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Cyclic (Alkyl)amino Carbene Complex of Aluminum(III) in Catalytic Guanylation Reaction of Carbodiimides

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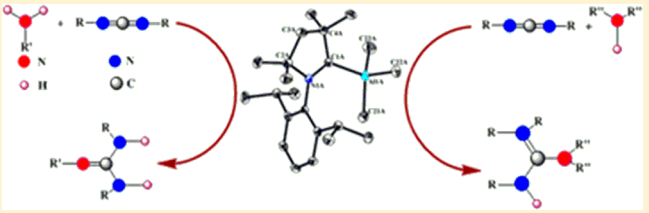
Supporting Information

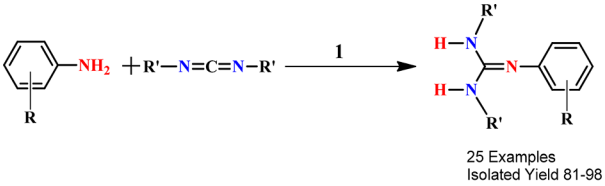
ABSTRACT: Herein we report the synthesis of a cyclic (alkyl)amino carbene (*c*AAC) complex of $AlMe_3$. This complex was used as an efficient catalyst for the guanylation reaction of carbodiimides with primary arylamines and secondary amines to deliver guanidine derivatives in good to excellent yields. This catalytic protocol can tolerate a wide range of functional groups. Furthermore, the longevity of the catalyst was tested in successive catalytic cycles, which indicated a sustained catalytic activity over a multiple cycles. The mechanistic pathway was well understood with the help of stoichiometric reaction and DFT study.



Catalytic C−N bond formation by activation of amine N−H bonds to carbodiimides (RN═C═NR), known as catalytic guanylation of amines with carbodiimides (CGAC reaction), to construct N-containing compounds is one of the most important chemical transformations in modern organic synthesis.[1−3] The catalytic guanylation reaction of amines is a straightforward and atom-economical route to prepare multi-substituted N-containing compounds, RN═C(NR′R″)-NHR,[4−15] which have unique value in pharmaceutical chemistry,[16−18] agrochemicals, natural products, sweeteners, explosives,[19] organometallic and coordination chemistry,[20−22] and organic synthesis.[23,24] It was well established that direct guanylation reaction of primary aliphatic amines with carbodiimides can be achieved under harsh conditions without using any catalyst.[25] However, because of lower nucleophilicity, the guanylation reaction cannot be achieved with aromatic amines or secondary amines without use of a suitable catalyst. In 2003, the guanylation reaction of some aromatic amines with activated *N,N′*-diaryl-substituted carbodiimides was reported with tetrabutylammonium fluoride (TBAF).[26] The first catalytic guanylation of primary aromatic amines with unactivated carbodiimides was reported by Richeson et al. in 2003.[13] In recent years, the guanylation reaction of primary aromatic amines has been explored catalytically with a large number of transition metal[8,13,27−30] and rare-earth metal complexes,[5,6,31−39] and sparse reports are known with main group metal complexes.[7,9,10,40−43] However, the most recent trend deals with development of non-transition metal based, earth-abundant, nontoxic, and inexpensive metals such as aluminum for guanylation reaction.

A thorough literature survey reveals that, though there are several reports on aluminum-catalyzed guanylation reactions of primary arylamines, well-designed aluminum carbene-based catalysts are still scarce.[42,44] This strongly motivated us to develop an efficient carbene-based aluminum catalyst for the guanylation reaction. As a part of our ongoing research program using carbene as ligands,[45−52] herein we used a strong *σ*-donor ligand, such as cyclic (alkyl)amino carbene (*c*AAC),[53−60] to design an aluminum-based catalyst. In this Article, we describe an efficient hydroamination reaction of carbodiimides (Scheme 1) with a well-defined aluminum(III) complex, [(*c*AAC)$AlMe_3$] (**1**).

