodiimide showed a better reactivity than the dialkylcarbodiimide (entries 1/2 vs 3/4, 5/6 vs 7/8).



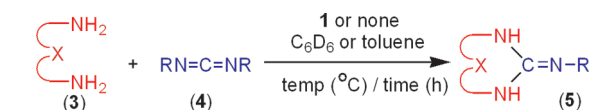
**Figure 1.** X-ray Structures for **5ac** and **5ec**.

According to the above observations, more substrates were included except for the highly nucleophilic amines. A series of di- and triamines were examined, and the corresponding results were compiled in Table 3. Reactions of diamines afforded five- to seven-membered cyclic guanidines (entries 1–11). The reaction of *cis*-1,4-cyclohexadiamine **3i** gave the bridged cyclic guanidine **5ic** (entry 12). Triamines **3k/3l** reacted with carbodiimides to produce the bicyclic guanidines **6k/6l** (entries 13–15). The chiral cyclic guanidine (**S-5ec**) was also prepared from the corresponding chiral amine (**S-3e**) with the retention of the *ee* value (entry 7). All of those products were fully characterized. Compounds **5ac** and **5ec** were further confirmed by X-ray analyses (Figure 1).

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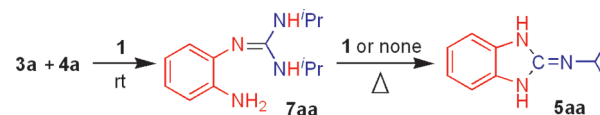
**Table 2.** Screening of Substrate Scope



entry	<b>3</b>	R ( <b>4</b> )	cat. %	temp/ time	<b>5<sup>a</sup></b>	yield (%)
1		<i>i</i> Pr ( <b>4a</b> )	0	140/ 32		<10 <sup>b</sup>
2		<i>i</i> Pr ( <b>4a</b> )	10	140/ 32		>95 <sup>b</sup> (95) <sup>c</sup>
3		4-tol ( <b>4c</b> )	0	115/ 36		30 <sup>b</sup>
4		4-tol ( <b>4c</b> )	10	115/ 36		>90 <sup>b</sup> (81) <sup>c</sup>
5		<i>i</i> Pr ( <b>4a</b> )	0	140/ 48		30 <sup>b</sup>
6		<i>i</i> Pr ( <b>4a</b> )	10	140/ 48		>80 <sup>b</sup> (70) <sup>c</sup>
7		4-tol ( <b>4c</b> )	0	140/ 48		>90 <sup>a</sup>
8		4-tol ( <b>4c</b> )	10	140/ 48		>90 <sup>b</sup> (86) <sup>c</sup>
9		4-tol ( <b>4c</b> )	0	115/ 12		>95 <sup>b</sup>
10		4-tol ( <b>4c</b> )	10	115/ 12		>90 <sup>b</sup> (90) <sup>c</sup>

<sup>a</sup> Ar = 4-tol. <sup>b</sup> NMR yield using ferrocene as an internal standard. <sup>c</sup> Isolated yield (shown in parentheses).

**Scheme 2.** Synthesis and Conversion of the Intermediate **7aa**



Although these reactions were developed on the basis of the well-established construction and reconstruction of guanidines (Scheme 1), the mechanism was further investigated. To gain some insight for the pathway, attempts to separate the intermediate were made. Treatment of *o*-phenylenediamine (**3a**) with 1 equiv of diisopropylcarbodiimide (**4a**) at room temperature for 3 h, in the presence of 10 mol % of **1**, led to the isolation of the intermediate **7aa** in 59% yield (Scheme 2). Two parallel reactions (**7aa** in C<sub>6</sub>D<sub>6</sub> vs **7aa** with 10 mol % of **1** in C<sub>6</sub>D<sub>6</sub>) were carried out at 140 °C, which were monitored by <sup>1</sup>H NMR using ferrocene as the internal standard. The experimental results showed that no obvious difference was observed and both of them resulted in the formation of **5aa** in more than 95% NMR yield in 30 h. This observation implies that the catalyst might not be involved in the cyclization step.

