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Atom-Economical Synthesis of *N*-Heterocycles via Cascade Inter-/Intramolecular C−N Bond-Forming Reactions Catalyzed by Ti Amides

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Abstract: Direct and efficient catalytic reactions with excellent regioselectivity for the preparation of a series of substituted isoindoles, isoquinolines, and imidazoles are reported. Reaction of C_6H_4(2-CN)C≡C-R with an array of amines, catalyzed by 10 mol % of [σ:η^1:η^5-(OCH_2)(Me_2NCH_2)$C_2B_9H_9$]Ti(NMe_2) (**1**), gives a series of substituted isoindoles in very high yields. In a similar manner, interaction of C_6H_4(2-CH_2CN)C≡C-Ph with various kinds of amines affords a wide range of substituted isoquinolines. On the other hand, treatment of propargylamines (R′C≡CCH_2NHR″) with nitriles in the presence of 10 mol % of **1** produces a class of substituted imidazoles in high yields. A possible reaction mechanism is proposed, involving sequential inter- and intramolecular C−N bond formation via hydroamination/cyclization reaction of cyanoalkynes with amines or nitriles with propargylamines catalyzed by titanium amides.

Introduction

Isoindoles, isoquinolines, and imidazoles are important classes of *N*-heterocycles that are finding many diverse applications,[1] with examples including drug cores,[2] natural products,[3] organic synthesis,[4] conjugated and functional polymers,[5] coordination complexes,[6] important ligands in metalloenzymes,[7] precursors to ionic liquids,[8] and stable carbenes.[9] As a result, preparative methodologies for these *N*-heterocyclic compounds have been intensively investigated.[1,10−13] Among many synthetic strategies

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developed, transition-metal-catalyzed reactions have the advantage of increasing functional group tolerance and providing heterocycles with greater structural diversity and often higher overall yields.[14,15] However, direct and general synthetic routes to these *N*-heterocyclic skeletons with atom-economy remain a challenge.[1g]

Catalytic hydroamination is a highly atom-efficient method for the addition of amines to unsaturated bonds to give new C−N bonds, which has led to intensified research efforts over the past decade.[16−19] Various catalyst systems based on rare-earth metals have been developed and proven to be particularly active.[16] Difficulties in the preparation and handling of organolanthanides have, however, limited their wide applications as hydroamination catalysts. Systems based on neutral group 4 metal complexes have also been found to be active in hydroamination reactions of alkynes,[17] allenes,[17a,e,h,u,v] and alkenes.[17z,18] On the other hand, cationic group 4 metal complexes can catalyze the hydroamination/cyclization of secondary aminoalkenes.[19] Although the cationic group 4 metal catalysts are

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reported to be more reactive than their neutral counterparts, the former are unreactive toward primary aminoalkenes, presumably owing to the formation of a metal imido species.[19]

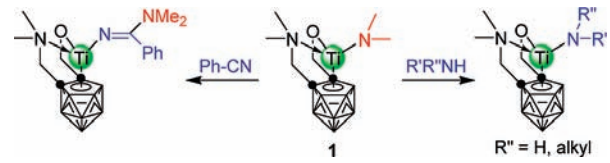
Inspired by the rich chemistry of direct amine addition to unsaturated organic molecules catalyzed by lanthanides[16] and early transition metal complexes,[17−19] and stimulated by our own work on the reactivity of the neutral group 4 metal monoamide [σ:η^1:η^5-$(OCH_2)(Me_2NCH_2)C_2B_9H_9$]Ti$(NMe_2)$ (**1**)[20] and catalytic construction[20b,21] and reconstruction of guanidines,[20b,22] we thought catalytic hydroamination may serve as a new approach for the construction of isoindole, isoquinoline, and imidazole cores through a proper combination of reactants. In fact, **1** can be viewed as an isoelectronic/isostructral analogue of constrained-geometry lanthanide amides or cationic group 4 metal amides.[23] The mechanisms of the reactions catalyzed by **1** do not involve any metal imido species.[24] It has two different functional side arms: one strongly bonds to the Ti atom, preserving the integrity of the constrained-geometry unit, and the other (amine) coordinates reversibly to the Ti atom, stabilizing the reactive intermediate. As part of an ongoing project focused on catalytic hydroamination reactions, we have recently found that **1** is a very robust catalyst for the cascade formation of C−N bonds both inter- and intramolecularly, leading to the formation of substituted isoindoles, isoquinolines, and imidazoles. These findings are reported in this article.

Results and Discussion

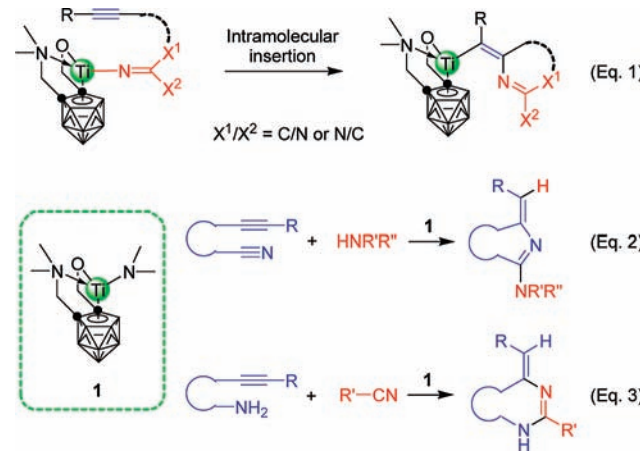
General Consideration. We have recently prepared a neutral group 4 metal monoamide, [σ:η^1:η^5-$(OCH_2)(Me_2NCH_2)$-$C_2B_9H_9$]Ti(NMe_2) (**1**), in 91% isolated yield by treatment of $[Me_3NH][\mu$-7,8-CH_2OCH_2-7,8-$C_2B_9H_{10}]$ with Ti$(NMe_2)_4$ in toluene.[20] It is found that benzonitrile (N≡C-Ph) can insert into the Ti−N bond in **1** to generate the amidinate complex [σ:η^1:η^5-$(OCH_2)(Me_2NCH_2)C_2B_9H_9$]Ti-[N═C(Ph)$NMe_2$],[20] and **1** can readily react with amines to afford new titanacarborane amides via amine-exchange reactions (Scheme 1).[20−22] However, **1** cannot catalyze the hydroamination reaction of nitriles, as the resulting titanacarborane amidinate complexes do not react with amines.

