Atom-Economical Synthesis of 2-Aminoimidazoles via [3+2] Annulation Catalyzed by Titanacarborane Monoamide

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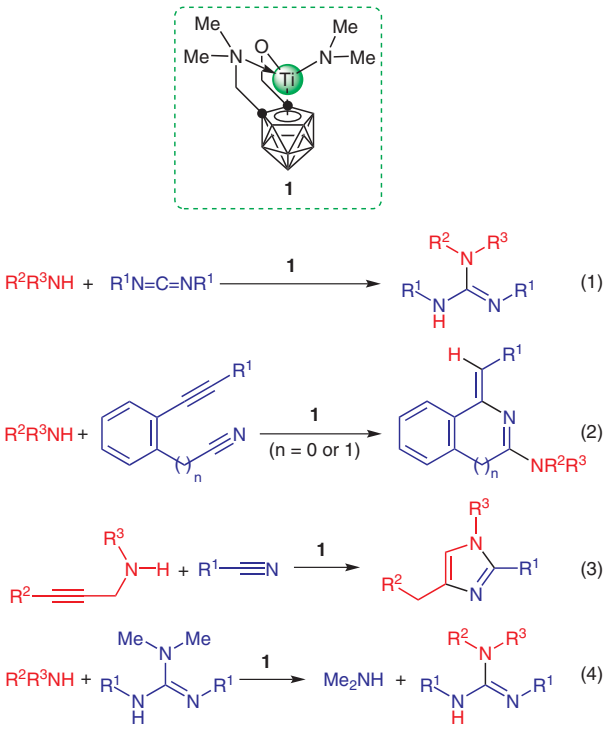
Abstract: An atom-economical synthesis of 2-aminoimidazoles catalyzed by a titanacarborane monoamide is reported. Reactions of propargylamines with carbodiimides, in the presence of 5 mol% [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)$C_2B_9H_9$]Ti(NMe_2), afford a new class of substituted 2-aminoimidazoles via [3+2] annulation in good to excellent yields. A possible reaction mechanism is proposed.

Key words: catalysis, heterocycles, hydroamination, imidazole, metallacarborane

The 2-aminoimidazole unit has been widely found in biologically active molecules and natural products,[1] and is emerging as a valuable pharmacophore for biomedical research.[2] As a result, synthetic strategies for the construction of this unique structural scaffold has been well-investigated.[2–4] Generally, there are two predominant methods among the various synthetic routes developed so far. The first approach includes the condensation of α-aminoketones with cyanamides or α-halogenated ketones with acetylated guanidine derivatives.[3a,b,f] The second approach relies on the modification of an imidazole core.[4] It is noted that these processes involve either long experimental procedures[4] or unstable precursors.[3a,b,f] Until very recently, two metal-catalyzed, short and efficient methods for the construction of the 2-aminoimidazole core had been reported.[5,6] Three-component coupling reactions of amines, aldehydes and terminal alkynes followed by lanthanide(III)-catalyzed hydroamination/cyclization lead, ultimately, to formation of the 2-aminoimidazole skeleton.[5] Reactions between secondary propargylamines and *S*-methylisothioureas in the presence of a silver(I) salt result in the generation of 2-aminoimidazole derivatives.[6] However, direct, atom-economic routes to 2-aminoimidazoles remain a challenge.

We have recently reported a highly reactive titanacarborane monoamide [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)$C_2B_9H_9$]Ti(NMe_2) (**1**).[7] This complex can efficiently catalyze the hydroamination of carbodiimides (Scheme 1, equation 1),[8] hydroamination/cyclization reactions of cyanoalkynes with amines (Scheme 1, equation 2) and propargylamines with nitriles (Scheme 1, equation 3),[9] as well as the transamination of guanidines (Scheme 1, equation 4).[10] Inspired by these results, we anticipated that the catalytic hydroamination/cyclization reaction between propargylamines and carbodiimides might serve as a new approach for the construction of 2-aminoimidazoles. Herein, we describe a titanacarborane monoamide catalyzed, direct and atom-economic synthesis of 2-aminoimidazoles from propargylamines and carbodiimides via [3+2] annulation.