Scheme 1. Hydroamination of Carbodiimides Catalyzed by Complex 1 in C_6D_6



RESULTS AND DISCUSSION

The synthesis of **1** was accomplished by the treatment of free *c*AAC in toluene with $AlMe_3$ (2.0 M solution in toluene) at −78 °C (Figure 1). Analytically pure off-white crystals of **1** were obtained in 70% isolated yield from a concentrated solution of hexane at 0 °C after 3 days. Compound **1** readily dissolves in toluene, benzene, hexane, THF, and Et_2O. Complex **1** was characterized by NMR spectroscopy (^1H, ^{13}C NMR), as well as by elemental analysis and single-crystal X-ray diffraction study. The ^1H and ^{13}C NMR spectra of **1** in C_6D_6 revealed resonances at δ −0.54 and −5.0 ppm,[52]

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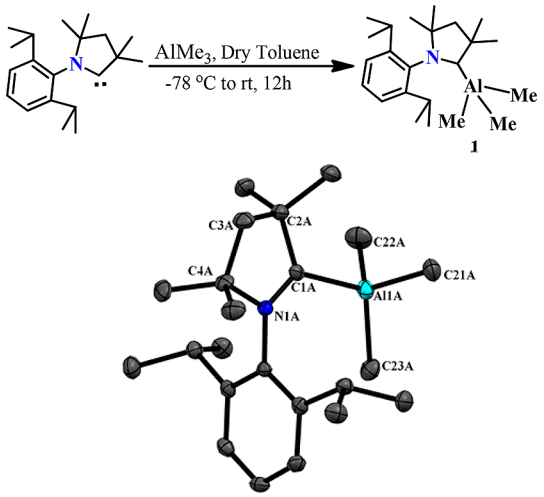
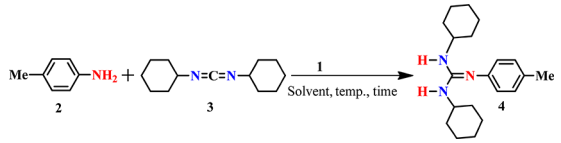


Figure 1. Synthesis of complex **1** and ORTEP diagram of **1** with thermal ellipsoids drawn at 50% probability. The hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Al1A−C1A 2.1241(16), Al1A−C23A 1.9895(19), Al1A−C21A 1.9979(19), Al1A−C22A 1.9958(18), N1A−C1A 1.3042(19), C2A−C1A 1.526(2), N1A−C4A 1.5345(19), C4A−C3A 1.528(2); C21A−Al1A−C1A 100.96(7), C3A−C2A−C1A 104.33(12), N1A−C1A−Al1A 128.98(11), N1A−C1A−C2A 108.12(13).

respectively, which may be assigned to the methyl group bound to the Al(III) ion. Also the ^{13}C NMR spectrum exhibits a resonance at δ 254.0 ppm, corresponding to the aluminum−carbene carbon resonance which is significantly upfield shifted upon metal coordination from the corresponding free *c*AAC (304.2 ppm)[52,60] but downfield shifted in comparison to the reported NHC−$AlMe_3$ adduct (174.3 ppm, NHC = 1,3-di-*tert*-butylimidazol-2-ylidene).[61] To unambiguously ascertain the expected bond connectivities, a suitable crystal was analyzed via single-crystal X-ray diffraction (Figure 1).[62] As anticipated, the X-ray crystal structure of **1** exhibits an aluminum(III) trapped in a distorted tetrahedral environment and bonded to the *c*AAC and three methyl groups. The Al−C_{cAAC} bond distance in **1** is 2.1241 (16) Å, which is comparable with previously crystallographically analyzed Al−C_{NHC} [2.162(2) Å, NHC = 1,3-di-*tert*-butylimidazol-2-ylidene][61] and Al−C_{aNHC} bond distances [2.033 and 2.104 Å] observed in $AlMe_3$−*a*NHC adducts.[52,63]