It is anticipated that the incorporation of a C≡C unit in the resultant amidinate complex would possibly result in the intramolecular insertion of the C≡C bond into the newly formed

Scheme 1. Insertion and Amine-Exchange Reactions of **1**



Scheme 2. Proposed Cascade C−N Bond-Forming Reactions To Give *N*-Heterocycles



Ti−N bond, subsequently leading to the construction of an *N*-heterocycle with the formation of a new Ti−C bond (Scheme 2, eq 1). The Ti−C bond would probably be quenched by an amine to regenerate a Ti amide and release an *N*-heterocyclic molecule.[25] On the basis of this scenario, the synthesis of *N*-heterocycles from reactions of cyanoalkynes with amines (Scheme 2, eq 2) and aminoalkynes with nitriles (Scheme 2, eq 3) catalyzed by **1** would be feasible. With this in mind, we examined the reactions of several cyanoalkynes (**2**) with amines (**3**) and propargylamines (**7**) with nitriles (**8**) in the presence of catalytic amounts of **1** and other metal amides.

Substituted Isoindoles. A model reaction of C_6H_4(2-CN)-C≡C-Ph (**2a**) with cyclohexylamine (**3a**) was initially examined in C_6D_6 (Table 1). There was no detectable reaction observed in the absence of a catalyst at 115 °C after prolonged heating in a sealed NMR tube (entry 1). Alkali metal salts showed no catalytic activity for this reaction (entries 2 and 3). However, addition of 10 mol % of group 4 metal amides resulted in the formation of cyclohexylamine-substituted isoindole derivative **4a** (entries 4−7). Among these metal amides, the Ti species was the most catalytically active (entries 4−6), probably due to its high Lewis acidity, facilitating the coordination of substrates. The catalytic activities of **1** and Ti$(NMe_2)_4$ are almost the same (entries 6, 7 vs 9, 10). The reaction temperature was optimized at 115 °C since the reaction was slow at lower temperatures, for example, 80 °C (entries 6 and 9). Lower catalyst loading (5 mol %) resulted in a slower reaction or a lower yield (entries 8 and 11).

We then extended the substrate scope to include other amines and cyanoalkynes in the presence of 10 mol % of titanium amides. The corresponding results are given in Table 2. It was found that Ti$(NMe_2)_4$ and **1** were almost equally active in the reactions of **2a**,**b** with primary amines (entries 1, 2, and 8). On the other hand, Ti$(NMe_2)_4$ exhibited a lower activity than **1** in

(18) For examples, see: (a) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354–358. (b) Majumder, S.; Odom, A. L. *Organometallics* **2008**, *27*, 1174–1177. (c) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959–1962. (d) Müller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* **2006**, 2499–2503. (e) Kim, H.; Lee, P. H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205–5207. (f) Thomson, R. K.; Bexrud, J. A.; Schafer, L. L. *Organometallics* **2006**, *25*, 4069–4071. (g) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731–4733. (h) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Organometallics* **2007**, *26*, 1729–1737. (i) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Commun.* **2008**, 1422–1424.

(19) For examples, see: (a) Gribkov, D. V.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5542–5546. (b) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894–895.

(20) (a) Shen, H.; Chan, H.-S.; Xie, Z. *Organometallics* **2007**, *26*, 2694–2704. (b) Shen, H.; Xie, Z. *J. Organomet. Chem.* **2009**, *694*, 1652–1657.

(21) Shen, H.; Chan, H.-S.; Xie, Z. *Organometallics* **2006**, *25*, 5515–5517.

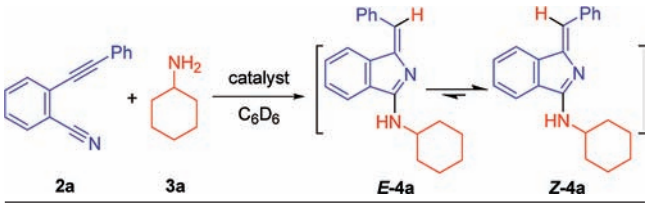
(22) Shen, H.; Xie, Z. *Organometallics* **2008**, *27*, 2685–2687.

(23) (a) Xie, Z. *Coord. Chem. Rev.* **2006**, *250*, 259–272. (b) Braunschweig, H.; Breitling, F. M. *Coord. Chem. Rev.* **2006**, *250*, 2691–2720. (c) Li, X.; Hou, Z. *Coord. Chem. Rev.* **2008**, *252*, 1842–1869.

(24) Reactions of **1** with both primary and secondary amines give Ti amido species, see refs 20−22.

(25) Intermolecular reaction of M−C/N bond with amine has been reported, see refs 16−19.

