JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

A Metal and Base-Free Chemoselective Primary Amination of Boronic Acids Using Cyanamidyl/Arylcyanamidyl Radical as Aminating Species: Synthesis and Mechanistic Studies by Density Functional Theory

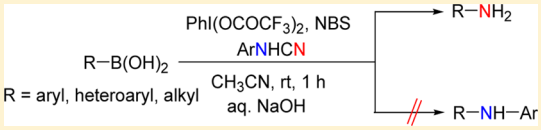
Nachiketa Chatterjee,[†] Minhajul Arfeen,[‡] Prasad V. Bharatam,[‡] and Avijit Goswami*[,†]

[†]Department of Chemistry, Indian Institute of Technology Ropar, Nangal Road, Rupnagar 140001, Punjab, India

[‡]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar 160062, Punjab, India

Supporting Information

ABSTRACT: An efficient, metal and base-free, chemoselective synthesis of aryl-, heteroaryl-, and alkyl primary amines from the corresponding boronic acids has been achieved at ambient temperature mediated by [bis(trifluoroacetoxy)iodo]benzene (PIFA) and *N*-bromosuccinimide (NBS) using cyanamidyl/arylcyanamidyl radicals as the aminating species. The primary amine compounds were initially obtained as their corresponding ammonium trifluoroacetate salts which, on treatment with aq NaOH, provide the free amines. Finally, the primary amines were isolated through column chromatography over silica-gel using hexane-EtOAc solvent system as the eluent. The reactions are sufficiently fast, completing within 1 h. Quantum chemical calculations in combination with experimental observations validate that the *ipso* amination of substituted boronic acids involves the formation of cyanamidyl/arylcyanamidyl radical, followed by regiospecific interaction of its nitrile-N center with boron atom of the boronic acids, leading to chemoselective primary amination.

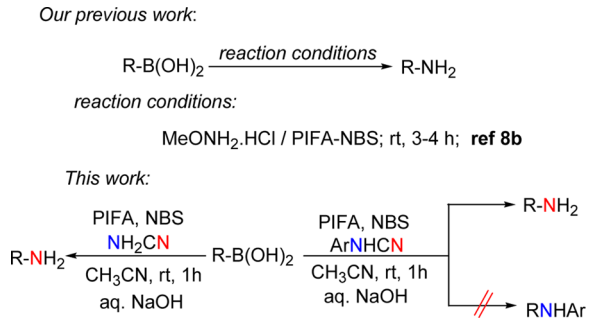


INTRODUCTION

Amines, especially aryl- and heteroaryl primary amines, serve as crucial building blocks in the field of pharmaceuticals, dyes, agrochemicals, polymers, xerographic and photographic materials.[1] The aromatic primary amines are the most vital moieties to construct different *N*-heterocycles[2] and thus play a significant role in the branch of medicinal chemistry.[3] Consequently, developing newer methodologies working under mild reaction conditions for synthesizing functionalized aromatic primary amines always remains a center of attention for the organic chemists. Apart from the conventional approaches toward the syntheses of aromatic primary amines,[1a−c,4] present-day methods give emphasis to the use of boronic acids as an attractive class of precursor not only to incorporate amine groups but also different other functional groups,[5] as numerously functionalized aryl/heteroarylboronic acids are easily accessible and are highly stable under atmospheric conditions. In this connection, some recent studies disclosed that the reactions of boronic acids/esters with various aminating reagents such as hydroxylamine-*O*-sulfonic acid (HSO_3ONH_2) [HSA],[6] $C_6H_3(NO_2)_2ONH_2$,[7] and $MeONH_2$·HCl[8a,b] lead to primary aromatic amines under metal-free reaction conditions (Scheme 1).