Due to the unique structure of **1** (the Ti atom is  $\sigma$ -bonded to only one amido group and strongly supported by the

**Table 3.** Synthesis of Cyclic Guanidines Catalyzed by **1**

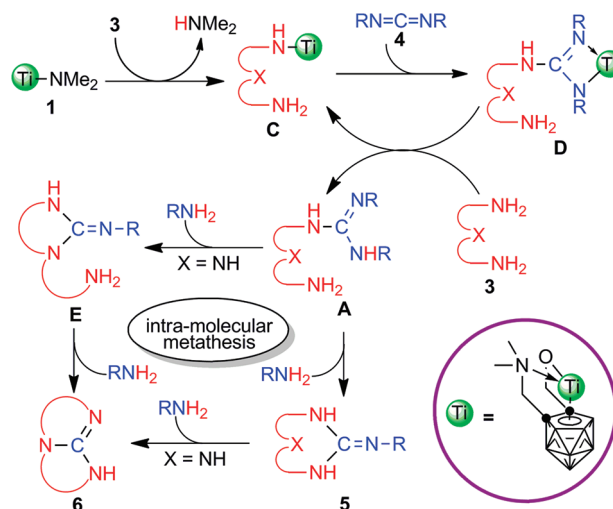
entry	<b>3</b>	R ( <b>4</b> )	temp /time	product <b>5</b> or <b>6</b> <sup>a</sup>	yield (%) <sup>b</sup>
1		Cy ( <b>4b</b> )	140 /120		62
2		4-tol ( <b>4c</b> )	115 /12		71
3		<i>i</i> Pr ( <b>4a</b> )	115 /8		95
4		Cy ( <b>4b</b> )	115 /8		94
5		4-tol ( <b>4c</b> )	115 /60		90
6		4-tol ( <b>4c</b> )	115 /12		77
7		4-tol ( <b>4c</b> )	140 /240		55 <sup>c</sup>
8	<i>rac</i> - <b>3e</b> <sup>d</sup>	4-tol ( <b>4c</b> )	140 /240	<i>rac</i> - <b>5ec</b> <sup>d</sup>	71
9		<i>i</i> Pr ( <b>4a</b> )	140 /120		65
10		4-tol ( <b>4c</b> )	115 /48		80
11		4-tol ( <b>4c</b> )	115 /168		67
12		4-tol ( <b>4c</b> )	140 /480		73
13		<i>i</i> Pr ( <b>4a</b> )	115 /168		71
14		4-tol ( <b>4c</b> )	115 /240		61
15		4-tol ( <b>4c</b> )	115 /240		76

<sup>a</sup> Ar = 4-tol. <sup>b</sup> Isolated yield. <sup>c</sup> ee = 99%. <sup>d</sup> *rac* = racemic.

trianionic ligand [ $\sigma:\eta^1:\eta^5-(\text{OCH}_2)(\text{Me}_2\text{NCH}_2)\text{C}_2\text{B}_9\text{H}_9$ ]<sup>3-</sup>, the involvement of any titanium-imido (Ti=O) species can be ruled out.<sup>5d,10,12–14</sup> Given these experimental results and those of well-established reactions (Scheme 1), a

(18) The intramolecular metathesis reaction of an amino-guanidine in the absence of a catalyst is supported by the parallel reactions of **7aa** (Scheme 2).

possible reaction mechanism is proposed in Scheme 3. Amine exchange reaction between **1** and amine **3** affords **C** to enter the catalytic cycle.<sup>5d,10,12–14</sup> An intermolecular insertion of carbodiimide into Ti–N bond leads to the formation of **D**.<sup>10,13,14</sup> Acid–base reaction of **D** with **3** regenerates **C** to complete the catalytic cycle and releases amino-guanidine **A**.<sup>13,14</sup> Intramolecular metathesis of **A** produces the cyclic guanidine **5**.<sup>18</sup> If a triamine is used as the starting material (X = NH), sequential intramolecular metathesis results in the production of bicyclic guanidine **6** from **A** via **E** or **5**.<sup>18</sup>

**Scheme 3.** Proposed Reaction Mechanism

In summary, we have developed a methodology for the synthesis of mono/bicyclic guanidines in good to excellent yields from di/triamines and carbodiimides, which is catalyzed by a titanium monoamide. A chiral guanidine can also be prepared with the retention of the *ee* value. The possible reaction mechanism, involving the Ti-catalyzed intermolecular hydroamination and intramolecular metathesis, is proposed as well.

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**Supporting Information Available.** Experimental procedures, spectroscopic data, and X-ray data in CIF format for **5ac** and **5ec**. This material is available free of charge via the Internet at <http://pubs.acs.org>.