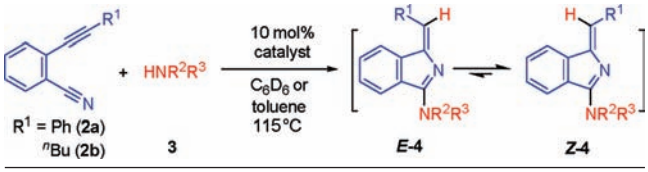
Table 1. Effects of Metal Catalysts on Reaction of **2a** with **3a**



entry	catalyst	cat loading (mol %)	temp (°C)	time (h)	yield (%)[a]
1	none	0	115	72	0[b]
2	$NaN(TMS)_2$	10	115	72	0[b]
3	$LiN(TMS)_2$	10	115	72	0[b]
4	$Hf(NMe_2)_4$	10	115	72	27
5	$Zr(NMe_2)_4$	10	115	72	57
6	$Ti(NMe_2)_4$	10	80	72	76
7	$Ti(NMe_2)_4$	10	115	18	>95
8	$Ti(NMe_2)_4$	5	115	18	59
9	**1**	10	80	72	80
10	**1**	10	115	18	>95
11	**1**	5	115	18	64

[a] NMR yield of **4** (*E*-**4** and *Z*-**4**) using ferrocene as an internal standard. [b] The concentration of **2a** remained almost unchanged.

Table 2. Synthesis of Substituted Isoindoles **4**

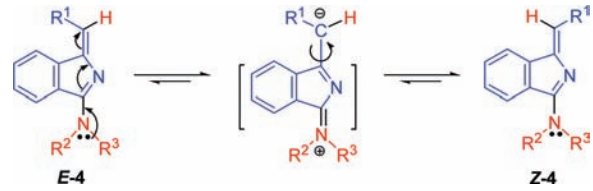


entry	R^1	3	catalyst: $Ti(NMe_2)_4$ time (h)	$Ti(NMe_2)_4$ yield (%)[a]	**1** time (h)	**1** yield (%)[a]	**1** product (yield%)[b]
1	Ph	3a	18	> 95	18	> 95	***Z*-4a** (84)
2	Ph	3b	48	> 95	48	> 95	***Z*-4b** (66)
3	Ph	3c	60	> 95	48	> 95	***Z*-4c** (88)
4	Ph	3d	60	49	48	> 95	***Z*-4d** (91)
5	Ph	3e	60	< 10	48	> 95	***Z*-4e** (67)
6	Ph	3f	60	< 10	48	> 95	***E*-4f** (22) ***Z*-4f** (71)
7	Ph	3g	100	0	100	53	***Z*-4g** (50)
8	^{n}Bu	3a	36	> 95	36	> 95	***Z*-4h** (77)
9	^{n}Bu	3e	48	< 10	48	> 95	***Z*-4i** (73)
10	^{n}Bu	3f	48	< 10	48	> 95	***Z*-4j** (81)

[a] NMR yield of **4** (*E*-**4** and *Z*-**4**) using ferrocene as an internal standard. [b] Isolated product/yield from a preparative-scale reaction.

reactions with five-membered cyclic amines **3c**,**d** (entries 3 and 4). A significant difference was observed in the reactions of **2a**,**b** with bulkier six-membered cyclic amines **3e**,**f**: $Ti(NMe_2)_4$ offered the products in <10% yields, whereas **1** gave >95% yields (entries 5, 6, 9, and 10). Though **1** displayed a moderate activity in the reaction of **2a** with diethylamine (**3g**), NMR showed that $Ti(NMe_2)_4$ could not catalyze the same reaction (entry 7). The reasons may be as follows. Complex **1** has only one active Ti−N σ-bond, and the central Ti atom has a very

Scheme 3. Isomerization between *E*-**4** and *Z*-**4**



open coordination sphere.[26] In contrast, two or more NMe_2 groups in $Ti(NMe_2)_4$ may be displaced by excess amine. As a result, poor activity was observed for $Ti(NMe_2)_4$ in the reactions with bulkier amines.

It was noted that aromatic amines were not compatible with these reactions. No obvious reactions of **2a**,**b** with anilines were observed at lower temperatures in the presence of 10 mol % of $Ti(NMe_2)_4$ or **1**. A complex mixture was observed after prolonged heating, as indicated by ^{1}H NMR. The NMR experiment also showed a slow decomposition of $[\sigma{:}\eta^1{:}\eta^5$-$(OCH_2)(Me_2NCH_2)C_2B_9H_9]Ti[NH\text{-}C_6H_4\text{-}4\text{-}OMe]$[20a] upon heating a C_6D_6 solution at 115 °C, whereas **1** was very thermally stable, and no decomposition was observed after heating at 115 °C for a week.

Although *Z*-isomers were isolated as the final products (except for *E*-**4f**, entry 6 in Table 2), a mixture of both *E*- and *Z*-isomers was observed in NMR experiments for all reactions. In addition, the NMR results clearly indicated that the major product initially formed was the *E*-isomer, which was finally converted to the *Z*-isomer under the reaction conditions. Such an isomerization also proceeded at room temperature in C_6D_6 in the absence of any catalysts, which was sped up by heating or treatment with silica gel. For example, a C_6D_6 solution of pure *E*-**4f** was slowly converted to a mixture of *E*-**4f** and *Z*-**4f** in a molar ratio of 65/35 (*E*/*Z*) after standing at room temperature for 5 days. A ratio of 26/74 (*E*-**4f**/*Z*-**4f**) was obtained if the solution was heated at 115 °C for 3 days. It was suggested that a zwitterionic intermediate may be involved in the isomerization (Scheme 3), and the *E*/*Z* ratio was dominated by the thermodynamic stability of the products. Therefore, the preparative-scale reactions were all heated at 115 °C in toluene for 120 h and followed by treatment with silica gel, in order to isolate the more stable products (*Z*-isomers) (the last column, Table 2). It was noteworthy that this reaction proceeded in a 5-*exo*-*dig* cyclization pattern without the observation of any 6-*endo*-*dig* product (*vide infra*).

