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Elucidation of Carbene Ambiphilicity Leading to the Discovery of Reversible Ammonia Activation

Jonathan P. Moerdyk, Garrett A. Blake, Daniel T. Chase, and Christopher W. Bielawski*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: An *N*,*N*′-diamidocarbene (DAC) was found to activate a broad range of primary as well as secondary aliphatic and aromatic amines. The relative rates measured for the insertion of the DAC into the primary amines were consistent with an electrophilic activation mechanism; in contrast, the DAC functioned as a nucleophile upon treatment with secondary aryl amines. Collectively, these results constituted the first ambiphilic process for an isolable carbene. By comparison, an analogous diaminocarbene was found to serve exclusively as a nucleophile under similar conditions and led to the discovery of the first organic reagent to reversibly activate ammonia.

While the activation of ammonia has garnered immense interest from both fundamental and practical perspectives, the process remains a challenging endeavor due to the high N−H bond strength (104 kcal/mol) and the propensity of ammonia to form Werner-type complexes with electrophilic reagents, particularly transition metals.[1,2] As first demonstrated by Bertrand with the alkylaminocarbenes[3] (AACs; e.g., **1** in Figure 1) in 2007[4] as well as more recently by our group with

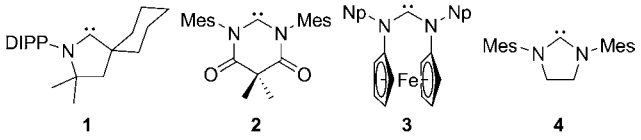


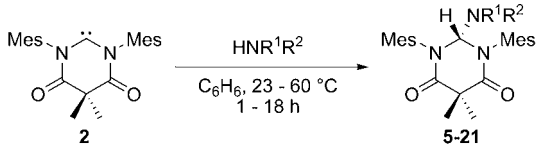
Figure 1. Structures of various carbenes: DIPP = 2,6-diisopropylphenyl, Mes = 2,4,6-trimethylphenyl. Np = neopentyl.

the diamidocarbenes[5] (DACs; e.g., **2**)[6] and Siemeling with the ferrocenophane **3**,[7] isolable carbenes[8] have emerged as attractive, metal-free alternatives for activating ammonia and other small molecules. Bertrand proposed that the high nucleophilicity intrinsic to the AACs facilitates N−H insertion processes and prevents the formation of Lewis acid−base adducts.[4,8d] However, high nucleophilicity may not be the only criterion for N−H activation, as conventional N-heterocyclic carbenes (NHCs), which are also strongly nucleophilic,[9] have traditionally been considered to be inert toward ammonia and have even been generated in liquid NH_3.[8d,10] Regardless, little is known about the scope[11] of stable carbene N−H insertion chemistry or its mechanism,[4] which encumbers optimization and utilization efforts.

We envisioned that the DACs, which feature relatively low HOMO and LUMO levels,[9] may function as electrophiles or ambiphiles in N−H activation processes and offer new organocatalyzed synthetic strategies,[12] small-molecule activation pathways,[8d] and other transformations. While Moss established the ambiphilicity[13] of transient chloroalkoxycarbenes more than three decades ago through elegant olefin cyclopropanation studies,[14] isolable carbenes have not hitherto displayed analogous reactivities within a given transformation.[15] Herein, we show that an isolable DAC is capable of undergoing N−H insertion processes via nucleophilic as well as electrophilic pathways. Moreover, through a comprehensive comparison to a prototypical NHC, we disclose the first example of an organic compound activating ammonia in a reversible manner.

