Alkane Activation

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Metal-Free Conversion of Methane and Cycloalkanes to Amines and Amides by Employing a Borylnitrene**

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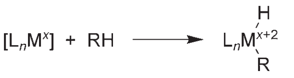
The selective transformation of methane into more reactive molecules, considered to be one of the "holy grails" of chemistry,[1] lies at the heart of our understanding of chemical reactivity and has potentially far-reaching practical implications. The challenge in achieving this transformation arises from the low reactivity of methane.[2] An economically feasible process for C–H activation is not available, but is highly desirable owing to the abundance of methane as the major constituent of natural gas. Although natural gas is the most abundant, low-cost, carbon-based feedstock, most basic chemicals are produced today indirectly from petroleum in energy-extensive processes.[3]

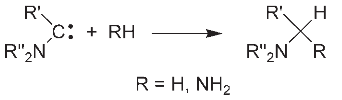
While superacids,[4] free radicals and radical cations,[2a] and enzymatic systems[2a] can be used to functionalize simple hydrocarbons, much success has been achieved in the field of transition-metal chemistry.[2c,5] A typical theme of transition-metal-mediated C–H bond activation is the oxidative addition of an alkane to a coordinatively unsaturated metal center [L_nM^x] [Eq. (1)], which is usually generated in situ by thermal or photochemical decomposition of a suitable precursor.[5b] The alkane RH acts then as a nucleophile towards the electrophilic metal center [L_nM^x] [Eq. (1)].



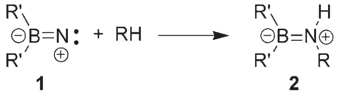
$$[L_nM^x] + RH \longrightarrow L_nM^{x+2}(H)(R) \qquad (1)$$

Frey et al. recently recognized the similarity of certain stable carbenes and coordinatively unsaturated metal centers in the splitting of dihydrogen and ammonia [Eq. (2)].[6]

This analogy may be extended to subvalent nitrogen compounds: the single nitrogen center of an electrophilic singlet borylnitrene **1** has a low-lying unoccupied and a high-lying occupied molecular orbital.[7] Here we show that certain borylnitrenes **1** are good reagents for the transformation of unactivated C(sp^3)–H bonds of hydrocarbons, including methane, according to Equation (3).



(2)



(3)

Nitrenes, short-lived reactive intermediates, can be generated from azides[8] and are known to undergo C–H bond-insertion reactions.[9] The intermolecular insertion of free nitrenes into C–H bonds, however, is usually not of synthetic value: for example, photolysis of phenyl azide in hydrocarbon solvents produces primarily polymeric materials.[10] Only very electrophilic nitrenes yield the C–H insertion product with hydrocarbon solvents in appreciable amounts.[11–14]

The current state of the art[15] in the amidation of C–H bonds thus relies on nitrene surrogates, for example iminoiodanes PhI=NR[16] and aryl azides,[17] in transition-metal-mediated reactions, although metal-free conversions are also known.[18] The groundbreaking work goes back to Breslow and co-workers,[19] who demonstrated in 1982 that cyclohexane can be amidated in 3–6 % yield based on the iminoiodane in the presence of metal porphyrins. Although since then considerable achievements have been made,[15] only a few examples exist in which the C(sp^3)–H bonds of saturated unactivated hydrocarbons can be functionalized in good yields in intermolecular reactions.[20–23]

Borylnitrenes **1** are transient species, which have been trapped successfully.[24] The recently characterized catechol derivative **1a** (Scheme 1), a triplet-ground-state nitrene obtained photochemically from the corresponding azidoborane **3a** under matrix-isolation conditions,[25] showed unusually high reactivity. We ascribed this to the electronic similarity between **1a** in its singlet state and difluorovinylidene, a "superelectrophilic" carbene that inserts into methane and dihydrogen at 20–40 K.[26]

In order to investigate the reaction of **1a** with methane, we isolated azide **3a** in argon doped with methane (1–2 % CH_4 or CD_4) at 10 K. Photolysis of **3a** using UV irradiation ($\lambda = 254$ nm) resulted in the complete disappearance of **3a** and the concomitant formation of nitrene **1a** according to the IR spectra. In addition, a set of new IR signals appears during the photochemical decomposition of **3a** (see Figure 1 as well as Tables S1 and S2, and Figure S2 in the Supporting Information).