Our aim was to come up with a method in which both primary and secondary amines could be synthesized from arylboronic acids utilizing a particular class of reagent under metal-free conditions. The simple structural moiety, required for *ipso* amination of arylboronic acids, is a nucleophilic amine center attached to a leaving group. Thus, for this purpose cyanamide and arylcyanamides in the presence of a base were anticipated to be fair choices for preparing primary and secondary aromatic amines, respectively. In accordance with this view, we applied cyanamide with arylboronic acids in the presence of [bis(trifluoroacetoxy)]iodobenzene (PIFA)[9] and *N*-bromosuccinimide (NBS) for obtaining the corresponding primary amines, and indeed, the anticipated primary aminations were achieved in good to excellent yields with the aforementioned reagent combination. In this connection, it is pertinent to mention that our group has recently documented methods for *ipso* functionalization of aryl-, heteroaryl-, and

Scheme 1. Transition Metal-Free PIFA-NBS Mediated Syntheses of Primary Amines from Boronic Acids

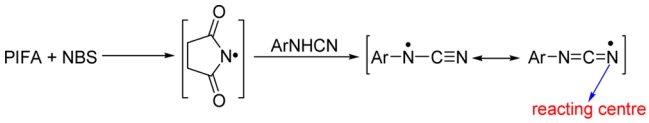


Received: March 29, 2016
Published: May 16, 2016

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120−5127

alkylboronic acids mediated by PIFA and NBS where the combination of PIFA and NBS was anticipated to produce a succinimidyl radical, which acted as an effective hydrogen atom (connected to an electronegative atom) abstractor.[8b,10] Prior to our reports, Gandelman et al. comprehensively reported the use of 1,3-diiodo-5,5-dimethylhydantoinyl (DIH) radical, a very similar one to succinimidyl radical, for abstracting hydrogen atom from carboxylic acid to generate an alkyl/aryl radical.[11] Therefore, taking the lead from our earlier work, we utilized the combination of PIFA-NBS to abstract the hydrogen atom from cyanamides to transform them to cyanamidyl radicals. After synthesizing the primary amines from the reactions of unsubstituted cyanamidyl radical with the arylboronic acids, we switched our attention to arylcyanamides (ArNHCN) to obtain diarylamines under similar reaction conditions. To our surprise, it was observed that the reactions with several arylcyanamides and arylboronic acids did not produce the desired diarylamines even after repeated attempts; rather it produced the primary amines of the corresponding arylboronic acids, as obtained in the reactions with unsubstituted cyanamide. Taken together, it can be envisaged that the succinimidyl radical, so produced by the reaction of PIFA and NBS, abstracts the hydrogen atom from cyanamide, resulting in the formation of cyanamidyl radical, which can act as an ambident nucleophilic radical (Scheme 2).

Scheme 2. Ambidency of the Cyanamidyl Radical

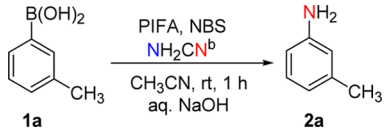


All amination reactions of boronic acids/esters reported to date including our previous work, involve attack of a nitrogen center, carrying a leaving group, on the boron atom which is subsequently followed by an anionotropic rearrangement to provide the corresponding primary amines. Interestingly, in the present method, unlike our previous report, the cyanide moiety of the arylcyanamide/cyanamide is not acting as a leaving group; rather, it is the nitrile-N radical (not the amine-N radical) of the cyanamides/arylcyanamide which is responsible for the nucleophilic attack to the boron center, leading to chemoselective primary amination in all cases. In the manuscript presented herein, we report a chemoselective *ipso* amination of various aryl-, heteroaryl-, and alkylboronic acids using cyanamide/arylcyanamide as aminating agent in the presence of PIFA and NBS under mild reaction conditions. The detailed mechanistic pathway of the amination reaction was substantialized through Density Functional Theory (DFT) using B3LYP/6-311++G(d,p). To the best of our knowledge, it is the first example of cyanamides being used as aminating reagents for *ipso* amination of boronic acids. Furthermore, the formation of cyanamidyl radical and its regiospecific utilization of the nitrile-N center radical for the nucleophilic attack to the boron atom have not yet been documented in the literature.

