Titanacarborane Amide Catalyzed Transamination of Guanidines†

Hao Shen and Zuowei Xie*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, People's Republic of China

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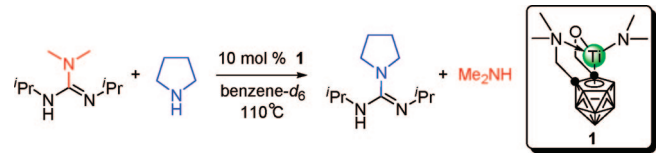
Summary: This work describes a catalytic transamination of guanidines with a broad substrate scope of primary, secondary, heterocyclic, aliphatic, and aromatic amines, using 5−10 mol % of the half-sandwich titanacarborane amide [σ:η¹:η⁵-(OCH₂)-(Me₂NCH₂)C₂B₉H₉]Ti(NMe₂) as catalyst. This reaction tolerates common functional groups. The reaction mechanism is also proposed.

The guanidine group is a prominent feature in many biologically active species.[1] A growing number of biologically and pharmaceutically relevant compounds incorporate the guanidine functionality. In addition, guanidine derivatives are capable of exhibiting a variety of coordination modes and a range of donor properties, leading to compatibility with a wide range of metal ions from all parts of the periodic table.[2,3] As a consequence, guanidine synthesis has been intensively investigated. Typical synthetic routes employ the reaction of an amine with an electrophilic guanylating reagent.[4] Recently, the catalytic construction of guanidines via the hydroamination of carbodiimides has also been reported.[5] As a result, a large number of guanidines are now available. We wondered whether these guanidines can be transformed into new ones through catalytic transamination processes in view of the well-established catalytic transamidation of carboxamides.[6] The only known example of guanidine transamination is the reaction of the homo-trisubstituted guanidine (^{i}Pr-NH)$_2$C═N-^{i}Pr with the primary aromatic amine ArNH$_2$ catalyzed by [(Me$_2$N)C(N^{i}Pr)$_2$]$_2$Ti═N(2,6-Me$_2$C$_6$H$_3$).[5a] However, the nature of this metal imide catalyst limits the reaction scope. Thus, a catalyst with a broad substrate spectrum of guanidines and amines is needed.

Scheme 1. Typical Transamination Reaction



Stimulated by our previous studies on the stoichiometric [σ:η⁵-(C$_9$H$_6$)C$_2$B$_9$H$_{10}$]Zr(NMe$_2$)(DME)-mediated C−N bond cleavage of the coordinated guanidinate ligand,[7] we investigated the catalytic properties of [σ:η¹:η⁵-(OCH$_2$)(Me$_2$NCH$_2$)C$_2$B$_9$H$_9$]-Ti(NMe$_2$) (**1**) in the transamination of guanidine ^{i}Pr-N═C(NMe$_2$)-NH-^{i}Pr with pyrrolidine, as shown in Scheme 1. In the absence of **1**, no detectable product was observed, even with prolonged heating at 110 °C. The addition of 10 mol % of **1** led to a clean transamination, giving quantitatively ^{i}Pr-N═C[N(CH$_2$)$_4$]NH-^{i}Pr within 40 h.[8] The catalytic reaction of ^{i}Pr-N═C(NMe$_2$)NH-^{i}Pr with the less volatile aniline in an open system (i.e., the generated Me$_2$NH was removed from the reaction mixture in refluxing toluene) resulted in a complete conversion within 30 h. A much longer reaction time (80 h) was required in a sealed NMR tube to achieve a quantitative conversion. On the other hand, treatment of ^{i}Pr-N═C(N^{n}Pr$_2$)NH-^{i}Pr with 4 equiv of

* To whom correspondence should be addressed. Fax: (+852) 2603-5057. Tel: (+852) 2609-6269. E-mail: zxie@cuhk.edu.hk.

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(1) (a) *Guanidines 2: Further Explorations of the Biological and Clinical Significance of Guanidino Compounds*; Mori, A., Cohen, B. D., Koide, H., Eds.; Plenum Press: New York, 1987. (b) 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.

(2) (a) Bailey, P. H.; Pace, S. *Coord. Chem. Rev.* **2001**, *214*, 91–141. (b) Chen, E. Y.-X.; Rodriguez-Delgado, A. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, U.K., 2007; Vol. 4, pp. 759−1004.