All products were fully characterized by ^{1}H and ^{13}C NMR spectra and HRMS. The configuration of C=C bonds was assigned according to NOESY experiments.[27] The molecular structures of *Z*-**4c** and *Z*-**4f** were further confirmed by single-crystal X-ray analyses, as shown in Figures 1 and 2.

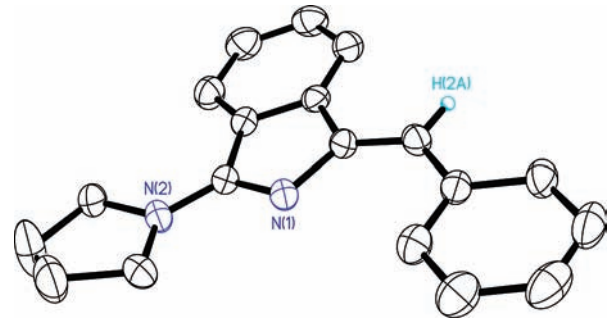


Figure 1. Molecular structure of *Z*-**4c**.

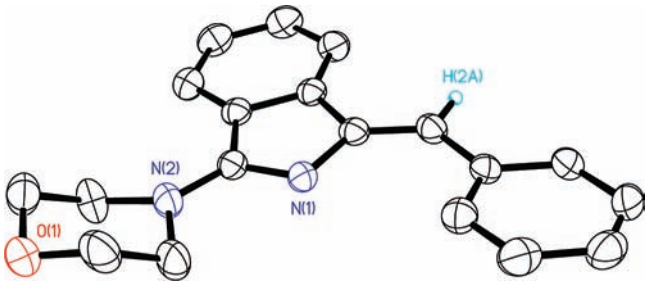
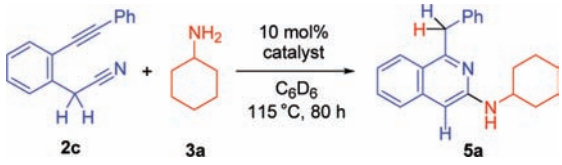


Figure 2. Molecular structure of *Z*-**4f**.

Table 3. Effects of Metal Catalysts on Reaction of **2c** with **3a**



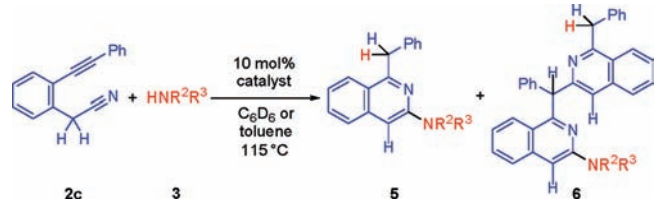
entry	catalyst	yield (%)[a]
1	none	0[b]
2	$NaN(TMS)_2$	0[c]
3	$LiN(TMS)_2$	0[c]
4	$Hf(NMe_2)_4$	<10
5	$Zr(NMe_2)_4$	26
6	$Ti(NMe_2)_4$	>95
7	**1**	>95

[a] NMR yield using ferrocene as an internal standard. [b] The concentration of **2c** remained unchanged. [c] Decomposition of **2c** was observed.

Substituted Isoquinolines. In a similar manner, we examined the reaction of $C_6H_4(2\text{-}CH_2CN)\text{-}C{\equiv}C\text{-}Ph$ (**2c**) with cyclohexylamine (**3a**) to possibly build isoquinoline cores. There was no detectable reaction observed in the absence of a catalyst upon heating a C_6D_6 solution at 115 °C for 80 h (entry 1, Table 3). Under the same reaction conditions, the decomposition of **2c** was observed in the presence of 10 mol % of strong bases such as $NaN(TMS)_2$ and $LiN(TMS)_2$ (entries 2 and 3, Table 3), which might be ascribed to the acidity of benzylic protons in **2c**. In contrast, addition of 10 mol % of group 4 metal amides resulted in the formation of the desired isoquinoline **5a**, and their activities followed the trend **1** ≈ $Ti(NMe_2)_4$ > $Zr(NMe_2)_4$ > $Hf(NMe_2)_4$ (entries 4−7, Table 3), probably due to the higher Lewis acidity of the Ti species.

Various kinds of amines were then examined using $Ti(NMe_2)_4$ and **1** as the catalysts. The results are summarized in Table 4. Reactions of **2c** with primary amines **3a**,**b** afforded **5a**,**b** as sole products, and no **6a**,**b** was observed by NMR (entries 1 and 2). However, reactions of **2c** with cyclic secondary amines **3c**,**e**,**f** gave a mixture of **5** and **6**, with their ratios mainly dependent upon the catalysts (entries 3−5). A much better selectivity in favor of the formation of **5** was observed in the reactions catalyzed by **1**. It was found that, in the case of diethylamine **3g**, $Ti(NMe_2)_4$ offered <10% NMR yield of **5g**, whereas **1** gave 55% NMR yield. After workup, **5g** was isolated in 52% yield in the latter case from a preparative-scale reaction. $Ti(NMe_2)_4$ is generally less reactive toward bulkier amines than **1**, probably due to steric effects imposed by several amido groups, as discussed in the previous reaction. It was noted that the reactions with aromatic amines were complicated under the same reaction conditions, which could be ascribed to the thermal instability of the aforementioned Ti arylamides, and no pure product was isolated. Excellent regioselectivity in favor of 6-*exo*-*dig* products and the effect of catalysts on the molar ratio of **5**/**6** will be discussed in the Reaction Mechanism section.