Knowing the structure of the complex, we next used **1** as a precatalyst for hydroamination reaction of primary arylamines with unactivated carbodiimides such as *N,N′*-dicyclohexylcarbodiimide (DCC). When a solution of complex **1** (5 mol%) and DCC in C_6D_6 was stirred in the presence of 1 equiv of *p*-toluidine at room temperature, >99% of substituted derivative **4** was realized (Table 1, entry 1−2). Upon decreasing the catalyst loading to 2 mol%, >99% of product **4** was observed within 1 h (Table 1, entry 3). Further decreases in catalyst loading to 1.5 and 1 mol% resulted in decreasing the conversion (Table 1, entries 4 and 5). The role of catalyst **1** in the guanylation of primary arylamine is eminent: as in a blank reaction, no product was detected by ^{1}H NMR spectroscopy even after 6 h (Table 1, entry 6). Upon further optimization of solvent (Table 1, entries 7−11) and temperature, quantitative yield of the guanylated product **4** was achieved in benzene-d_6 and toluene-d_8, though 2 mol% catalyst loading afforded the full conversion within 15 min at 60 °C (Table 1, entry 12).

Table 1. Optimization Study for the Guanylation Reaction of *p*-Toluidine with DCC[a]



entry	**1** (mol%)	solvent	time (h)	yield (%)[b]
1	5	C_6D_6	6	>99
2	5	C_6D_6	1	>99
3	**2**	$\mathbf{C_6D_6}$	**1**	**>99**
4	1.5	C_6D_6	1	81
5	1	C_6D_6	1	59
6	–	C_6D_6	6	–
7	2	toluene-d_8	1	>99
8	2	THF-d_8	1	52
9	2	DMSO-d_6	1	27
10	2	$CDCl_3$	1	15
11[c]	1	C_6D_6	1	>99
12[d]	2	C_6D_6	15 min	>99

[a]Reaction conditions: *p*-toluidine (0.2 mmol), *N,N′*-dicyclohexylcarbodiimide (0.2 mmol), **1** (x mol%), room temperature, 0.6 mL of solvent. [b]Yields determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard. [c]Hydroamination reaction was performed at 60 °C. [d]Catalytic hydroamination reaction was performed with 2 mol% catalyst loading at 60 °C for 15 min.

With the optimized reaction conditions in hand (Table 1, entries 3 and 7), we explored the scope of the guanylation reaction of various primary arylamines with carbodiimides to give their corresponding guanidine derivative (Table 2). Under the standardized conditions, the presence of an electron-donating group at the para or ortho position of an aniline moiety such as 4-methylaniline, 4-isopropylaniline, and 2-methoxyaniline afforded high yields of 98%, 92%, and 90% of the corresponding guanidine derivatives **5a**, **5b**, and **5c**, respectively (Table 2). Under similar reaction conditions, the aniline moieties containing electron-withdrawing substituents at the *para*-position offered nearly quantitative yields of the corresponding products, 89−96% (Table 2). 4-Bromo-, 4-chloro-, 4-fluoro-, and 4-nitroaniline afforded excellent isolated yields, such as 96%, 92%, 90%, and 89%, of the corresponding guanidine derivatives **5d−5g**, respectively. Under the same reaction conditions, when 2-bromoaniline was subjected to react with carbodiimide **3**, almost quantitative yield (97%) of the corresponding product **5h** was observed (Table 2). In contrast, 2-hydroxyaniline did not react at all with carbodiimide **3** to afford the guanidine product **5i** (Table 2).

