Guanylation of Amines Catalyzed by a Half-Sandwich Titanacarborane Amide Complex

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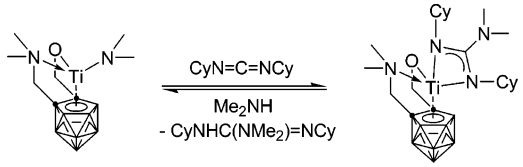
Received September 5, 2006

Summary: This work describes a new atom-economical catalytic process for the guanylation of amines with a broad substrate scope using the half-sandwich titanacarborane amide [σ:η¹:η⁵-(OCH₂)(Me₂NCH₂)(C₂B₉H₉)]Ti(NMe₂) as catalyst. This species bears two different sidearms: one is strongly bonded to the Ti center by taking the advantage of its high oxophilicity, whereas the other is hemilabile in nature, binding the Ti center reversibly.

The guanidine group is a decisive feature in many biologically active species.[1] It is found in a growing number of biologically and pharmaceutically relevant compounds.[2] Guanidine derivatives have also been widely used as ancillary ligands for the stabilization of various metal complexes, including those of early transition metals and lanthanides.[3] As a consequence, guanidine synthesis has been intensively investigated using various methods. Among these, the reaction of an amine with an electrophilic amidine species generating mono- or N,N′-disubstituted guanidines is a typical one.[4] On the other hand, addition of amine N−H bonds to carbodiimides (RN═C═NR) provides a direct and atom-economical approach to guanidines without the formation of any byproduct. It has been documented that only primary and cyclic secondary aliphatic amines can react directly with carbodiimides to yield tri- or tetraalkylguanidines under forcing conditions.[5] Catalytic hydroamination of carbodiimides was recently reported using Ti[6] and V[7] imido complexes as catalysts. However, this transformation proceeded only with primary aromatic amines. During completion of our paper, an yttrium-mediated catalytic addition of aliphatic secondary amines to carbodiimides was reported.[8] Consequently, new efficient and catalytic methods for assembling the guanidines from a diverse set of amines would be valuable. We report here a new catalytic guanylation of amines using a half-sandwich titanacarborane amide as catalyst with a broad substrate scope of primary, secondary, heterocyclic, aliphatic, and aromatic amines.

Scheme 1. Interconversion between 1 and 2



Treatment of [σ:η¹:η⁵-(OCH₂)(Me₂NCH₂)C₂B₉H₉]Ti(NMe₂) (**1**) with 1 equiv of CyN═C═NCy (Cy = cyclohexyl) gave [σ:η¹:η⁵-(OCH₂)(Me₂NCH₂)C₂B₉H₉]Ti[η³-CyNC(NMe₂)NCy] (**2**) in 82% isolated yield (quantitative NMR yield), which reacted readily with dimethylamine to regenerate **1** with the formation of CyN═C(NMe₂)NHCy, as indicated by NMR (Scheme 1). Both **1** and **2** were fully characterized by various spectroscopic techniques and single-crystal X-ray analyses (Figures 1 and 2).[9] We then explored the catalytic hydroamination reaction of carbodiimides. The results are compiled in Table 1. Except for the primary and cyclic secondary aliphatic amines (entries 1−3), no reaction was observed to any detectable degree, even with prolonged heating of carbodiimides (**3**) and

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(1) (a) *Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds*; Mori, A., Cohen, B. D., Lowenthal, A., Eds.; Plenum Press: New York, 1985. (b) *Guanidines 2: Further Explorations of the Biological and Chemical Significance of Guanidino Compounds*; Mori, A., Cohen, B. D., Koide, H., Eds.; Plenum Press: New York, 1987. (c) Greenhil, J. V.; Lue, P. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: New York, 1993; Vol. 30, Chapter 5.

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(4) (a) Schow, S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Sussex, U.K., 1995; pp 1408−1410. (b) Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300−2309. (c) Moroni, M.; Kokschy, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. *J. Org. Chem.* **2001**, *66*, 130−133. (d) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 3138−3141.

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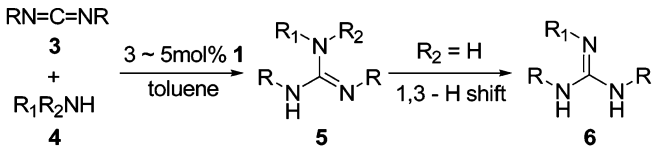
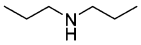
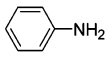
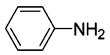
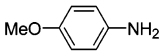
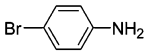
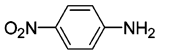
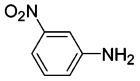
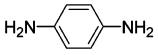
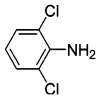
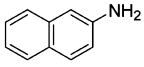
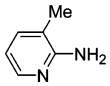
(8) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Synlett* **2006**, *8*, 1213−1216.