Our efforts began by exploring the ability of a DAC to react with a broad range of amines. As summarized in Scheme 1, the

Scheme 1. Summary of N−H Activation Reactions using 2



5: R^1 = H, R^2 = nBu, 86%
6: R^1 = H, R^2 = Ph, 73%
7: R^1 = H, R^2 = 4-Me_2NPh, 89%
8: R^1 = H, R^2 = 4-MeOPh, 88%
9: R^1 = H, R^2 = 4-MePh, 97%
10: R^1 = H, R^2 = 4-tBuPh, 97%
11: R^1 = H, R^2 = 4-FPh, 90%
12: R^1 = H, R^2 = 4-MeSPh, 90%
13: R^1 = H, R^2 = 4-ClPh, 97%
14: R^1 = H, R^2 = 4-BrPh, 95%
15: R^1 = H, R^2 = 4-CF_3Ph, 88%
16: R^1 = R^2 = Et, 69%
17: R^1 = R^2 = nBu, 72%
18: R^1 = Me, R^2 = Ph, 55%
19: R^1 = R^2 = 4-MeOPh, 88%
20: R^1 = R^2 = Ph, 59%
21: R^1 = R^2 = 4-BrPh, 87%

N−H insertion products derived from **2** and a variety of alkyl (**5**, **16**, **17**) as well as electron-rich and -deficient aryl amines (**6**−**15**, **18**−**21**) were obtained under mild conditions in good to excellent yield (55−98%). Mechanistically, the N−H insertion processes may reside between two distinct, asynchronous pathways, as depicted in Scheme 2. Polarization of an amino N−H bond followed by the formation of a C−N bond (pathway A) would be expected if **2** functioned as the nucleophile. Alternatively, the amine could attack electrophilic **2** to form an aza-ylide-type intermediate followed by proton transfer (pathway B). To differentiate, we evaluated the kinetics

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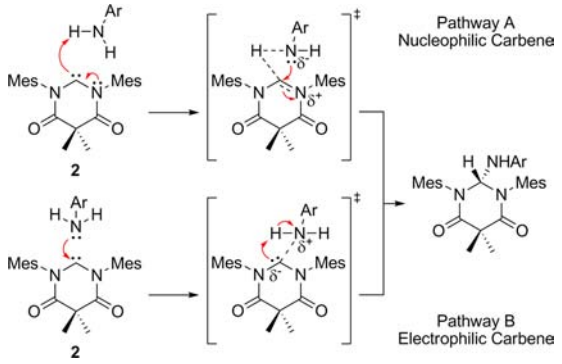
Scheme 2. Mechanistic Pathways Leading to N−H Activation



of the aforementioned N−H insertion reactions using ^{1}H NMR spectroscopy. Unfortunately, due to the rapid rate of N−H insertion, attempts to determine the rate constants (k) for the formation of **5**−**15** under pseudo-first-order conditions via variable-temperature (VT) ^{1}H NMR spectroscopy were unsuccessful. For example, treating a C_7D_8 solution of **2** ($[\mathbf{2}]_0$ = 66 mM) with 10 equiv of aniline was found to quantitatively form **5** within 120 s at −80 °C. However, the rate of DAC insertion into secondary amines was relatively slow and enabled the calculation of the corresponding rate constants for the formation of **16**−**21** in C_6D_6 at 30 °C (Table 1).

Table 1. Observed Second-Order Rate Constants (k)[a]

product	R^1	R^2	k (M^{-1} min^{-1})
16	Et	Et	0.036
17	Bu	Bu	0.009
18	Me	Ph	0.0009
19	4-OMe-Ph	4-OMePh	0.62
20	Ph	Ph	0.82
21	4-Br-Ph	4-Br-Ph	≥3.5[b]

[a]Conditions: $[\mathbf{2}]_o$ = 0.066 M, $[amine]_o$ = 0.66 M, 30 °C, C_6D_6, 1 h. [b]Rate constant calculated on the basis of ≥99% conversion within 2 min.