Further, we extended the substrate scope of the catalytic guanylation reaction of various aniline derivatives with *N,N′*-diisopropylcarbodiimide (DIC) to realize the corresponding guanidine derivatives (Table 2). In a fashion similar to that observed with *N,N′*-DCC, 4-methylaniline, 4-isopropylaniline, or aniline was reacted under the standardized conditions with DIC to obtain the corresponding product **6a**, **6b**, or **6c** in excellent yields of 97%, 89%, and 98%, respectively. Under the standardized conditions, 2-methoxy-, 2,6-dimethyl-, and 2,6-diisopropylaniline yielded 93%, 86%, and 81% of the corresponding product **6d**, **6e**, or **6f** (Table 2). This result suggests that introduction of a more sterically hindered group in aniline moiety somewhat suppresses the yield of the

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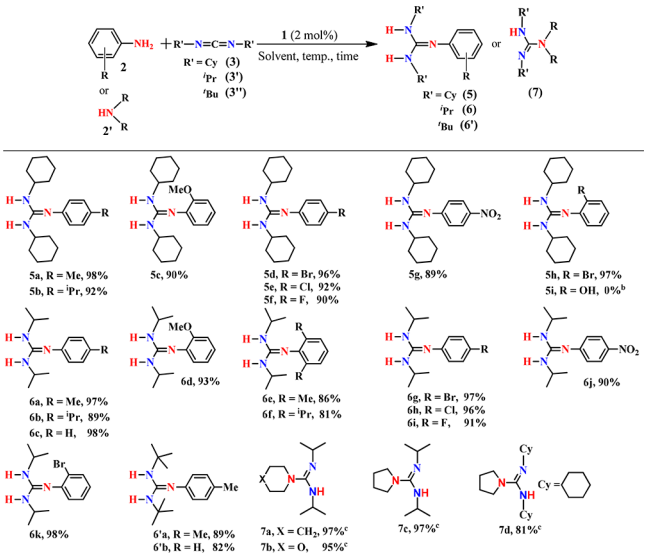
Table 2. Catalytic Guanylation Reaction of Primary Aromatic Amines or Secondary Aliphatic Amines with Carbodiimides[a]



[a]Reaction conditions unless specified otherwise: primary aromatic amines (2 mmol), *N,N′*-dicyclohexylcarbodiimide or *N,N′*-diisopropylcarbodiimide (2 mmol), complex **1** (2 mol%), toluene (5 mL), 25 °C, 1 h, N_2 atmosphere. All products were isolated by extracting with ether. [b]NMR yield. [c]Secondary amines (2 mmol), *N,N′*-dicyclohexylcarbodiimide or *N,N′*diisopropylcarbodiimide or *N,N′*−ditertiarybutylcarbodiimide, complex **1** (2 mol%), neat condition, 60 °C, 6 h, N_2 atmosphere. All products were isolated by extracting with ether.

guanidine product (**6d**−**6f**). Moreover, when aniline containing electron-withdrawing substituents such as 4-bromo, 4-chloro, 4-fluoro, or 4-nitro was subjected to react with DIC under the same reaction conditions, the catalytic guanylation products **6g**, **6h**, **6i**, and **6j**, respectively, were achieved in high yield (91−97%, Table 2). The incorporation of an electron-withdrawing substituent such as bromo at the *o*-position does not alter the yield of the corresponding guanidine product **6k** (98%). When a bulkier carbodiimide such as *N,N′*-di-*tert*-butylcarbodiimide (DTC) was subjected to react with *p*-toluidine or aniline under the optimized conditions for catalytic guanylation reaction, a very good isolated yield of the corresponding product **6′a** (89%) or **6′b** (82%) was realized. Overall the catalytic activity of complex **1** for primary amines is by and large comparable to that reported earlier with $AlMe_3$,[42] except in the case of bulkier amines such as 2,6-dimethylaniline. A control experiment under identical conditions using 2 mol% $AlMe_3$ revealed that a sterically hindered substrate such as 2,6-dimethylaniline leads to only 25% yield of the desired product, whereas the present catalyst **1** leads to an 86% yield.