(9) Detailed experimental procedures and complete characterization data, including X-ray data for complexes **1** and **2**, are provided in the Supporting Information. Crystal data for **1** ($C_8H_{25}B_9N_2OTi$; fw = 310.49): monoclinic, space group *Cc*, a = 13.647(3) Å, b = 7.167(2) Å, c = 18.496(4) Å, β = 110.722(4)°, V = 1692.0(6) Å^3, T = 293 K, Z = 4, d_{calcd} = 1.219 g/cm^3, R1 = 0.042 ($I > 2\sigma(I)$), wR2(F^2) = 0.106. Crystal data for **2** ($C_{21}H_{47}B_9N_4OTi$, fw = 516.82): triclinic, space group $P\bar{1}$, a = 9.799(2) Å, b = 11.521(2) Å, c = 14.453(3) Å, α = 100.07(3)°, β = 105.59(3)°, γ = 104.93(3)°, V = 1465.4(5) Å^3, T = 293 K, Z = 2, d_{calcd} = 1.171 g/cm^3, R1 = 0.047 ($I > 2\sigma(I)$), wR2(F^2) = 0.144.

10.1021/om060811x CCC: $33.50
Publication on Web 10/14/2006

Table 1. Catalytic Addition of Amines to Carbodiimides



entry	R_1R_2NH	R	temp(°C)/ time (h)	product	yield (%)[a]
1	$CH_3(CH_2)_7NH_2$	Pr^i	110/8	**6a**	92
2		Pr^i	r.t./24	**5a**	97
3		Pr^i	110/3	**5b**	95
4		Pr^i	110/6	**5c**	93
5		Pr^i	110/6	**5d**	90
6		Cy	110/36	**5e**	71
7		Pr^i	110/36	**5f**	70
8		Pr^i	110/36	**5g**	71
9		Pr^i	110/36	**5h**	82
10		Pr^i	110/36	**5i**	70
11		Pr^i	110/6	**5j**	88
12		Cy	r.t./18	**6b**	96
13		Pr^i	r.t./18	**6c**	97
14		Pr^i	r.t./18	**6d**	97
15		Pr^i	r.t./18	**6e**	95
16		Pr^i	110/6	**6f**	92
17		Pr^i	110/6	**6g**	87
18		Pr^i	110/6	**6h**	92[b]
19		Pr^i	110/48	**6i**	94
20		Pr^i	110/3	**6j**	90
21		Pr^i	r.t./18	**6k**	92
22		Pr^i	r.t./18	**6l**	91

[a] Isolated yield. [b] Two equivalents of RN=C=NR was used, and the product is the biguanidine $(Pr^iNH)_2C{=}NC_6H_4N{=}C(Pr^iNH)_2$.

amines (**4**) at 110 °C in the absence of catalyst. However, the addition of 3−5 mol % of catalyst **1** led to efficient generation of guanidines (**5**). Complex **1** is a very robust, effective, and elegant catalyst for the catalytic addition of primary and secondary aliphatic and aromatic amines to carbodiimides with good functional group tolerance. Less nucleophilic pyrrole, indole, and benzotriazole also offered good yields (entries 6−10), indicating that **1** is a more powerful catalyst than the yttrium complex.[8]

Since **1** and **2** exhibited the same catalytic activity and reaction of **2** with Me_2NH generated **1**, it is therefore suggested that **2** serves as the intermediate for the reactions. Accordingly, a possible catalytic cycle is proposed in Scheme 2. Interaction of **A** with RN=C=NR (**3**) yields **B** or **B′**.[10] An acid−base reaction between **B**/**B′** and R_1R_2NH (**4**) releases the product **5**/**6**, meanwhile regenerating **A** to complete this catalytic cycle. Significantly different from Richeson's work,[6] no titanium imido

(10) Examples of insertion of unsaturated molecules into a group 4 metal M−N bond: (a) Wang, H.; Li, H.-W.; Xie, Z. *Organometallics* **2003**, *22*, 4522−4531. (b) Wang, H.; Chan, H.-S.; Okuda, J.; Xie, Z. *Organometallics* **2005**, *24*, 3118−3124. (c) Wu, Z. Z.; Diminnie, J. B.; Xue, Z. L. *Organometallics* **1999**, *18*, 1002−1010.

(11) Examples of group 4 metallacarboranes with a functional sidearm: (a) Xie, Z. *Coord. Chem. Rev.* **2006**, *250*, 259−272. (b) Lee, Y.-J.; Lee, J.-D.; Ko, J.; Kim, S.-H.; Kang, S. O. *Chem. Commun.* **2003**, 1364−1365. (c) Gao, M.; Tang, Y.; Xie, M.; Qian, C.; Xie, Z. *Organometallics* **2006**, *25*, 2578−2584. (d) Cheung, M.-S.; Chan, H.-S.; Xie, Z. *Organometallics* **2005**, *24*, 5217−5220. (e) Cheung, M.-S.; Chan, H.-S.; Bi, S.; Lin, Z.; Xie, Z. *Organometallics* **2005**, *24*, 4333−4336. (f) Cheung, M.-S.; Chan, H.-S.; Xie, Z. *Organometallics* **2005**, *24*, 3037−3039.