Table 4. Synthesis of Substituted Isoquinolines **5** and **6**



entry	3	Prod (**5**/**6**)	catalyst: $Ti(NMe_2)_4$ time (h)	$Ti(NMe_2)_4$ yield%[a] (yield%)[b]	**1** time (h)	**1** yield%[a] (yield%)[b]
1	**3a**	**5a**/**6a**	80	>95/<5 (79/0)	80	>95/<5 (90/0)
2	**3b**	**5b**/**6b**	80	>95/<5 (81/0)	80	>95/<5 (71/0)
3	**3c**	**5c**/**6c**	48	37/51[c] (35/40)	48	93/7 (90/--[d])
4	**3e**	**5e**/**6e**	48	40/31[c] (30/17)	48	81/19 (70/--[d])
5	**3f**	**5f**/**6f**	48	32/30[c] (30/30)	48	77/23 (70/--[d])
6	**3g**	**5g**/**6g**	160	<10/--[c]	160	55/<5 (52/--[d])

[a] NMR yields of **5**/**6**. [b] Isolated yields of **5**/**6** are shown in parentheses. [c] Dimethylamino (from the catalyst)-substituted products **5k**/**6k** ($R^2 = R^3 =$ Me) were also observed. [d] No compound **6** was isolated.

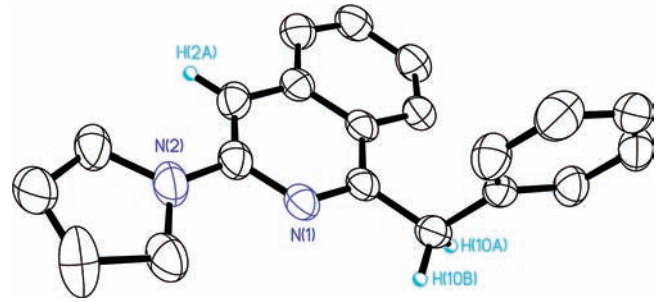


Figure 3. Molecular structure of **5c**.

Products **5** and **6** were fully characterized by ^1H and ^{13}C NMR spectra and HRMS. The solid-state structure of **5c** was further confirmed by single-crystal X-ray diffraction studies as shown in Figure 3.

Substituted Imidazoles. To explore the generality of group 4 amides in the hydroamination catalysis, an equimolar reaction of propargylamines ($R^4C{\equiv}CCH_2NHR^5$, R^4/R^5 = Ph/H, H/H, and H/Me) with 2-cyanofuran was examined. It was found that no detectable reaction was observed in C_6D_6 at 115 °C for 5 h in the absence of a catalyst (entry 1, Table 5). Some commercially available or commonly used metal complexes that are known to be active catalysts in hydroamination reactions[28] were also

(26) It has been documented that the coordination number of the Ti atom in this kind of metallacarboranes can be increased at least by 2 units, as evidenced by the molecular structure of $[\sigma{:}\eta^1{:}\eta^5\text{-}(OCH_2)\text{-}(Me_2NCH_2)C_2B_9H_9]Ti[\sigma{:}\eta^1\text{-}(2\text{-}NH\text{-}3\text{-}CH_3\text{-}C_5H_3N)](\eta^1\text{-}C_5H_3N\text{-}2\text{-}NH_2\text{-}3\text{-}CH_3)$, see refs 20a, b.

(27) See the Supporting Information for details.

Table 5. Effects of Metal Catalysts in Reactions of Propargylamines with 2-Cyanofuran

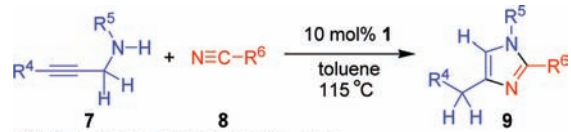
entry	catalyst	cat (mol %)	yield (%)[a] R⁴/R⁵ = Ph/H (**7a**)	H/H (**7b**)	H/Me (**7c**)
1	none	0	0	0	0
2	$LiNMe_2$	10	0	0	0
3	$LiN(TMS)_2$	10	0	0	0
4	$NaN(TMS)_2$	10	0	0	0
5	$Ti(NMe_2)_4$	10	0	0	trace
6	$Zr(NMe_2)_4$	10	0	0	<20
7	$Hf(NMe_2)_4$	10	0	0	<20
8	Cp_2TiMe_2	10	0	0	0
9	Cp_2ZrMe_2	10	0	0	0
10	Cp_2HfMe_2	10	0	0	0
11	**1**	10	>90	>90	>90
12	**1**	5	74	45	47

[a] NMR yield using ferrocene as an internal standard.

examined (entries 2−10, Table 5). Except for $M(NMe_2)_4$ (M = Ti, Zr, Hf), which showed small activities only for **7c** (entries 5−7), the others did not offer any of the desired products, and the concentration of 2-cyanofuran remained almost unchanged. However, addition of 10 mol % of **1** under the same reaction conditions resulted in the formation of substituted imidazoles in >90% NMR yields (entry 11, Table 5). Lower catalyst loading (5 mol %) resulted in a lower yield under the same conditions (entry 12, Table 5). It is noteworthy that $Ti(NMe_2)_4$ showed high catalytic activities in the reactions of cyanoalkynes with amines, as shown in the synthesis of isoindoles and isoquinolines (*vide supra*), but not in the current reactions. These results again suggest that $Ti(NMe_2)_4$ is very sensitive to substrates and that **1** is a very robust catalyst due to its unique molecular structure.[29] For metallocenes Cp_2MMe_2, the presence of two Cp ligands may block the coordination of the substrates, leading to no catalytic activity in the reactions.