Given the importance of guanidine derivatives as essential structural moieties in various drugs and natural products, next we probed the catalytic guanylation reaction of secondary aliphatic amines with different carbodiimides.[64−66] It is well established that secondary amines are less reactive than primary amines in guanylation reaction of carbodiimides.[67] Here, we have investigated the substrate scope for cyclic secondary amines with 2 mol% of **1** at higher temperature (60 °C) under neat conditions. When cyclohexylamine or morpholine was reacted with DIC for 6 h, the corresponding guanidine product **7a** or **7b** was realized in 97% or 95% isolated yield (Table 2). Under the same reaction conditions, pyrrolidine afforded 97% yield of **7c** with DIC, whereas 81% yield of **7d** was obtained with DCC. It implies that steric interaction lowers the yield of the guanylation product for DCC.

Furthermore, to check whether the catalyst **1** remains active over several catalytic cycles, we assessed its longevity for the catalytic guanylation reaction. In this study, we carried out five successive catalytic runs using 2 mol% of catalyst loading in an NMR tube, and to maintain the homogeneity, this reaction was performed at 60 °C. After every 15 min time interval, we checked the conversion to the guanidine product through ^{1}H NMR in C_6D_6 and added a fresh batch of both the substrates DCC and *p*-toluidine under an inert atmosphere without adding any additional catalyst into the reaction mixture. The ^{1}H NMR spectrum after every 15 min time interval indicates a complete consumption of the substrates for three successive catalytic runs (Figure 2), decreasing after the third cycle, and

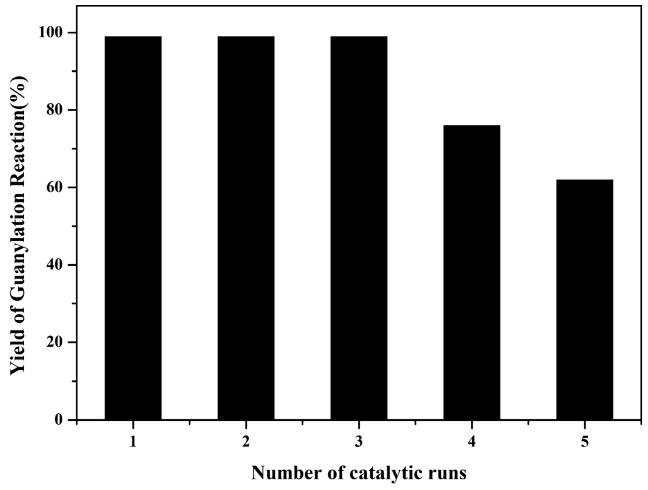


Figure 2. Longevity of the catalyst, tested by monitoring the time required for complete consumption of substrates by ^{1}H NMR spectroscopy in five consecutive catalytic cycles. Reaction conditions: 2 mol% complex **1**, *N,N′*-dicyclohexylcarbodiimide (0.2 mmol), *p*-toluidine (0.2 mmol), and 600 μL of benzene-d_6 as solvent at 60 °C. After completion of each catalytic cycle, fresh *N,N′*-dicyclohexylcarbodiimide (0.2 mmol) and *p*-toluidine (0.2 mmol) were added without addition of any catalyst. Yields were determined for each cycle after 15 min by recording the ^{1}H NMR spectrum of the reaction mixture.

reaching almost 60% after the fifth run. This longevity test clearly demonstrates that the catalyst stays active for at least three consecutive catalytic runs without losing its efficacy.

Next, the catalytic guanylation reaction was performed between DCC and *p*-toluidine in the presence of catalyst **1** at room temperature in C_6D_6 in an NMR tube, and the conversion was monitored by ^{1}H NMR spectroscopy at every 5 min time interval. The plot of NMR yield of guanylation product (%) vs time (min) clearly suggests that the reaction proceeds very fast in the initial 5 min, and then the rate of conversion gradually decreases until the maximum is reached within 1 h (Figure 3).