RESULTS AND DISCUSSION

To accomplish the initial investigation for PIFA-NBS mediated *ipso* amination of arylboronic acid, *m*-tolylboronic acid (**1a**) was taken as a reference substrate along with unsubstituted cyanamide as an aminating agent, and the results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	organoiodine(III)/equiv	additive/equiv	solvent	yield[c]
1	-	-	CH_3CN	n.r[e]
2	PIDA/3.0[d]	-	CH_3CN	n.r[e]
3	PIDA/3.0[d]	NBS/2.0	CH_3CN	n.r[e]
4	HTIB/3.0[d]	-	CH_3CN	n.r[e]
5	HTIB/3.0[d]	NBS/2.0	CH_3CN	n.r[e]
6	PIFA/3.0	-	CH_3CN	42
7	PIFA/2.0	NBS/1.0	CH_3CN	61
8	**PIFA/2.0**	**NBS/2.0**	**CH_3CN**	**89**
9	PIFA/2.0	NBS/2.0	THF	65
10	PIFA/2.0	NBS/2.0	$CHCl_3$	72
11	PIFA/2.0	NBS/2.0	CH_2Cl_2	69
12	PIFA/2.0	NBS/2.0	CH_2Cl_2	87[f]

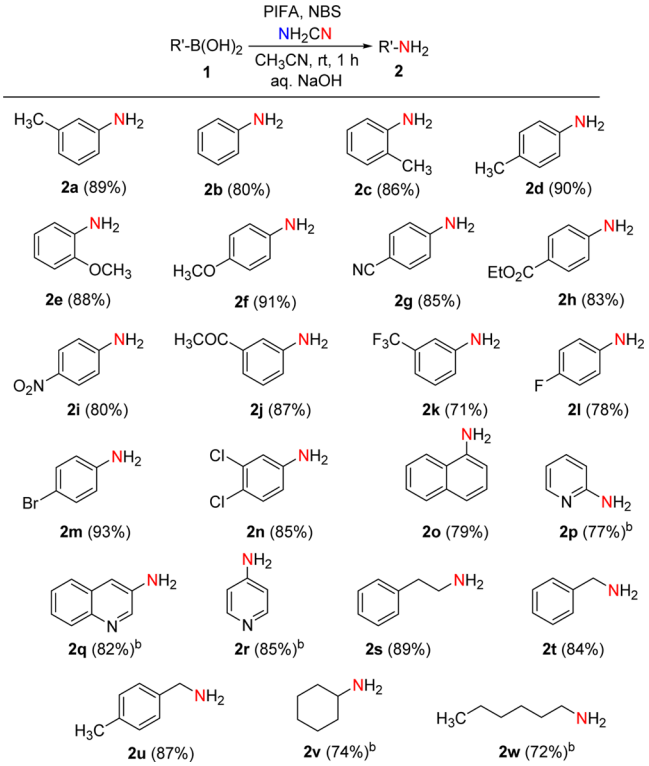
[a]Optimized reaction conditions: **1a** (2.0 mmol, 1.0 equiv), PIFA (4.0 mmol, 2.0 equiv), NBS (4.0 mmol, 2.0 equiv), NH_2CN (2.2 mmol, 1.1 equiv), CH_3CN (8 mL), rt, 1 h, open air. [b]All optimization reactions were carried out with 1.1 equiv of NH_2CN. [c]Isolated yield of **2a**. [d]PIDA: PhI(OAc)$_2$; HTIB: PhI(OH) (OTS). [e]No amination was observed; starting boronic acid remained unreacted even after 24 h at ambient temperature. [f]The reaction was carried out in argon atmosphere.