Scheme 1 Hydroamination reactions catalyzed by **1**

A model reaction with the phenyl-substituted propargylamine **2a** and diisopropylcarbodiimide (**3a**) was initially examined in C_6D_6 (Table 1). There was no reaction detected in the absence of a catalyst at 115 °C after 18 h in a sealed NMR tube (entry 1). Some commercially available or commonly used metal complexes that are known to be active catalysts in hydroamination reactions[11] were also examined (Table 1, entries 2–9). Alkali metal amides (entries 2 and 3), group IV metal amides (entries 4–6) and metallocenes (entries 7–9) showed no catalytic activity for this reaction. However, addition of 5 mol% **1** under the same reaction conditions resulted in the formation of the

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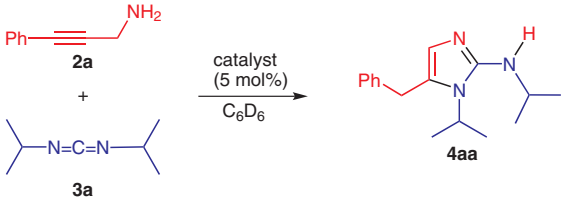
substituted 2-aminoimidazole **4aa** in more than 95% NMR yields (entries 10 and 11). Around 40% yield was observed when the reaction temperature was decreased to 80 °C (entry 12), suggesting that the temperature is crucial to such reactions.

Table 1 Metal Complexes in Reaction of **2a** with **3a**[a]



Entry	Catalyst (5 mol%)	Temp (°C)	Time (h)	Yield (%)[b]
1	None	115	18	0
2	$LiN(TMS)_2$	115	18	<5
3	$NaN(TMS)_2$	115	18	<5
4	$Ti(NMe_2)_4$	115	18	<5
5	$Zr(NMe_2)_4$	115	18	<5
6	$Hf(NMe_2)_4$	115	18	<5
7	Cp_2TiMe_2	115	18	<5
8	Cp_2ZrMe_2	115	18	<5
9	Cp_2HfMe_2	115	18	<5
10	**1**	115	18	>95
11	**1**	115	8	>95
12	**1**	80	18	~40

[a] Reaction conditions: An NMR tube was charged with a C_6D_6 solution (0.5 mL) of the catalyst (5 mol%) and ferrocene (internal standard, 0.05 mmol), to which was added **2a** (0.1 mmol) and **3a** (0.1 mmol) in a dry-box. It was heated after the valve was closed.
[b] NMR yield using ferrocene as the internal standard.

We then extended the substrate scope to include various propargylamines and carbodiimides on a preparative scale.[12] The results were summarized in Table 2. Most of the reactions under the optimal reaction conditions gave the expected 2-aminoimidazoles with excellent regioselectivity (5-*exo*-dig) (entries 1–19).[13] The corresponding products were isolated in good to excellent yields, and were characterized by ^1H and ^{13}C NMR analysis, and by HRMS. The structure of compound **4aa** was further confirmed by single-crystal X-ray analysis (Figure 1).[14] It was found that *N*,*N*′-(*i*-Pr)$_2$-, *N*,*N*′-(Cy)$_2$-, and *N*,*N*′-(4-Tol)$_2$-carbodiimides are compatible with this reaction. However, no desired product was isolated from the reaction of propargylamines with *N*,*N*′-(*t*-Bu)$_2$- or *N*,*N*′-(TMS)$_2$-carbodiimide, probably for steric reasons. On the other hand, the following general trends were observed: (1) the reaction works well for both primary and secondary propargylamines without obvious differences in the reaction rate (Table 2, entries 4–6 vs. 7–9); (2) reactions of propargylamines bearing an alkyl-substituted internal alkyne do not generate 2-aminoimidazoles, possibly due to their relatively low reactivity (entries 20 and 21); (3) the nature of the substituents on the phenyl ring does not significantly influence the reactions (entries 1–3 and 10–19), and (4) the reaction system is tolerant of many functional groups, such as halides, trifluoromethyl, methoxy, and terminal alkynes.