To explore the mechanistic course of the hydroamination of carbodiimide catalyzed by **1**, we embarked on a tandem experimental and computational approach. In this study, we performed several stoichiometric reactions. At first, when

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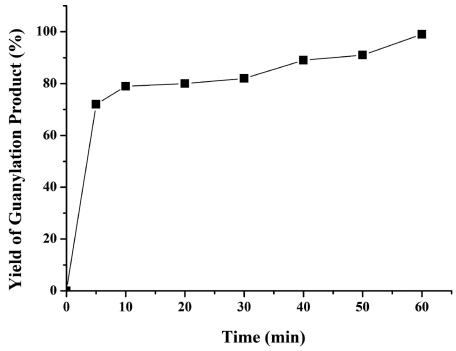
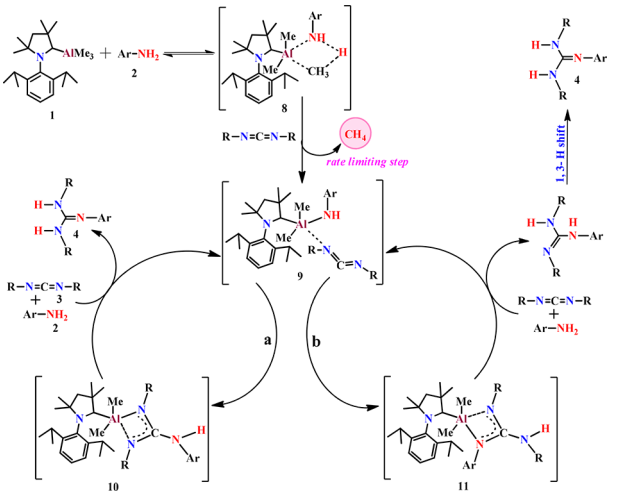


Figure 3. Plot of the yield of the guanylation product (%) vs time (min) as monitored by ^{1}H NMR spectroscopy.

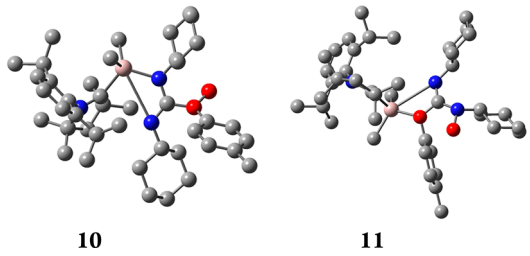
catalyst **1** was subjected to react with DCC in a 1:1 ratio in benzene-d_6, no change in the ^{1}H NMR spectrum was found, which suggests no reaction between catalyst **1** and DCC (SI, Figure S55). However, the reaction between complex **1** and *p*-toluidine in a 1:1 ratio in benzene-d_6 revealed a sharp change in the ^{1}H NMR spectrum within 10 min, and we observed a new peak at δ 0.19 ppm, indicating the formation of methane gas[42,68] (SI, Figure S56). Furthermore, the 1:1 mixture of **1** and *p*-toluidine showed a resonance at −0.39 ppm corresponding to Al-Me peak, shifted to the deshielded region as compared to the Al-Me resonance in **1** (δ −0.54 ppm). Based on this observation, we proposed that the first step of the catalytic cycle is formation of an Al-amido complex under evolution of methane via the four-centered **TS-8**, which subsequently reacts with DCC to form the intermediate **9**, where carbodiimide is coordinated with Al (Scheme 2). Such

Scheme 2. Plausible Mechanism for Catalytic Hydroamination of Carbodiimides



Al-amido bond formation under methane evolution was proposed in earlier reports.[19,42] The computationally optimized (M06/6-31G(d)/IEFPCM level of theory) structure of **TS-8** clearly exposes the elongation of Al−Me bonds of **1** upon addition of *p*-toluidine, and it favors the evolution of methane gas (see SI, Figure S58 and Table S2).