We then extended the substrate scope to include various nitriles on a preparative scale. The results are compiled in Table 6. Catalyst **1** exhibited an excellent regioselectivity. Table 6 shows that alkylnitriles, heteroarylnitriles, arylnitriles with various functional groups at the *ortho*-, *meta*-, or *para*-position, propargylamines with an internal/terminal C≡C bond, and propargylamines with a mono-/disubstituted amino group are all compatible with this reaction. The following general trends were observed: (1) sterically demanding nitriles give much lower yields (entries 4−13 vs 15 and 16; entry 19 vs 20); (2) arylnitriles are more reactive than alkylnitriles, as aryl substituents can activate the C≡N unit, offering higher yields (entries 1−13 vs 18−20); (3) for *ortho*-substituted arylnitriles, the donor substituents facilitate the coordination of a nitrile to the catalyst, resulting in the faster reaction and higher yields (entry 14 vs 15 and 16; entry 25 vs 26); (4) the nature of substituents on the phenyl ring does not significantly influence the reactions (entries

Table 6. Synthesis of Substituted Imidazoles **9**



R^4/R^5 = Ph/H (**7a**); H/H (**7b**); H/Me (**7c**)

entry	R^4/R^5 (**7**)	R^6 (**8**)	time (h)	product (**9**)	yield (%)[a]
1	Ph/H	*o*-furyl- (**8a**)	5	**9aa**	92
2	Ph/H	*o*-thiophenyl- (**8b**)	5	**9ab**	86
3	Ph/H	*m*-Py- (**8c**)	48	**9ac**	52
4	Ph/H	Ph- (**8d**)	48	**9ad**	61
5	Ph/H	*p*-Me-Ph- (**8e**)	48	**9ae**	64
6	Ph/H	*p*-MeO-Ph- (**8f**)	48	**9af**	68
7	Ph/H	*p*-CF_3-Ph- (**8g**)	48	**9ag**	66
8	Ph/H	*p*-F-Ph- (**8h**)	48	**9ah**	60
9	Ph/H	*p*-Cl-Ph- (**8i**)	48	**9ai**	59
10	Ph/H	*p*-Br-Ph- (**8j**)	48	**9aj**	63
11	Ph/H	*m*-Me-Ph- (**8k**)	48	**9ak**	58
12	Ph/H	*m*-MeO-Ph- (**8l**)	48	**9al**	62
13	Ph/H	*m*-CF_3-Ph- (**8m**)	48	**9am**	51
14	Ph/H	*o*-MeO-Ph- (**8n**)	48	**9an**	60
15	Ph/H	*o*-CF_3-Ph- (**8o**)	168	**9ao**	21
16	Ph/H	*o*-Br-Ph- (**8p**)	168	**9ap**	34
17	Ph/H	pyrrolyl-$(CH_2)_2$- (**8q**)	72	**9aq**	56
18	Ph/H	*cyclo*-Pr-CH_2- (**8r**)	168	**9ar**	39
19	Ph/H	*i*-Pr- (**8s**)	168	**9as**	36
20	Ph/H	*t*-Bu- (**8t**)	168	—	—[b]
21	H/H	*o*-furyl- (**8a**)	5	**9ba**	84
22	H/H	*o*-thiophenyl- (**8b**)	5	**9bb**	82
23	H/H	Ph- (**8d**)	60	**9bd**	28
24	H/H	*p*-Cl-Ph- (**8i**)	60	**9bi**	29
25	H/H	*o*-MeO-Ph- (**8n**)	60	**9bn**	44
26	H/H	*o*-Br-Ph- (**8p**)	60	**9bp**	24
27	H/Me	*o*-furyl- (**8a**)	5	**9ca**	80
28	H/Me	Ph- (**8d**)	60	**9cd**	21
29	H/Me	*p*-MeO-Ph- (**8f**)	60	**9cf**	25
30	H/Me	*p*-Cl-Ph- (**8i**)	60	**9ci**	20
31	H/Me	pyrrolyl-$(CH_2)_2$- (**8q**)	60	**9cq**	22

[a] Isolated yield. [b] No detectable reaction was observed.

4−13, 23, 24, and 28−30); (5) the catalytic system is tolerant to many functional groups, such as halides, trifluoromethyl, methoxyl, furyl, thiophenyl, pyridyl, pyrrolyl, and cyclopropyl; and (6) the reaction proceeds in a 5-*exo*-*dig* pattern without the observation of any 6-*endo*-*dig* cyclization products, indicating an excellent regioselectivity (*vide infra*). It is noted that the reactions of propargylamines with 2-cyanofuran (**8a**) or 2-cyanothiophene (**8b**) (entries 1, 2, 21, 22, and 27) are much faster than those with other nitriles and offer very high yields, which is probably due to the joint effects of the smaller aromatic rings and the presence of β-donor atoms (O or S). Compound **8n** shows a much higher reactivity than other *ortho*-substituted nitriles (entries 14 and 25), which may be ascribed to the coordination effect of *o*-OMe. On the other hand, **7b** and **7c** are poorer starting materials than **7a** in the reactions with less reactive nitriles, probably because the terminal alkyne can quench the [Ti]−C/N bond after prolonged heating, leading to lower yields (entries 23−26 and 28−31).

The products (**9**) were fully characterized by ^1H NMR, ^{13}C NMR, and HRMS. Compound **9ae** was further confirmed by single-crystal X-ray analyses as shown in Figure 4.

Reaction Mechanism. In view of the unique structure of **1** (the Ti atom is σ-bonded to only one amido group and strongly supported by the trianionic ligand $[\sigma:\eta^1:\eta^5\text{-}(OCH_2)(Me_2NCH_2)\text{-}C_2B_9H_9]^{3-}$), the involvement of any titanium imido (Ti═N) species in the aforementioned reactions can be ruled out, as evidenced by the experimental results shown in Scheme 1.[24]

(28) For examples, see refs 17a−d,k−n,r,s,18c,d and the following: (a) Ong, T.-G.; O'Brien, J. S.; Korobkov, I.; Richeson, D. S. *Organometallics* **2006**, *25*, 4728–4730. (b) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1153–1156.