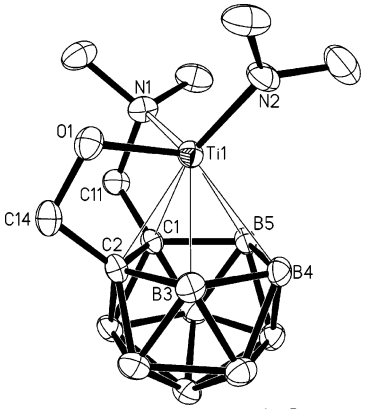


Figure 1. Molecular structure of [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)-($C_2B_9H_9$)]Ti(NMe_2) (**1**). Selected distances (Å) and angles (deg): Ti−C1 = 2.282(3), Ti−C2 = 2.302(3), Ti−B3 = 2.376(4), Ti−B4 = 2.477(4), Ti−B5 = 2.386(3), Ti−O1 = 1.833(2), Ti−N1 = 2.205(3), Ti−N2 = 1.862(3); Ti−O1−C14 = 105.6(2), Ti−N1−C11 = 94.3(2), O1−C14−C2 = 103.1(2), N1−C11−C1 = 106.6(2).

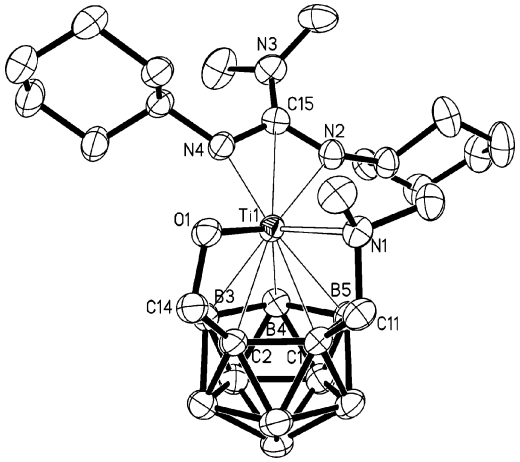
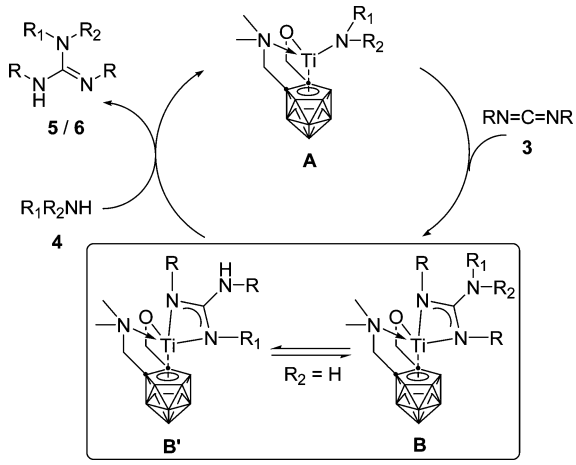


Figure 2. Molecular structure of [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)-($C_2B_9H_9$)]Ti[η^3-CyNC(NMe_2)NCy] (**2**). Selected distances (Å) and angles (deg): Ti−C1 = 2.391(2), Ti−C2 = 2.360(2), Ti−B3 = 2.386(3), Ti−B4 = 2.485(3), Ti−B5 = 2.467(3), Ti−O1 = 1.901(2), Ti−N1 = 2.322(2), Ti−N2 = 2.179(2), Ti−C15 = 2.546(2), Ti−N4 = 2.028(2); Ti−O1−C14 = 107.3(1), Ti−N1−C11 = 96.0(1), O1−C14−C2 = 103.1(2), N1−C11−C1 = 107.1(2), N2−C15−N4 = 110.9(2).

species are involved in our system, which largely broadens the reaction scope. The NMR experiments showed that aniline underwent a fast reaction with **1** in $CDCl_3$ at room temperature to generate a new titanium amide, presumably [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)($C_2B_9H_9$)]Ti(NHPh), and release Me_2NH. Upon addition of another 2 equiv of aniline, the chemical shifts of the coordinated sidearm Me_2N protons (two singlets) were shifted from 2.77 and 2.62 ppm to 2.40 and 2.28 ppm, suggesting that the interaction between Me_2NCH_2− and the Ti atom becomes weaker. The coordination of the amine substrates to the Ti center facilitates the protonation step. The hemilabile nature of the amine sidearm[11] might play a role in the catalytic cycle, since it could reversibly coordinate to the Ti center, thus stabilizing a highly reactive, electronically and sterically unsaturated species.

Scheme 2. Proposed Catalytic Cycle



In summary, we have described a new atom-economical catalytic process for the guanylation of amines with a broad substrate scope using a half-sandwich titanacarborane amide as catalyst. This new catalyst bears two different sidearms: one is strongly bonded to the Ti center by taking advantage of its high oxophilicity, whereas the other is hemilabile in nature, binding the Ti center reversibly. These features allow the catalyst to tolerate many functional groups.

Acknowledgment. This work was supported by a grant from the Research Grants Council of the Hong Kong Special Administration Region (Project No. 403103).

Supporting Information Available: Text, tables, and figures giving detailed experimental procedures and full characterization data and CIF files giving X-ray data for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM060811X