The intermediate **9** can subsequently undergo nucleophilic attack by the amido N to the DCC carbon, resulting in two possible intermediates, **10** and **11**. We undertook a density functional theory (DFT) study to understand further details on this step. DFT study suggests that path **b**, leading to formation of intermediate **11**, is more favorable thermodynamically as compared to the path **a**, where the intermediate complex **10** is proposed (Figure 4). The Gibbs free energy difference



10 **11**

Figure 4. Computationally optimized structures of intermediates **10** and **11** for nucleophilic attack of arylamido N atom to carbodiimide. All hydrogens except for arylamido N−H have been omitted for clarity.

between **11** and **10** was calculated as −0.33 eV, indicating a preference for **11** which does not necessitate the cleavage of an Al−amido bond. Intermediate **11**, upon further consumption of both the substrates carbodiimide and *p*-toluidine, yields the product **4** through a 1,3-H shift, and the intermediate **9** is regenerated.

CONCLUSIONS

In conclusion, we have developed an efficient cyclic (alkyl)-amino carbene complex of aluminum(III) which can guanylate various primary arylamines and secondary aliphatic amines. The catalytic reactions were accomplished under mild reaction conditions with a wide range of amine substrates. The catalyst remained active for three successive catalytic runs without any loss of its catalytic activity. A combined experimental and theoretical investigation discloses that the hydroamination reaction of carbodiimide proceeds through the elimination of methane. The present methodology may be considered as an inexpensive and convenient way to prepare guanidine.

EXPERIMENTAL SECTION

General Methods and Instrumentation. Unless stated otherwise, reactions were performed in flame-dried glassware under an oxygen-free atmosphere (N_2) using standard Schlenk techniques or inside an MBraun glovebox maintained below 0.1 ppm of O_2 and H_2O level. All solvents were distilled from Na/benzophenone prior to use. Trimethylaluminum (2.0 M in toluene) solution was purchased from Sigma-Aldrich. All other chemicals were purchased from commercial sources and used as received. The liquid carbodiimides and amines were distilled from CaH_2 twice and stored over 4 Å molecular sieves before use. Elemental analysis was carried out using a PerkinElmer 2400 CHN analyzer, and sample was prepared by keeping them under reduced pressure (10^{-2} mbar) overnight. The melting point was measured in a sealed glass tube on a Büchi B-540 melting point apparatus and was uncorrected. Deuterated solvents were purchased from Cambridge Isotope Laboratories, dried by sodium/potassium alloy, and stored over 4 Å molecular sieves prior to use. Crystallographic data for the structural analysis of **1** have been deposited at the Cambridge Crystallographic Data Center (CCDC No. 1571838). These data can be obtained free of charge from the Cambridge Crystallographic Data Center. NMR spectra were recorded on a JEOL ECS 400 MHz spectrometer and on a Bruker Avance III 500 MHz spectrometer. All chemical shifts were reported in ppm using tetramethylsilane as a reference. Chemical shifts (δ) downfield from the reference standard were assigned positive values.

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Synthesis of Complex 1, (*c*AAC)AlMe$_3$. In a glovebox, an oven-dried 50 mL Schlenk flask was charged with cyclic (alkyl)amino carbene (300 mg, 1.04 mmol), and dry toluene (10 mL) was added through a cannula at 25 °C in nitrogen atmosphere. Subsequently, $AlMe_3$ solution (2.0 M in toluene; 0.62 mL, 1.1 mmol, 1.06 equiv) was added dropwise in the reaction mixture at −78 °C. The reaction mixture was then stirred overnight, and during the course of the reaction, the color changed to pale yellow. After removal of all the volatiles under high vacuum, the pale yellow colored compound was extracted in dry hexane (25 mL) followed by filtration through a Celite pad, and the reaction mixture was concentrated to ca. 8 mL. Storage of this reaction mixture at 0 °C for 2−3 days afforded colorless crystals (262 mg, 70%). Complex **1** decomposes at 125 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 7.13 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 7.7 Hz, 2H), 2.71−2.61 (m, 2H), 1.42 (s, 6H), 1.36−1.32 (m, 9H), 1.06 (d, J = 6.9 Hz, 6H), 0.82 (s, 6H), −0.54 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 254.0, 145.4, 134.7, 129.9, 125.4, 80.9, 56.5, 50.9, 29.1, 28.8, 28.7, 26.0, 24.3, −5.0 ppm. Anal. Calcd for $C_{23}H_{41}AlN$ (358.56): C, 77.04; H, 11.53; N, 3.91. Found: C, 76.95; H, 11.48; N, 3.92.