(29) Many attempts to prepare the Zr and Hf analogues of **1** were not successful, see ref 20a.

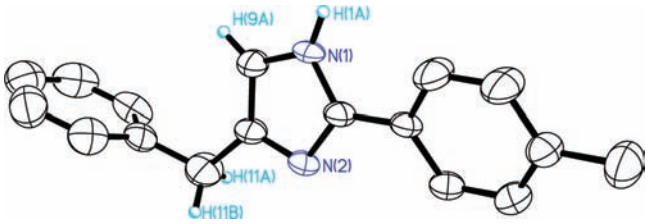
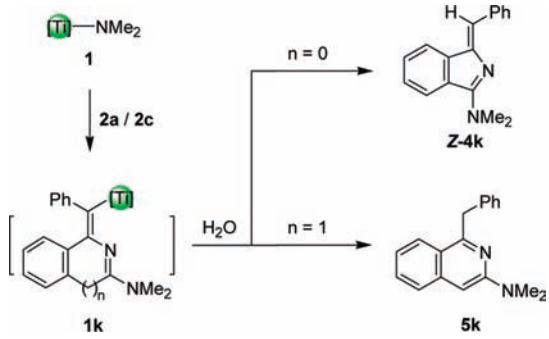


Figure 4. Molecular structure of **9ae**.

Scheme 4. Stoichiometric Reactions of **1** with **2a**/**2c**

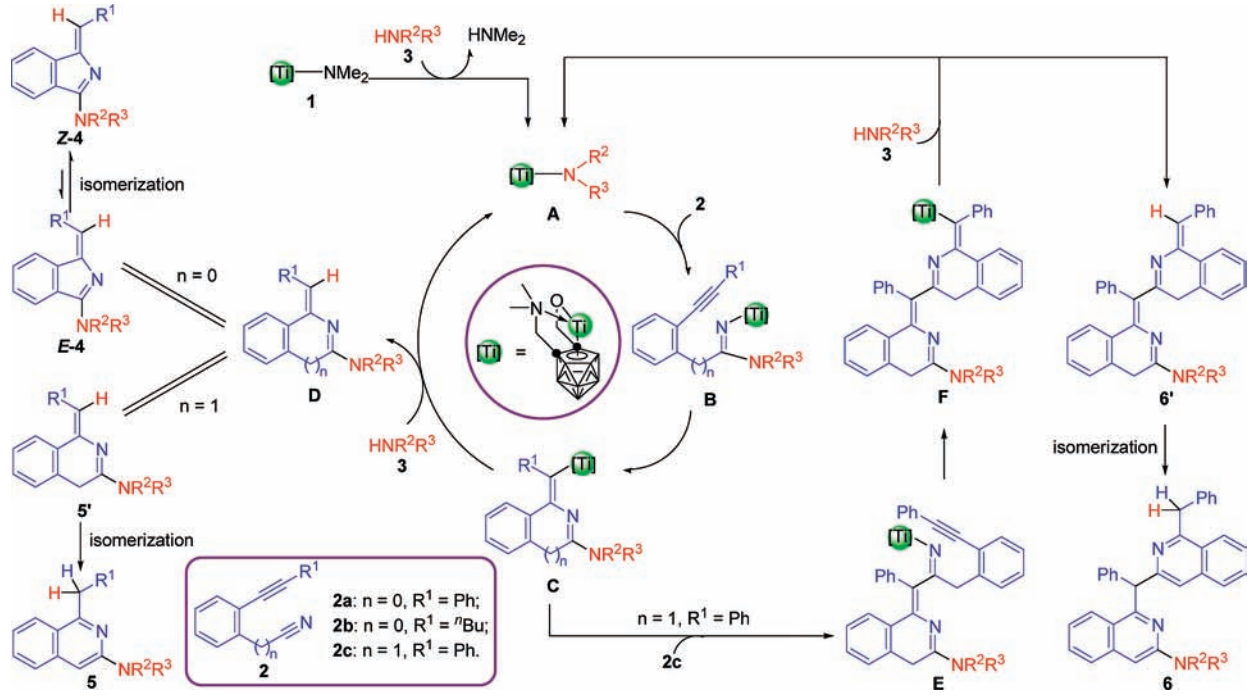


However, **1** cannot catalyze the direct addition of amines to nitriles, which implies that the resulting titanacarborane amidinate complexes do not react with amines. On the other hand, stoichiometric reactions of **1** with **2a** or **2c** at 75 °C for 4 h (in the absence of free amines) followed by hydrolysis afforded a dimethylamino-group-substituted isoindole (*Z*-**4k**) or isoquinoline (**5k**) in 77% and 61% isolated yields (Scheme 4), respectively. Many attempts to grow X-ray-quality crystals of the Ti complexes before the hydrolysis failed. Nevertheless, after heating a C_6D_6 solution of **2a** and an equimolar amount of **1** at 75 °C for 4 h, the ^{13}C NMR spectrum displayed a characteristic signal at 209.4 ppm assignable to the α-carbon of the Ti−*C*═C unit[30] with the disappearance of *C*≡*C* resonances in the range 80−100 ppm. These observations suggest intermolecular insertion of the C≡N bond into the Ti−N bond (in **1**) and intramolecular insertion of the C≡C triple bond into the newly formed Ti−N bond (in the amidinate unit Ti−NCN) and strongly support the formation of the intermediate **1k** in Scheme 4.