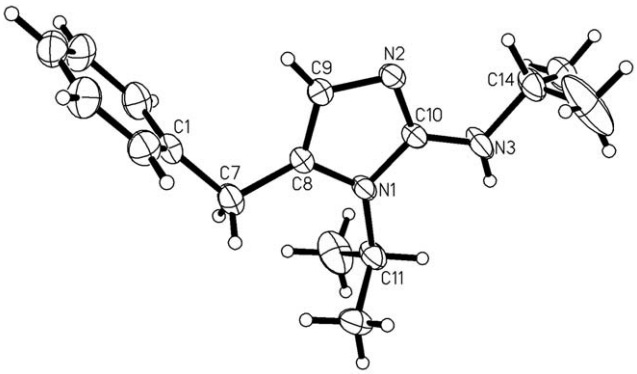
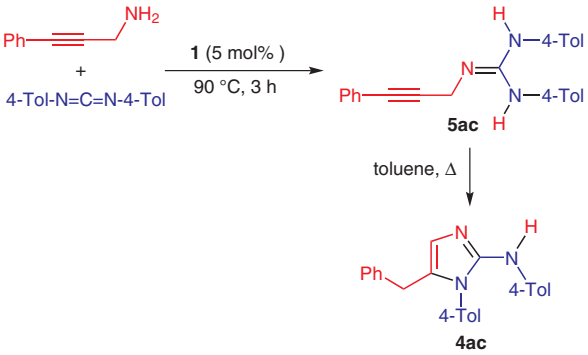


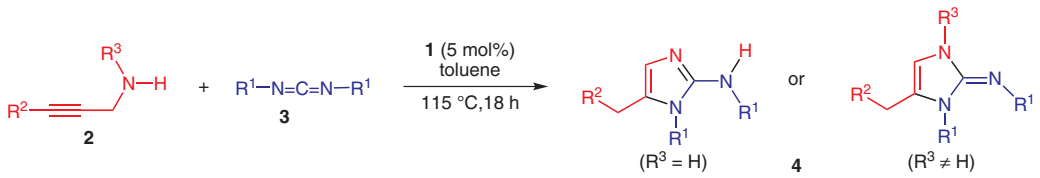
Figure 1 Molecular structure of **4aa**

It is noted that an intermediate was always observed by NMR analysis of the reaction of propargylamine with a carbodiimide when it was heated at 90 °C for a few hours. To gain some insight into the reaction pathway, attempts to separate the intermediate were made. Interaction of **2a** with **3c** in the presence of 5 mol% **1** at 90 °C for three hours gave, after flash column chromatographic separation, the guanidinoalkyne **5ac** in 76% isolated yield (Scheme 2). With this compound in hand, two parallel reactions (**5ac** in C_6D_6 vs. **5ac** with 5 mol% **1** in C_6D_6) were carried out at 115 °C, which were closely monitored by ^1H NMR analysis. The experimental results showed that no obvious difference was observed for these two reactions and both of them resulted in the clean formation of 2-aminoimidazole **4ac**, indicating that the catalyst might not be involved in the cyclization step.