Inspection of the kinetic data revealed that the rate constants measured for reactions involving electron-deficient diarylamines were higher than those measured for analogous reactions involving electron-rich analogues and were consistent with **2** functioning as a nucleophile. Moreover, a small kinetic isotope effect (KIE) of 1.5 was measured for reactions that utilized diphenylamine or its d_1 analogue as substrates, consistent with an early transition state wherein the carbene polarized the N−H (D) bond prior to C−N bond formation.[16] Surprisingly, however, *N*-methylaniline was found to be less reactive toward **2** than the more basic dibutyl- or diethylamine, which suggested to us a change in the insertion mechanism. Thus, a series of competition studies were performed wherein a C_6D_6 solution of **2** was added dropwise to a vigorously stirred mixture of aniline and a para-substituted aniline derivative (5 equiv of each aniline) in C_6D_6 at 23 °C. The proton signals corresponding to the resultant products **6** and **7**−**15** were then integrated (see the Supporting Information for details) and used to calculate the molar ratio of the para-substituted product versus **6** (defined as P_R/P_H, where R is the corresponding para substituent). As shown in Figure 2A, an inverse relationship between the $\log(P_R/P_H)$ values and the corresponding

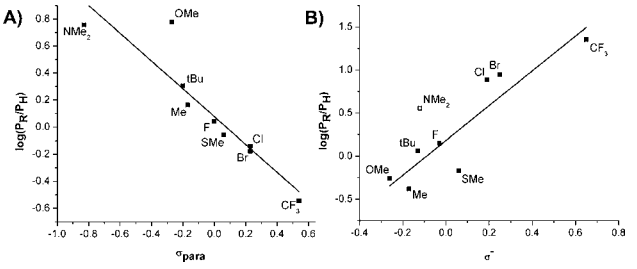
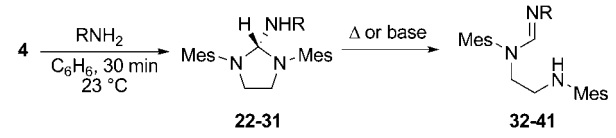


Figure 2. Plots of the logarithm of the product ratios (P_R/P_H) versus (A) σ_{para} for the reaction of DAC **2** or (B) σ^- for the reaction of NHC **4** with a mixture of aniline and the indicated para-substituted derivative (5 equiv each).[20] Conditions: C_6D_6, 23 °C. The data points are the numerical average of three separate experiments.

Hammett substituent parameters, σ_{para},[17,18] was observed, which indicated that the DAC **2** served as the electrophile in the aforementioned aniline N−H insertion processes (cf. pathway B).

For comparison, the analogous diaminocarbene **4** was treated with various aniline derivatives in C_6D_6 under similar conditions to those described above. A broad range of substrates were observed to undergo activation (see Scheme 3), although the products were found to ring-open (**32**−**41**)

Scheme 3. Summary of N−H Activation Reactions using 4



R = X

22: X = H, 92%
23: X = NMe_2, 82%
24: X = OMe, 86%
25: X = tBu, 74%
26: X = Me, 79%
27: X = SMe, 88%
28: X = F, 88%
29: X = Cl, 84%
30: X = Br, 80%
31: X = CF_3, 81%

32: X = H, 93%
33: X = NMe_2, 83%
34: X = OMe, 81%
35: X = tBu, 76%
36: X = Me, 75%
37: X = SMe, 84%
38: X = F, 79%
39: X = Cl, 79%
40: X = Br, 85%
41: X = CF_3, 78%

upon prolonged standing or in the presence of excess base. Thus, to elucidate the N−H activation mechanism involving **4**, a series of competition experiments involving aniline and its derivatives with isolated **4** (i.e., devoid of the residual base used for its synthesis) were conducted in a manner analogous to those described above for the DAC. For these studies, the P_R/P_H ratios were calculated <15 min after the addition of **4** to a C_6D_6 solution of the amines, as the N−H insertion process was found to be reversible over the course of hours via ^{1}H NMR scrambling experiments.[19,20] As shown in Figure 2B, the relationship between $\log(P_R/P_H)$ versus σ^- was linear and positive,[21] consistent with the NHC functioning as a nucleophile (cf. pathway A).

To corroborate this conclusion and to preclude the influence of amine exchange or other side reactions, the rate constants for the reaction between the NHC **4** and various aniline derivatives were determined at −25 °C in C_7D_8 using VT NMR spectroscopy. In general, the NHC was treated with excess amine (≥10 equiv) and the corresponding reaction was monitored over time, with the exception of the 4-trifluoromethylaniline reaction, which was found to proceed too rapidly under these conditions. Consistent with the

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aforementioned competition studies, the measured rate constants were found to increase in accordance with the electron-withdrawing nature of the para substituent. Indeed, a plot of the logarithm of the ratio of the observed rate constants (k_R/k_H), where R is the corresponding para substituent, against σ^- resulted in a linear, positive relationship (Figure 3).