Primarily, cyanamide (NH_2CN) was applied with **1a** in the absence of any organoiodine(III) and additive, and as expected, no amination was found to take place even after 24 h at ambient temperature (entry 1). Subsequently, different organoiodine(III) regeants were screened, both in the presence and absence of NBS as an additive for the said reaction. It was observed that PIDA and HTIB failed to promote the desired amination either in the presence or in the absence of NBS (entries 2–5). On the other hand, PIFA was able to exhibit the amination reaction successfully even in the absence of NBS, but with a lower yield (entry 6). The presence of NBS was found necessary for full consumption of the arylboronic acid. The optimization process with PIFA and NBS revealed that complete conversion of **1a** to its corresponding ammonium trifluoroacetate salt was found to take place within 1 h at ambient temperature when 2.0 equiv of PIFA and 2.0 equiv of NBS were employed using acetonitrile as solvent (entries 7 and 8). Other solvents, like THF, $CHCl_3$, and CH_2Cl_2, were also evaluated; however, lower yields were obtained with these solvents (entries 9–11). No significant change in the reaction outcome was noticed when the reaction was performed under inert environment (entry 12).

In the course of our in-depth study, the investigations were further extended to other substrates to figure out the substrate scope of the newly developed PIFA-NBS-NH_2CN mediated method for primary amination of the aryl-, heteroaryl-, and alkylboronic acids, and the results are summarized in Scheme 3. The present method developed herein exhibited a broad range of functional group compatibility; diversely functionalized (CN, CO_2Me, NO_2 and COMe) arylboronic acids were easily transformed to their corresponding primary amines (**2g–j**) in very good yields. It was also observed that arylboronic acids, substituted by different groups with different electronic properties at the *o*/*m*/*p* positions, were converted to the respective primary amines with comparable yields under these

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120–5127

Scheme 3. PIFA-NBS-NH_2CN Mediated *ipso*-Amination of Different Boronic Acids[a]



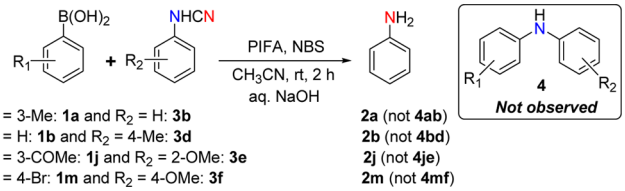
[a]Reaction conditions: Corresponding boronic acid **1** (2.0 mmol), PIFA (4.0 mmol), NBS (4.0 mmol), NH_2CN (2.2 mmol), CH_3CN (8 mL), rt, 1 h, open air. [b]Reactions were carried out in 3.0 mmol scale with respect to corresponding boronic acids.

reaction conditions, demonstrating the insignificant effect of steric (**2c**, **2e**) and electronic factors (**2f**–**j**) on the reaction outcome. We noted that *N*-heteroarylboronic acids were found to undergo facile amination following the presently developed reactions conditions (**2p**–**r**). The protocol, developed herein, was successfully employed to various alkylboronic acids to achieve primary aliphatic amines (**2s**–**w**) in good yields. On the other hand, aryl-, heteroaryl-, or alkylboronic acids pinacol esters were not observed to undergo amination under these reaction conditions.

Encouraged by these results, the methodology was explored to the reactions of arylcyanamides with the arylboronic acids in order to obtain the diarylamines (**4**). Four arylcyanamides (**3b**, **3d**–**f**) were treated with different arylboronic acids under optimized reaction conditions. To our surprise, formations of diarylamines (**4**) were not detected in any of the cases; rather the reactions resulted in the formation of the primary amines of the corresponding arylboronic acids exclusively (Scheme 4). This phenomenon clearly indicated the exclusive involvement of the nitrile-N center in the nucleophilic attack toward the boron center of the boronic acids.

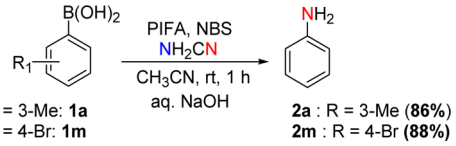
Next, the optimized reaction conditions were applied to a gram scale substrate to judge the practicality of this method (Scheme 5). The amination reactions, performed between **1a**/**1m** and unsubstituted cyanamide on a 10.0 mmol scale, produced the corresponding primary amines in comparable yields to those with small scale experiments, indicating the practical applicability of the protocol.