Scheme 2 Synthesis and conversion of the intermediate **5ac**

Table 2 Synthesis of 2-Aminoimidazoles **4** from **2** and **3**



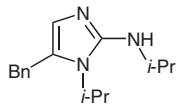
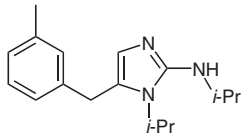
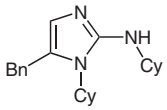
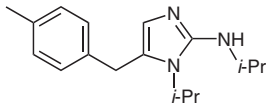
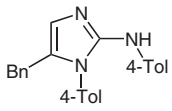
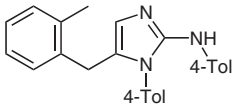
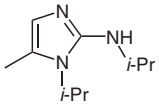
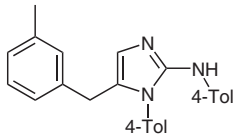
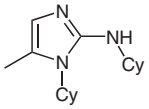
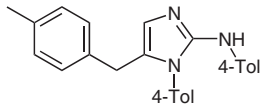
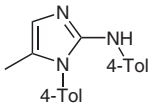
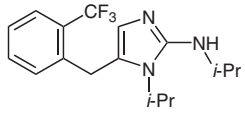
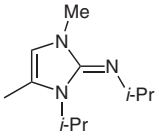
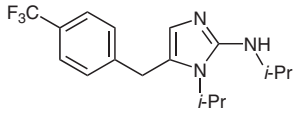
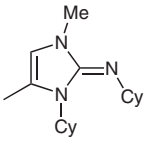
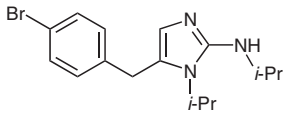
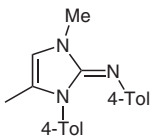
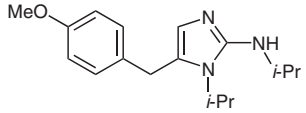
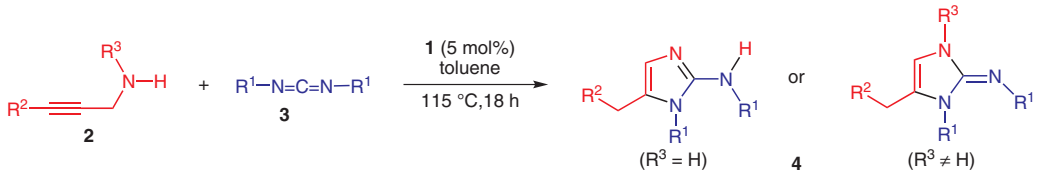
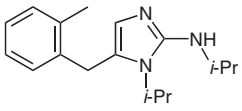
Entry	R^2, R^2 (**2**)	R^1 (**3**)	Product (**4**)	Yield (%)[a]	Entry	R^2, R^2 (**2**)	R^1 (**3**)	Product (**4**)	Yield (%)[a]
1	Ph, H (**2a**)	*i*-Pr (**3a**)	 **4aa**	83	11	3-MeC_6H_4, H (**2e**)	*i*-Pr (**3a**)	 **4ea**	82
2	Ph, H (**2a**)	Cy (**3b**)	 **4ab**	90	12	4-MeC_6H_4, H (**2f**)	*i*-Pr (**3a**)	 **4fa**	87
3	Ph, H (**2a**)	4-Tol (**3c**)	 **4ac**	62	13	2-MeC_6H_4, H (**2d**)	4-Tol (**3c**)	 **4dc**	81
4	H, H (**2b**)	*i*-Pr (**3a**)	 **4ba**	83	14	3-MeC_6H_4, H (**2e**)	4-Tol (**3c**)	 **4ec**	80
5	H, H (**2b**)	Cy (**3b**)	 **4bb**	90	15	4-MeC_6H_4, H (**2f**)	4-Tol (**3c**)	 **4fc**	84
6	H, H (**2b**)	4-Tol (**3c**)	 **4bc**	89	16	2-$F_3CC_6H_4$, H (**2g**)	*i*-Pr (**3a**)	 **4ga**	73
7	H, Me (**2c**)	*i*-Pr (**3a**)	 **4ca**	81	17	4-$F_3CC_6H_4$, H (**2h**)	*i*-Pr (**3a**)	 **4ha**	77
8	H, Me (**2c**)	Cy (**3b**)	 **4cb**	82	18	4-BrC_6H_4, H (**2i**)	*i*-Pr (**3a**)	 **4ia**	69
9	H, Me (**2c**)	4-Tol (**3c**)	 **4cc**	86	19	4-$MeOC_6H_4$, H (**2j**)	*i*-Pr (**3a**)	 **4ja**	88