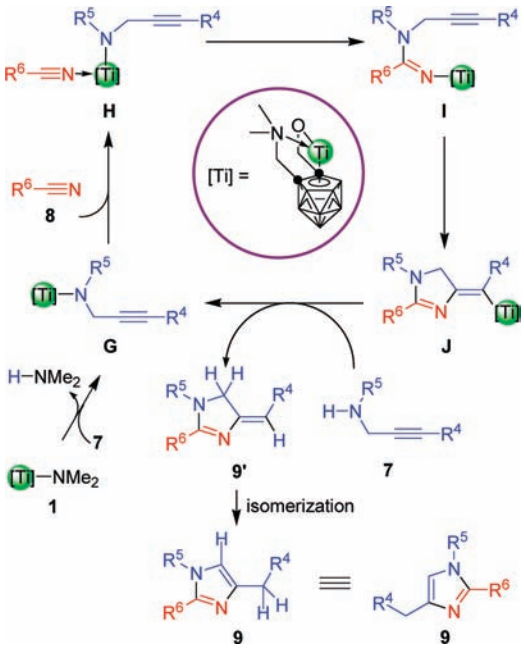
Given the above experimental results, a possible reaction pathway for the formation of **4**, **5**, and **6** is proposed in Scheme 5. Amine-exchange reaction between **1** and **3** generates the titanacarborane amide **A**[20−22] to enter the catalytic cycle. Intermolecular insertion of nitrile into the Ti−N bond in **A** results in the formation of intermediate **B**,[20] followed by an intramolecular insertion of the C≡C bond into the newly formed Ti−N bond to afford **C**.[31] The catalytic cycle is completed by the acid−base reaction of **C** with amines **3** to regenerate **A** and release **D**.[31] **D** undergoes isomerization to give substituted isoindoles **4** ($n = 0$) or isoquinolines **5** ($n = 1$), respectively. On the other hand, sterically less hindered cyanoalkyne **2c** can further insert into the newly formed Ti−C bond in **C** to produce **E**, during which the steric factor may play a role on the basis of the fact that the di-insertion was observed only in the case of **2c** but not in **2a**,**b**. Consequently, the constrained-geometry dicarbollyl ligand may disfavor the second insertion of **2c**, leading to a much better selectivity of **1** over $Ti(NMe_2)_4$ in the reactions of **2c** with **3** (Table 4). Intramolecular insertion reaction of **E** yields **F**.[31] Protonation between **F** and **3** regenerates **A** to complete the catalytic cycle with the formation of **6′**.[31] Again, tautomerization, which is driven by the formation of aromatic systems, affords products **6**. In addition, the insertion of C≡C into the M−N bond is a *cis*-addition.[31] As a result, *E*-**4** products are initially formed after the metathesis reaction of **C** ($n = 0$) with **3**, which isomerize to the thermodynamically more stable *Z*-**4** products (*vide supra*).

Scheme 6 shows a possible reaction pathway for the formation of **9**. Amine-exchange reaction between **1** and **7** generates the titanacarborane amide **G** to enter the catalytic cycle.[20−22] Coordination of nitrile **8** to the Ti atom results in the formation of **H**,[26] followed by a migratory insertion to give intermediate

Scheme 5. Possible Reaction Mechanism for the Formation of **4**, **5**, and **6**



Scheme 6. Possible Reaction Mechanism for the Formation of **9**



I.[20] Intramolecular insertion of the C≡C bond into the newly formed Ti−N bond affords **J**.[31] Finally, the catalytic cycle is completed by the acid−base reaction of **J** with amine **7** to regenerate **G** and release **9′**.[31] **9′** undergoes isomerization, which is favored by the formation of an aromatic system, to produce substituted imidazole **9**. Excellent regioselectivity of these reactions (in favor of *exo*-*dig*-cyclization) can be ascribed to the constrained geometry of **I**, which makes the *endo*-cyclization impossible.

Conclusion

We have developed new methodologies for the synthesis of a series of substituted isoindoles, isoquinolines, and imidazoles with excellent regioselectivity in the presence of a catalytic amount of titanium amides. This work shows that titanacarborane monoamide **1** is a very robust catalyst, which is thermodynamically and kinetically very stable and tolerant to many common functional groups. The unique structure of **1** rules out the involvement of Ti═N (titanium imido) species in catalysis. Thus, a sequential inter- and intramolecular hydroamination pathway is proposed for the catalytic reactions. Other possible applications of **1** in catalytic reactions are under investigation.

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Supporting Information Available: Complete ref 2j; experimental section; crystallographic data in CIF format for *Z*-**4c**, *Z*-**4f**, **5c**, and **9ae**; and ^{1}H NMR, ^{13}C NMR, NOESY, DEPT-135, and HSQC spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA101796K

(30) For examples of the ^{13}C chemical shift of Ti-*C*═C, see: (a) Selby, J. D.; Schulten, C.; Schwarz, A. D.; Stasch, A.; Clot, E.; Jones, C.; Mountford, P. *Chem. Commun.* **2008**, 5101–5103. (b) Wang, H.; Chan, H.-S.; Xie, Z. *Organometallics* **2005**, *24*, 3772–3779. (c) Ward, B. D.; Maisse-François, A.; Mountford, P.; Gade, L. H. *Chem. Commun.* **2004**, 704–705. (d) Vujkovic, N.; Ward, B. D.; Maisse-François, A.; Wadepohl, H.; Mountford, P.; Gade, L. H. *Organometallics* **2007**, *26*, 5522–5534. (e) Basuli, F.; Aneetha, H.; Huffman, J. C.; Mindiola, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 17992–17993.

(31) For examples of intramolecular insertion of C≡C into the M−N bond and the subsequent metathesis reaction of M−C bond with N−H bond, see refs 16a,b,e.