(3) Selected examples: (a) Jones, C.; Junk, P. C.; Platts, J. A.; Stasch, A. *J. Am. Chem. Soc.* **2006**, *128*, 2206–2207. (b) Holland, A. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 9010–9011. (c) Duncan, A. P.; Mullins, S. M.; Arnold, J.; Bergman, R. G. *Organometallics* **2001**, *20*, 1808–1819. (d) Ong, T.-G.; Yap, G. P. A.; Richeson, D. S. *Organometallics* **2002**, *21*, 2839–2841. (e) Carmalt, C. J.; Newport, A. C.; O'Neill, S. A.; Parkin, I. P.; White, A. J. P.; Williams, D. J. *Inorg. Chem.* **2005**, *44*, 615–619. (f) Mullins, S. M.; Duncan, A. P.; Bergman, R. G.; Arnold, J. *Inorg. Chem.* **2001**, *40*, 6952–6963. (g) Tin, M. K. T.; Yap, G. P. A.; Richeson, D. S. *Inorg. Chem.* **1998**, *37*, 6728–6730. (h) Tin, M. K. T.; Thirupathi, N.; Yap, G. P. A.; Richeson, D. S. *Dalton Trans.* **1999**, 2947–2951.

(4) For examples, see: (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.; Koksch, 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. (e) Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566–1568. (f) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1038–1042. (g) Ghosh, A. L.; Hol, W. K.; Fan, E. *J. Org. Chem.* **2001**, *66*, 2161–2164. (h) Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. *J. Org. Chem.* **2002**, *67*, 7553–7556. (I) Musiol, H.-J.; Moroder, L. *Org. Lett.* **2001**, *3*, 3859–3861. (j) Katrizky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080–8082.

(5) For examples, see: (a) Ong, T.-G.; Yap, G. P. A.; Richeson, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 8100–8101. (b) Shen, H.; Chan, H.-S.; Xie, Z. *Organometallics* **2006**, *25*, 5515–5517. (c) Li, Q.; Wang, S.; Zhou, S.; Yang, G.; Zhu, X.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 6763–6767. (d) Zhou, S.; Wang, S.; Yang, G.; Li, Q.; Zhang, L.; Yao, Z.; Zhou, Z.; Song, H. *Organometallics* **2007**, *26*, 3755–3761. (e) Ong, T.-G.; O'Brien, J. S.; Korobkov, I.; Richeson, D. S. *Organometallics* **2006**, *25*, 4728–4730. (f) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Synlett* **2006**, *8*, 1213–1216. (g) Zhang, W.-X.; Nishiura, M.; Hou, Z. *Chem. Eur. J.* **2007**, *13*, 4037–4051. (h) Montilla, F.; Pastor, A.; Galindo, A. *J. Organomet. Chem.* **2004**, *689*, 993–996. (I) Montilla, F.; del Río, D.; Pastor, A.; Galindo, A. *Organometallics* **2006**, *25*, 4996–5002.

(6) For examples, see: (a) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422–3423. (b) Kissounko, D. A.; Guzei, I. A.; Gellman, S. H.; Stahl, S. S. *Organometallics* **2005**, *24*, 5208–5210. (c) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 5177–5183. (d) Kissounko, D. A.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776–1783. (e) Bell, C. M.; Kissounko, D. A.; Gellman, S. H.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 761–763. (f) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 647–654.

(7) Shen, H.; Chan, H.-S.; Xie, Z. *J. Am. Chem. Soc.* **2007**, *129*, 12934–12935.

(8) Complete characterization data are provided in the Supporting Information.

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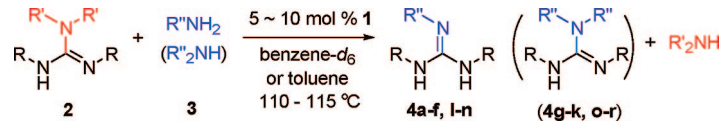
Table 1. Catalytic Transamination of Guanidines with Amines[a]



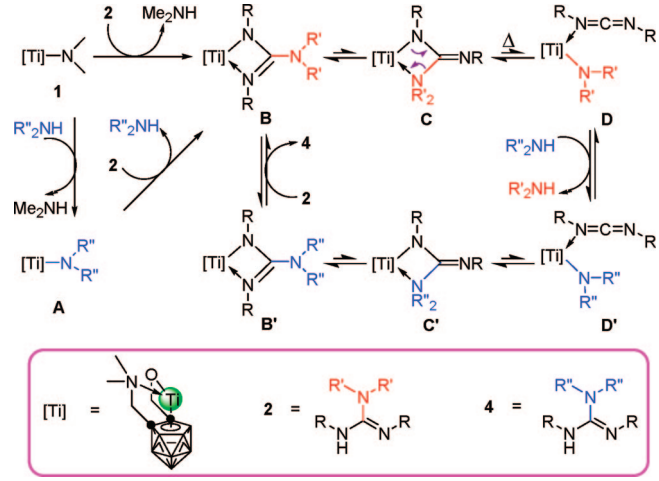
entry	R'/R (**2**)	amine **3**	time (h)	product **4**	yield (%)[b]	entry	R'/R (**2**)	amine **3**	time (h)	product **4**	yield (%)[b]
1[c,d]	Me / ^{i}Pr (**2a**)	(3a)	40	(4a)	>95(94)	10	Me / ^{i}Pr (**2a**)	(3j)	80	(4j)	75
2[c]		(3b)	40	(4b)	>95(92)	11		(3k)	80	(4k)	65
3		(3c)	80	(4c)	>95	12[c,d]		(3a)	40	(4l)	>95(97)
4		(3d)	80	(4d)	>95	13[c]		(3b)	40	(4m)	>95(98)
5		(3e)	80	(4e)	>95	14		(3d)	80	(4n)	>95
6		(3f)	80	(4f)	>95	15	Me / Cy[e] (**2b**)	(3g)	40	(4o)	>95(97)
7		(3g)	40	(4g)	>95	16		(3h)	40	(4p)	>95(96)
8		(3h)	40	(4h)	>95	17		(3i)	40	(4q)	>95(83)
9		(3i)	40	(4i)	>95	18		(3j)	120	(4r)	78