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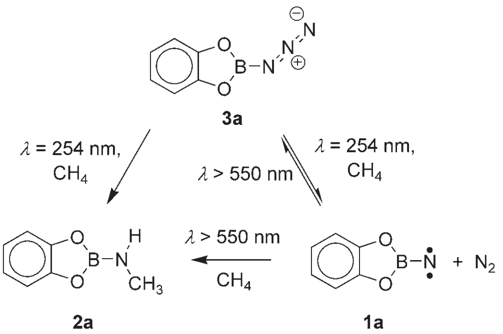
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Photochemistry of azidoborane **3a** in an argon matrix doped with 1–2% methane.

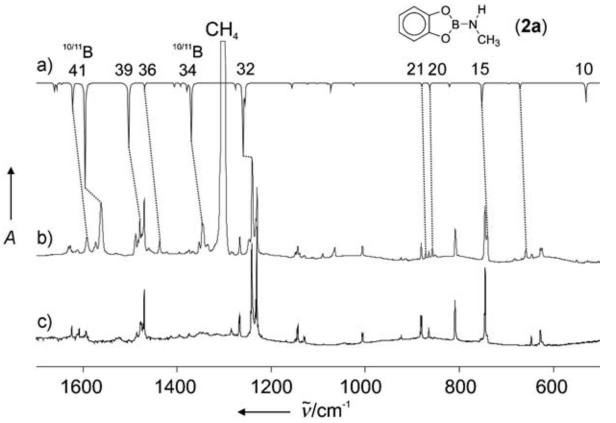
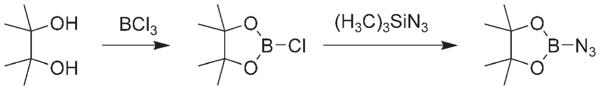


Figure 1. IR spectra obtained from the photolysis of azide **3a** in solid argon at 10 K. a) IR spectrum computed for the C–H insertion product **2a** at the B3LYP/6-311+G** level of theory. The numbers of the assigned vibrational modes (see Table S1 in the Supporting Information) are given on top. b) IR spectrum obtained after three photolysis cycles (254 nm followed by 550 nm) of **3a** in the presence of CH_4 (2% in Ar). c) IR spectrum of borylnitrene **1a** obtained in Ar in the absence of methane.

Based on the signal in the NH-stretching region (ν(N–H): 3480 cm^{-1}, ν(N–D): 2572 cm^{-1}) and the computed IR spectrum, the new spectral features are assigned to the aminoborane **2a**. As **2a** is known to be oligomeric in the solid state and in solution,[27] we have made no attempts to synthesize it independently.

Annealing of the matrix to 35 K did not increase the yield of **2a**, but upon irradiation with visible light ($\lambda > 550$ nm) nitrene **1a** reacted with methane at 10 K to give **2a**. As a side reaction, formation of azide **3a** was also observed under these conditions (Scheme 1).

The high tendency of **1a** to insert into the unreactive C–H bond of methane suggests that this reaction should also be observable under photochemical conditions in solution. To avoid problems associated with the possible oligomerization of catecholates,[27] we investigated the pinacolate system **3b**, which was synthesized as outlined in Scheme 2. Photolysis ($\lambda = 254$ nm) of the novel azide **3b** in (cyclo)alkane solutions at room temperature indeed yielded the expected aminoboranes according to spectral information (see the Supporting Information).[28] The identity of the cyclohexyl (**2b-cy6**) and cyclopentyl (**2b-cy5**) products was confirmed further by single-crystal X-ray analysis (Figure 2).[29]



3b

Scheme 2. Synthesis of azidoborane **3b** (2-azido-4,4,5,5-tetramethyl-1,3-dioxaborolane, $pinBN_3$).

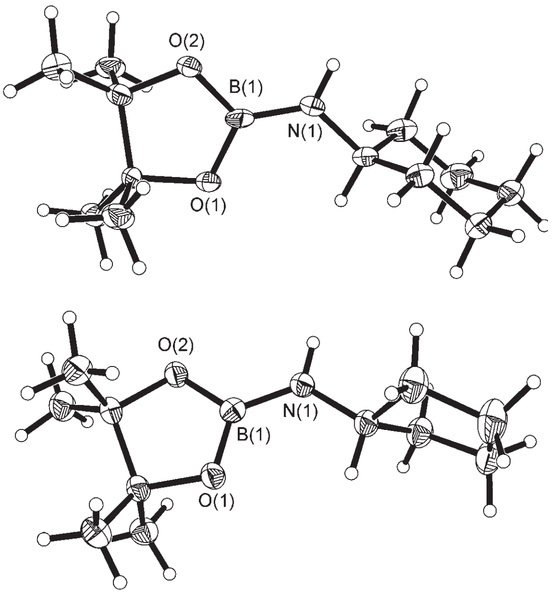


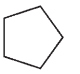
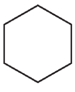
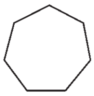
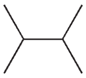
Figure 2. Single-crystal structure of **2b-cy6** (top) and **2b-cy5** (bottom) determined at 108 K and 113 K, respectively.[29] BN bond lengths: 1.386(4) Å (**2b-cy6**) and 1.393(2) Å (**2b-cy5**).