Scheme 4. Reactions with Arylcyanamides and Arylboronic Acids Mediated by PIFA-NBS[a]



[a]Reaction conditions: **1** (1.0 mmol), **3** (1.1 mmol), PIFA (2.0 mmol), NBS (2.0 mmol), CH_3CN (8 mL), rt, 2 h, open air.

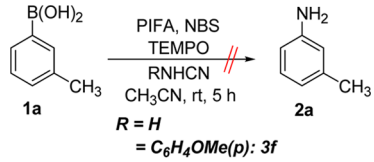
Scheme 5. Scale-Up Experiment to Gram Scale[a]



[a]Reaction conditions: **1a** (1.35 g, 10.0 mmol)/**1m** (2.0 g, 10.0 mmol), PIFA (20.0 mmol), NH_2CN (11.0 mmol), NBS (20.0 mmol), CH_3CN (14 mL), rt, 1 h, open air.

From our previous experiences, these amination reactions were anticipated to follow a radical pathway, yet, to get confirmation, radical scavenging experiment with TEMPO was performed (Scheme 6). No amination of **1a** was found to take

Scheme 6. Radical Scavenging Experiment with TEMPO[a]



[a]Reaction Conditions: **1a** (1.0 mmol), NH_2CN/**3f** (1.1 mmol), PIFA (2.0 mmol), NBS (2.0 mmol), TEMPO (1.2 mmol), CH_3CN (8 mL), rt, 5 h.

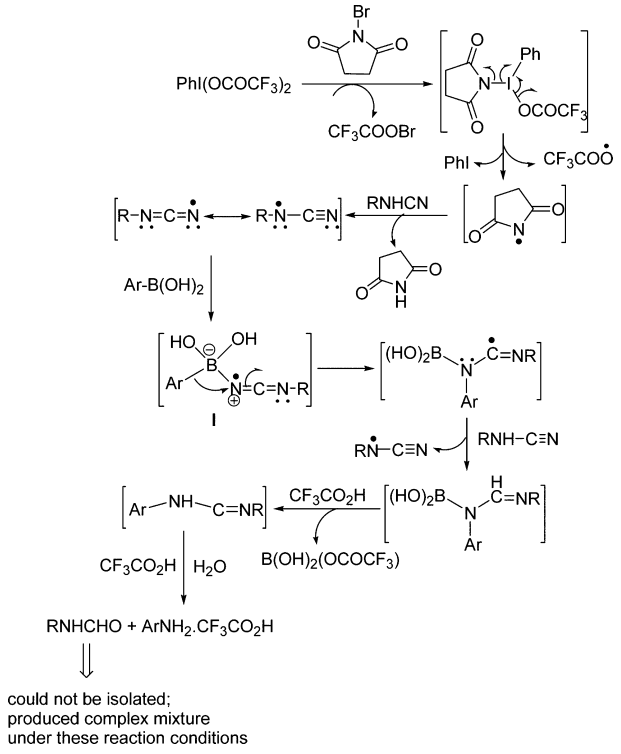
place at ambient temperature even after 5 h in the presence of 1.2 equiv of TEMPO, keeping the optimized reaction conditions otherwise fixed. The radical scavenging experiment with TEMPO clearly indicates our hypothesized radical pathway of the reaction.

In this perspective, it could be stated that interaction of radical with organoboranes leading to the generation of carbon-centered radicals by cleavage of carbon–boron bonds has been under extensive study for the last three decades.[13] Brown et al. comprehensively reported the formation of a carbon centered radical by the displacement of the alkyl group attached to the boron atom through nucleophilic attack of a dimethylaminyl radical to the boron center.[13a,14] Therefore, from our experimental results and literature references, the reaction pathway for the *ipso* amination of boronic acids can be explained by considering that PIFA and NBS first readily reacts to produce a succinimidyl radical[8b,10,11] which abstracts the hydrogen atom of the sufficiently acidic cyanamide[12] to generate cyanamidyl radical. The cyanamidyl radical subsequently attacks the boron atom, specifically through its nitile-N center, to form a "tetracoordinate boranyl radical complex (**I**)",[13a,15] and finally, amine salts are produced via intramolecular B–N 1,2-aryl