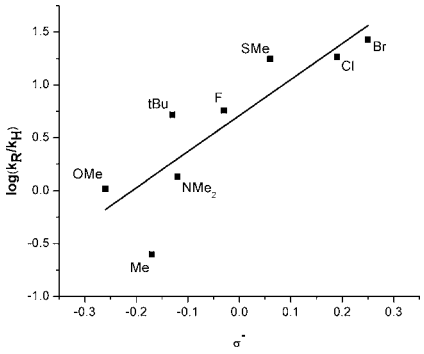


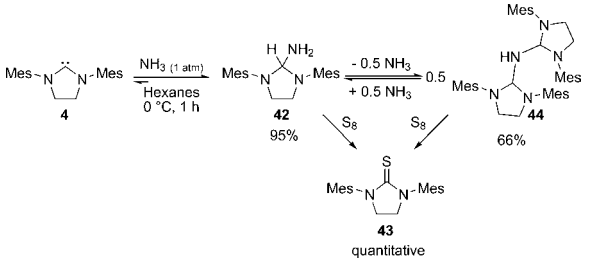
Figure 3. Plot of the logarithm of the rate constant ratio (k_R/k_H) versus σ^- for the reaction of **4** with aniline and a variety of para-substituted anilines. Conditions: C_7D_8, −25 °C.

Collectively, these results were consistent with a mechanism analogous to pathway A shown in Scheme 2, wherein the NHC functioned as the nucleophile during the N−H activation process.

While more basic amines should disfavor a nucleophilic carbene insertion mechanism, Merten reported in 1972 that the electron-rich olefin 1,1′,3,3′-tetraphenyl-2,2′-bisimidazolinylidene (i.e., an NHC dimer) inserted into cyclohexylamine.[22] This result suggested to us that **4** may also react with relatively basic amines, including ammonia (pK_a = 41).[23] To test, a solution of the NHC in C_6D_6 ($[\mathbf{4}]_0$ = 0.2 M) was transferred to a medium-pressure NMR tube equipped with a PTFE screw cap. Upon cooling to −78 °C, the atmosphere was removed under reduced pressure and replaced with ammonia upon warming to 23 °C. Complete consumption of **4** was observed within 30 min at 23 °C and was accompanied by the appearance of new ^{1}H NMR signals recorded at 1.15 (d, 2H) and 5.44 ppm (t, 1H), consistent with the formation of the N−H-inserted product **42**, as well as a minor product with a doublet at 5.22 ppm. Moreover, the addition of excess sulfur to the crude reaction mixture cleanly and quantitatively afforded the thiourea **43**.[24] These results led us to conclude that the ammonia activation process was reversible and that the secondary product formed was the doubly inserted ammonia adduct **44** (Scheme 4).

To verify the reversibility of the aforementioned reaction, **42** was isolated in 95% yield by mixing **4** (0.4 mmol) in hexanes (5 mL) under an atmosphere of ammonia at 0 °C for 1 h followed by the rapid removal of the solvent. Subsequent stirring of **42** in C_6H_6 under nitrogen for 48 h followed by removing the residual solvent and washing the residue with pentane afforded **44** in 66% isolated yield, as indicated by the observation of the aforementioned doublet as well as a triplet at 2.13 ppm in the corresponding ^{1}H NMR spectrum. Subsequent addition of ammonia to **44** afforded a mixture containing **42** and **44** which, in combination with the formation of thiourea **43** upon stirring either **42** or **44** (or a mixture thereof) with elemental sulfur, supported the reversibility of the N−H insertion processes. In parallel with the aforementioned experiments, a C_6D_6 solution of **42** was frozen at −30 °C before adding a suspension of sulfur in C_6D_6 and sealing the NMR tube. When the temperature was raised to room temperature, the ^{1}H NMR spectrum of the product mixture revealed the formation of **43** as well as a broad triplet at −0.17 ppm characteristic of ammonia. The presence of ammonia was also observed in the headspace of a standing solution of **42** in benzene via gas chromatography and high-resolution mass spectrometry (Figure S25, Supporting Information).[25] While it is tempting to suggest that **4** activated ammonia through a nucleophilic carbene pathway and that the reversibility is due to the relatively high LUMO of the NHC, a change in mechanism wherein **4** functioned as an electrophile cannot be excluded.[26] Regardless, the result adds to the paucity of carbenes reported to activate ammonia and is the first example to do so in a reversible manner.