The good yields of up to 85% (Table 1) are remarkable in view of the lower reactivity of most other free nitrenes in intermolecular C–H bond-insertion reactions.[11–13] Phosphoryl nitrenes show reactivity similar to that of borylnitrene **1b**.[14]

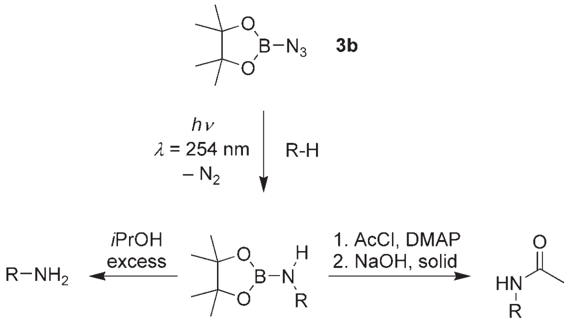
The aminoboranes of type **2b** can conveniently be transformed into primary amines RNH_2 **4** by alcoholysis or into amides RNHCOAc **5** by acylation (Scheme 3). The amidation of the reaction products **2b** to give **5** allows the investigation of the selectivity of the C–H transformation by GC–MS analysis using 2,3-dimethylbutane as the substrate. Comparison with an authentic sample of *N*-(1,1,2-trimethylpropyl)-acetamide shows that the combined yield of C–H insertion products is 74%. The relative amount of insertion is statistical and thus the reaction at the stronger primary C–H bonds yields the major product (Table 1). The observation of the insertion into the primary C–H bonds demonstrates the unusually high reactivity of borylnitrene **1b**. For comparison, the very reactive pentafluorophenyl nitrene inserts exclusively into the tertiary C–H bonds of 2,3-dimethylbutane under similar conditions.[11c]

In summary, this investigation shows that borylnitrenes are very active reagents for intermolecular amination and

Table 1: Yields (in % based on **3b**) of aminoboranes **2b** and organic amides **5** obtained from the reaction of **3b** (pinBN$_3$) with a number of hydrocarbons.

Entry	Substrate	pinBNHR **2b**[a]	CH$_3$CONHR **5**[b]
1		84	77
2		85	83
3		79	75
4		77[c]	69[d]

[a] Yield of isolated product. [b] Amides were obtained from pinBNHR and the RNHB(OH)$_2$ precipitate[28] according to Scheme 3 and were determined by GC–MS based on authentic samples. [c] Combined yield of derivatization products from insertion into primary (63%) and tertiary (11%) C–H bonds. [d] Combined yield of derivatization products from insertion into primary (58%) and tertiary (11%) C–H bonds.



Scheme 3. Derivatization of aminoboranes **2b**. DMAP = *N,N'*-dimethylaminopyridine, Ac = acetyl.

amidation of unactivated C–H bonds. The high yields of insertion products indicate that these insertion reactions are fast relative to the rate of intersystem crossing to the triplet ground state of borylnitrene **1b**.[30] The boryl group fulfills two purposes in this chemistry: 1) it transforms the nitrene into a very active BN vinylidene analogue and 2) it is easily cleaved to yield the desired organic substrate. Borylnitrene **1b** thus allows the efficient one-pot transformation of an alkane into a primary amine or into an amide. We expect that modification of the boryl group will allow utilization of visible-light irradiation and regeneration of the borylazide, and will possibly also provide increased selectivity in this transformation. Investigations on the transition-metal-catalyzed intermolecular aminations using azidoboranes are also underway in our laboratory.

Experimental Section

Detailed descriptions of the matrix isolation experiments and vibrational data of **2a** and [D$_4$]-**2a**, the synthesis and characterization of novel compounds, and the photolysis experiments are given in the Supporting Information.

Caution: Boron azides may be explosive, and appropriate precautions must be taken when handling these compounds.