[a] Reaction conditions unless otherwise specified (not optimized): 1/4 guanidine/amine (mol/mol), 10 mol % of **1** in 0.5 mL of benzene-d_6 at 110−115 °C in a sealed NMR tube. [b] Yields determined by integration of ^{1}H NMR relative to internal standard of ferrocene; isolated yield in parentheses from scale-up reactions. [c] 5 mol % of **1**. [d] 15 equiv of amine. [e] Cy = cyclohexyl.

pyrrolidine in a sealed NMR tube gave the transamination product in ~60% yield, even after heating at 110 °C in benzene-d_6 for 240 h. These results suggest that the removal of volatile Me_2NH can shift the equilibrium to the right-hand side, facilitating the transamination process. We then extended the substrates to include other amines. The corresponding results were compiled in Table 1. Except for Et_2NH and $^nPr_2NH$ (entries 10, 11, and 18), the yields are almost quantitative, spanning a broad scope of primary, secondary, heterocyclic, aliphatic, and aromatic amines. It is noted that the trisubstituted guanidines are much more stable than the tetrasubstituted ones in this reaction system. No further transamination reaction of the products was observed in entries 1−6 and 12−14, as indicated by ^{1}H NMR. The catalyst can also tolerate functional groups such as methoxyl and bromo.

The reaction mechanism of the aforementioned transamination is obviously different from that of the titanium imide catalyzed system, in which the regeneration of the Ti=N moiety is essential.[5a] To gain some insight into the reaction pathway, the following reactions were examined.[8] A complete amine exchange reaction of **1** with excess pyrroline was observed by ^{1}H NMR at room temperature within 1 h.[8] The exchange reaction between **1** and primary aromatic amines to give new amides (not imides) was previously reported.[9] The NMR experiments also showed that **1** reacted with excess ^{i}Pr-N=C(NMe_2)NH-^{i}Pr to afford free dimethylamine and [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)$C_2B_9H_9$]Ti[η^2-(^{i}Pr-N)$_2$C(NMe_2)], which was stable at 110 °C in a sealed NMR tube in the presence of excess guanidine.[8] On the other hand, a ~40% exchange product was achieved from an equimolar reaction between [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)$C_2B_9H_9$]Ti[η^2-(^{i}Pr-N)$_2$C(NMe_2)] and ^{i}Pr-N=C[$N(CH_2)_4$]NH-^{i}Pr at 110 °C in a sealed NMR tube for 4 h,[8] as indicated by ^{1}H NMR. These results clearly suggested the presence of exchange reaction between guanidine and Ti amide or Ti guanidinate.

Scheme 2. Proposed Catalytic Cycle



Given these observations, a catalytic cycle for the transamination of guanidines is proposed in Scheme 2. Complex **1** undergoes amine exchange with R″$_2$NH to give the amide species **A**.[8] The acid−base reaction of **1** or **A** with guanidine R-N=C(NR′$_2$)NH-R (**2**) results in the formation of Ti guanidi-

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nate **B** to enter the catalytic cycle.[8,10] Isomerization of **B** to **C**,[3f] followed by C−N bond cleavage,[7] which is promoted by heat, forms **D**. An amine exchange reaction releases R'_2NH and generates **D′**. Insertion of carbodiimide into the Ti−N bond and isomerization of **C′** affords **B′**.[9] Guanidine exchange between **B′** and **2** affords the product R-N═C(NR″$_2$)NH-R (**4**) and **B** to complete the cycle.[8] It is noteworthy that the formation of a Ti imido complex can be ruled out, as the trianionic ligand $[(OCH_2)(Me_2NCH_2)C_2B_9H_9]^{3-}$ does not support such a metal imido complex.

In summary, we report a titanacarborane amide catalyzed transamination of guanidines with a broad substrate scope of primary, secondary, heterocyclic, aliphatic, and aromatic amines. This new catalytic system proceeds via pathway completely different from that reported.[5a] Studies on guanidine metathesis are ongoing.

(10) Such exchange reactions were known.[3g,h,7]

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Supporting Information Available: Text and figures giving detailed experimental procedures, full characterization data, and in situ ^{1}H NMR spectra for mechanistic study. This material is available free of charge via the Internet at http://pubs.acs.org.

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