Table 2 Synthesis of 2-Aminoimidazoles **4** from **2** and **3** (continued)

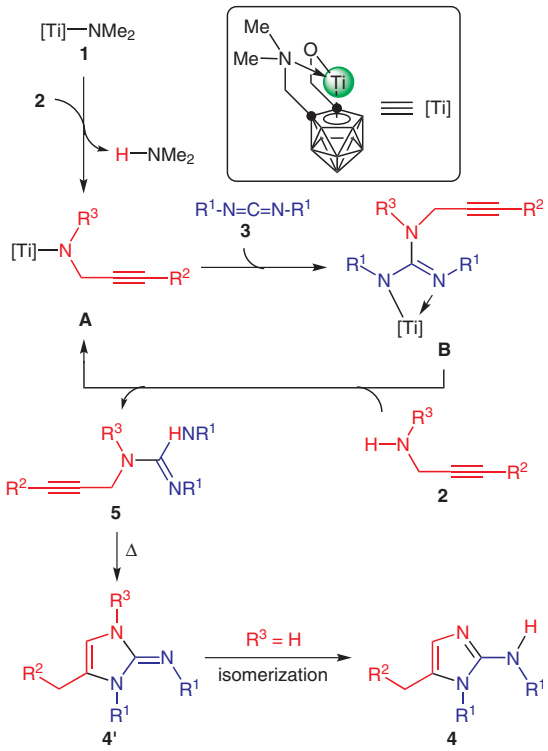


Entry	R^2, R^2 (**2**)	R^1 (**3**)	Product (**4**)	Yield (%)[a]	Entry	R^2, R^2 (**2**)	R^1 (**3**)	Product (**4**)	Yield (%)[a]
10	2-MeC_6H_4, H (**2d**)	*i*-Pr (**3a**)	 **4da**	95	20	*n*-Bu, H (**2k**)	*i*-Pr (**3a**)	–[b]	–[b]
					21	*n*-Bu, H (**2k**)	4-Tol (**3c**)	–[b]	–[b]

[a] Isolated yield.
[b] No desired product was detected.

Given the aforementioned experimental data and the well-established chemistry of complex **1**,[8–10] a possible reaction mechanism for this catalytic [3+2] annulation reaction of **2** with **3** is proposed in Scheme 3. The interaction of **1** with propargylamine **2** yields **A**, which enters the catalytic cycle.[7–10] Insertion of carbodiimide **3** into the Ti–N bond in **A** leads to the formation of guanidinate complex **B**.[7,8,10] Reaction between **B** and propargylamine **2** releases the guanidinoalkyne **5**, regenerating **A** to complete the catalytic cycle.[8,10] The guanidinoalkyne **5** cyclizes in a 5-*exo*-dig pattern to afford 2-aminoimidazole derivative **4′**.[15] When a primary amine was used as the starting material (R^3 = H), isomerization of **4′** gives 2-aminoimidazole **4**, which is driven by the formation of an aromatic system. On the basis of the availability of only one active Ti–N bond in **1**, and the fact that the reaction of **1** with primary/secondary amines produces Ti amide (instead of Ti imido) species,[7–10] the involvement of Ti=N can be ruled out.

In summary, we have developed a new methodology for the synthesis of 2-aminoimidazoles in good to excellent yields from propargylamines and carbodiimides via [3+2] annulation in the presence of a catalytic amount of the titanacarborane monoamide. A possible reaction mechanism, involving the hydroamination of carbodiimides and the cyclization of guanidinoalkynes, is proposed after the isolation and characterization of the intermediate.



Scheme 3 Proposed reaction mechanism

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(12) Some reactions were complete within 18 h, although the reaction of **2a** and **3a** was finished in 8 h.

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(14) CCDC-803540 contains the supplementary crystallographic data of **4aa** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

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