X-ray diffraction: Single crystals of **2b-cy5** and **2b-cy6** were grown by slow evaporation of the cycloalkane solvent. Intensity data for **2b-cy5** and **2b-cy6** were both collected on an Oxford Diffraction Xcalibur2 CCD employing the ω scan method using Cu$_{K\alpha}$ radiation for **2b-cy6** and Mo$_{K\alpha}$ radiation for **2b-cy5**. The data were corrected for Lorentz, polarization, and absorption (multiscan, compound **2b-cy6** only) effects. **2b-cy6** and **2b-cy5** were solved by using direct methods (SHELXS-97)[31a] and refined by using a full-matrix least-squares refinement procedure (SHELXL-97).[31b] In both compounds, the hydrogen atoms bonded to carbon atoms were placed at geometrically estimated positions while those bonded to nitrogen atoms were found in the Fourier difference synthesis and refined freely with only the distance fixed to the literature value. CCDC 671485 and 671486 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Photolysis in solution and workup: a) Photolysis of **3b**: A solution of **3b** (250 mg, 1.48 mmol) in 30 mL of the cycloalkane was photolyzed in quartz tubes for 16 h with a low-pressure mercury lamp (λ = 254 nm) under an argon atmosphere at room temperature. The pale yellow reaction mixture was then filtered, and the solvent was removed from the filtrate under reduced pressure. Sublimation (70 °C, oil pump) yielded aminoborane **2b**. b) Alcoholysis: A small amount of the photoproduct was dissolved in 1.5 mL of dry isopropanol. The reaction mixture was stirred for 30 min at room temperature, and the formation of the free amine of **4** was confirmed by GC–MS. c) Acylation: After photolysis the soluble and the insoluble products were collected by removal of the hydrocarbon in vacuo and then dissolved in 20 mL of anhydrous Et$_2$O. The catalyst *N,N'*-dimethylaminopyridine (10–20 mg) and acetyl chloride (0.50 mL, 7.03 mmol) were added. The resulting suspension was stirred for 18 h at room temperature. Solid NaOH (1.00 g, 25 mmol) was added, and the reaction mixture was stirred for one more day. Then a solution of hexamethylbenzene (internal standard; 0.240 g, 1.48 mmol) in 20 mL Et$_2$O was added, the mixture was filtered, and the solid was washed with Et$_2$O (3 × 10 mL). The filtrate was separated and the mixture was analysed by GC–MS.

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[28] During the photolysis, variable amounts of solid material precipitated. Based on NMR data (^{1}H, ^{13}C, ^{11}B), solubility, and chemical transformation to the corresponding *N*-alkyl amide, this solid material was tentatively identified as RNHB(OH)$_2$ (see the Supporting Information).

[29] a) **2b-cy6**, R = cyclohexyl: colorless plate, $0.32 \times 0.28 \times 0.04$ mm^3, triclinic, $P\bar{1}$, $a = 5.9731(5)$, $b = 10.7650(9)$, $c = 11.0285(8)$ Å, $\alpha = 79.999(7)$, $\beta = 84.840(7)$, $\gamma = 75.462(7)°$, $V = 675.2(1)$ Å^3, $\rho_{calc} = 1.107$ g cm^{-3}, $2\theta_{max} = 119.98°$, $\lambda = 1.54178$ Å, $T = 108$ K, 2762 measured reflections, 1948 independent reflections ($R_{int} = 0.0417$), 1330 observed reflections ($I > 2\sigma(I)$), $\mu = 0.568$ mm^{-1}, semiempirical absorption correction, $T_{min} = 0.829$, $T_{max} = 0.970$, 154 parameters, $R1(I>2\sigma(I)) = 0.0661$, wR_2(all data) = 0.1750, max./min. residual electron density 0.296/–0.414 e Å^{-3}; b) **2b-cy5**, R = cyclopentyl: colorless prism, $0.42 \times 0.23 \times 0.21$ mm^3, triclinic, $P\bar{1}$, $a = 6.0622(5)$, $b = 10.1366(9)$, $c = 10.556(1)$ Å, $\alpha = 84.346(7)$, $\beta = 75.625(7)$, $\gamma = 86.723(7)°$, $V = 624.9(1)$ Å^3, $\rho_{calc} = 1.122$ g cm^{-3}, $2\theta_{max} = 50.0°$, $\lambda = 0.71073$ Å, $T = 113$ K, 5212 measured reflections, 2195 independent reflections ($R_{int} = 0.0281$), 1589 observed reflections ($I > 2\sigma(I)$), $\mu = 0.074$ mm^{-1}, 144 parameters, $R1(I>2\sigma(I)) = 0.0366$, wR_2(all data) = 0.0931, max./min. residual electron density 0.231/–0.159 e Å^{-3}.

[30] Zero-field-splitting parameters in methylcyclohexane at 4 K for **1b**: $|D/hc| = 1.573$ cm^{-1} and $|E/hc| = 0.005$ cm^{-1}.

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