General Procedure for the Catalytic Hydroamination of Primary Arylamines. A 25 mL Schlenk tube was charged with complex **1** (0.0143 g, 2 mol%, 0.04 mmol), carbodiimide (2.0 mmol), and aromatic primary amine (2.0 mmol) followed by the addition of toluene (5.0 mL) under N_2 atmosphere. The resulting mixture was stirred at 25 °C for 1 h. After the reaction was completed, the reaction mixture was extracted with ether and filtered to give a clean solution. After removal of the solvent under vacuum, the final products were further purified by washing with diethyl ether or hexane.

General Procedure for the Catalytic Hydroamination of Secondary Amines. A 25 mL Schlenk tube was charged with complex **1** (0.0143 g, 2 mol%, 0.04 mmol), carbodiimide (2.0 mmol), and secondary amine (2.0 mmol) under N_2 atmosphere. The resulting mixture was stirred at 60 °C for 6 h under neat conditions. After the reaction was completed, the reaction mixture was extracted with ether and filtered to give a clean solution. After removal of the solvent under vacuum, the final products were further purified by washing with diethyl ether or hexane.

Procedure for Catalyst Longevity Experiment. A screw-capped NMR tube was charged with catalyst **1** (2 mol%), *p*-toluidine (0.2 mmol), DCC (0.2 mmol), and hexamethylbenzene as an internal standard (0.033 mmol) in C_6D_6 (0.6 mL). The catalytic reaction was performed at 60 °C by applying *in situ* recycling methodology. We monitored the longevity of catalyst **1** by performing several catalytic runs within the same reaction pot to test whether the catalyst remained live for several catalytic cycles or not. We repeated the catalysis up to five times by charging a fresh batch of substrates after each catalytic run in the same reaction vessel but without adding more catalyst into the reaction mixture. After full consumption of the substrate, a fresh batch of substrates was introduced in the reaction medium. After each 15 min interval, conversion into the product was checked by recording a ^{1}H NMR spectrum of the reaction mixture. The catalytic runs were repeated for five successive cycles. It was found that catalyst **1** remained catalytically active up to three consecutive runs (Figure 2) without losing any catalytic activity as evidenced from ^{1}H NMR spectroscopy. This result clearly indicates that the catalyst stays live for several catalytic cycles in the reaction medium.

Computational Details. Gaussian 09 software[69] was used to perform numerical calculations at the DFT level with the M06 functional[70] in toluene medium within the IEFPCM model.[71] The 6-31G(d)[72] basis set was employed for optimizing the molecular structures without any symmetry constraints. The real harmonic vibrational wavenumbers obtained for each optimized structure confirmed the energy-minimized geometry. An isosurface value of 0.03 has been used to visualize the frontier Kohn−Sham molecular orbitals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00358.

Spectroscopic data, scanned spectra, X-ray crystallographic data for **1**, and details on DFT calculations (PDF)

Cartesian coordinates of calculated structures (XYZ)

JMol structure for **TS-8** (MOL)

JMol structure for intermediate **10** (MOL)

JMol structure for intermediate **11** (MOL)

Accession Codes

CCDC 1571838 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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