Scheme 4. Reversible Ammonia Activation



In summary, a DAC was found to function as a nucleophile in the activation of diaryl N−H bonds and as an electrophile when treated with anilines, which together comprised the first example of an isolable carbene functioning as an ambiphile within a given class of transformation. While nearly all current applications of isolable carbenes originate from their nucleophilic properties, the results herein validate the ability of isolable carbenes to react as electrophiles. Such electrophilic characteristics are expected to inspire new applications of stable carbenes wherein the carbene serves primarily as an electrophile. Moreover, the ambiphilic N−H activation processes described above underscore the potential to control product selectivity and scope through the modification of the carbene's electronic properties.

In addition to activating aniline N−H bonds via a nucleophilic mechanism, an NHC was found to reversibly activate ammonia under mild conditions. Dynamic N−H insertion is an important step toward understanding the role and mechanism of carbenes in transformations such as amidations[27] and incorporating ammonia and other amines into organocatalytic processes (e.g., metal-free aminations or hydroaminations)[28] wherein the transfer or release of the activated/functionalized substrate is essential for catalytic turnover. Exploiting the reversibility of the N−H insertion process may also find utility in sensing or the latent release of amines, particularly gaseous ammonia, from a solid precursor.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving additional experimental details, Hammett plots, kinetic plots, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

bielawski@cm.utexas.edu

Notes

The authors declare no competing financial interest.

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(16) Adding **2** to a stirred mixture of 5 equiv of diphenylamine and 5 equiv of diphenylamine-d_1 afforded a 62:38 mixture of the corresponding H:D products containing **20** and a measured KIE value of 1.3.

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(18) As the negative slope reflected the build-up of positive charge at the amine nitrogen that could not be resonance delocalized, the σ_{para} value (which also provided the best linear fit) was utilized rather than σ^- or σ^+ values, although negative slopes were observed in all cases (see the Supporting Information).

(19) For example, the addition of 5 equiv of 4-chloroaniline to **4** in C_6D_6 at 23 °C resulted in the quantitative formation of **29**; subsequent addition of aniline (5 equiv) resulted in a 9/1 mixture of **29** and **22** after 1 h at 23 °C. Similar studies with **2** showed no detectable scrambling, even after several days.

(20) Even in the absence of exogenous base, treating a mixture of *N*,*N*-dimethyl-*p*-phenylenediamine and aniline to **4** irreversibly afforded the ring-opened products **32** and **33** rather than **22** and **23**. The reversibility of the N−H insertion combined with the irreversibility of the ring-opening reaction indicated that the P_{NMe_2}/P_H ratio may have been influenced by thermodynamic rather than kinetic factors, and therefore these data were excluded from the fit. However, including the P_{NMe_2}/P_H data still afforded a linear fit with a positive slope of similar magnitude (see the Supporting Information).

(21) As the positive slope reflected the buildup of negative charge that could be resonance-stabilized through delocalizing the amine lone pair into the aromatic ring, the σ^- value (which also provided the best linear fit) was utilized rather than σ_{para} or σ^+ values, although a positive slope was observed in all cases (see the Supporting Information).

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(25) Similarly, gas chromatography and HRMS analysis of the reaction mixture of **42** and sulfur at room temperature in benzene also confirmed the presence of ammonia.

(26) 1,3-Dimesitylimidazolylidene was found to be unreactive toward aniline or ammonia under conditions similar to those described above.

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