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120–5127

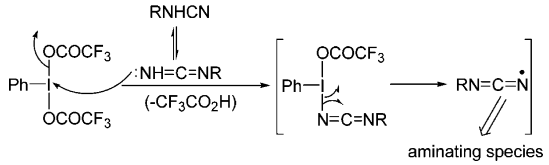
migration from the aforementioned tetracoordinate boranyl radical complex **I** (Scheme 7).

Scheme 7. Anticipated Reaction Pathway



In this context, it should be mentioned that during the optimization process, it was observed that PIFA itself was able to promote the desired primary amination of the boronic acids even in the absence of NBS (Table 1, entry 6). The reason behind this is that in the absence of NBS, cyanamide could slowly react with PIFA to undergo a ligand exchange reaction to produce metastable intermediate **II**, which, via radical cleavage of the I–N bond, would culminate the cyanamidyl radical, the aminating species (Scheme 8).[9a,16]

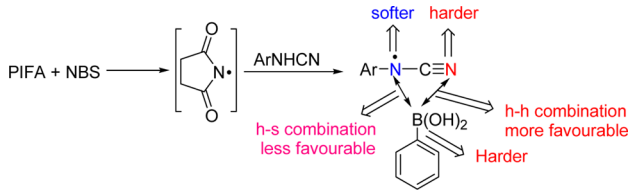
Scheme 8. Generation of Cyanamidyl Radical in the Absence of NBS



The nucleophilic attack on the boron atom specifically through the nitrile-N center of the cyanamidyl radical can be attributed to HSAB interaction; the boron being a hard center prefers to combine with relatively harder nitrile-N center than the amine-N center of the ambident cyanamidyl radical (Scheme 9). Also, higher electron spin density on the nitrile-N cetre compared to the amine-N center, along with the steric environment surrounding the amine-N center of arylcyanamide, further facilitated the specific interaction of its nitrile-N centered radical.

To understand the underlying mechanism (Scheme 7) of the reaction in detail, quantum chemical evaluation was taken up

Scheme 9. Probable Hard–Hard (h–) and Hard-Soft (h–) Combination of Arylboronic Acid and Arylcyanamidyl Radical



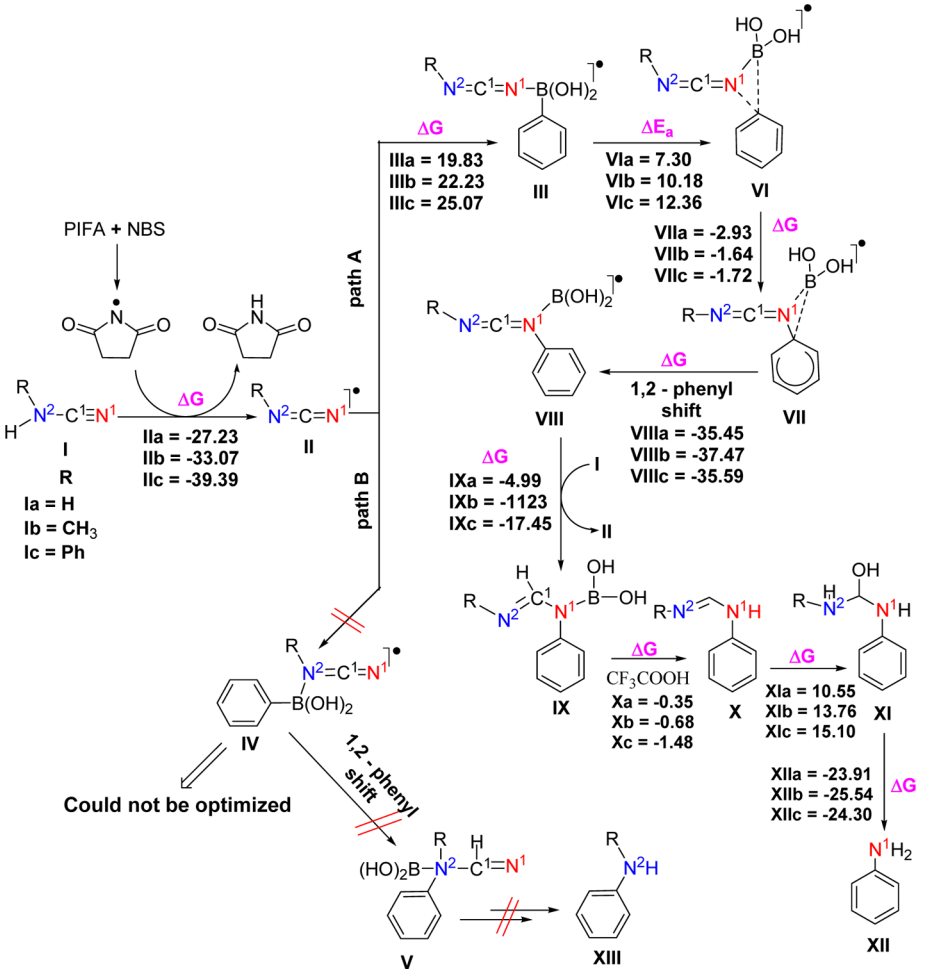
with phenylboronic acid (**1b**) and cyanamide (**Ia**)/methylcyanamide (**Ib**)/phenylcyanamide (**Ic**) to generate aniline (**2b**) (Scheme 10).[17] B3LYP exchange-correlation functional was used to define the quantum chemical method and 6-311++G(d,p) basis set was used to define the wave function. Overall, the mechanistic pathway leading to the formation of primary amines can be divided into five steps: (i) formation of cyanamidyl radical, (ii) reaction of phenylboronic acid with one of the nitrogen centers of cyanamidyl radical, (iii) 1,2 phenyl shift leading to the formation of C–N bond, (iv) formation of the neutral iminamine species, and (v) hydrolysis of the imine moiety. The optimized geometry of species **Ia** reveals that C^1–N^1 and C^1–N^2 bond distances are 1.16 and 1.33 Å, wheres, in case of cyanamidyl radical (**IIa**),they are 1.19 and 1.27 Å, respectively. The initiations of cyanamidyl radicals **IIa**, **IIb**, and **IIc**, from cyanamides (**Ia**, **Ib**, **Ic**) are found to be stabilized by 27.23, 33.33, and 39.38 kcal/mol (Figure 1), respectively, which clearly indicate that strong exothermic processes are involved in all of the cases. This phenomenon clearly establishes that the formation of cyanamidyl radical from cyanamide is a highly favorable process. The spin density analysis indicates that spin densities on both nitrogens in **IIa**/**IIb**/**IIc** (path A, Scheme 10) are comparable, though some little excesses are observed on the nitrile N (N^1) centers of the cynamidal radicals. Considering the ambidentate nature of cyanamidyl radical and the spin density analysis, it might be expected that the reaction between **II** (in Scheme 10) and boronic acid could occur through either of the nitrogen centers leading to both primary and secondary amines. However, during the quantum chemical optimization process, it was convincingly noticed that the quantum chemical optimization could be carried out only on **IIIa–c** (path A, Scheme 10) but not on **IVa–c** (path B, Scheme 10). This evidently confirms that the reaction between boronic acid and cyanamidyl radical takes place through N^1, the nitrile N center, but not via N^2, the amine N center. This is in accordance with the experimental observation where the reactions between arylcyanamides and boronic acids did not produce secondary amines in any of the cases.

The potential energy calculations based on the free energy changes with respect to local reaction steps for the entire amination process could be depicted in a graphical form as shown in Figure 1.

In this context, it should be mentioned that the formation of intermediate **III** is overall energetically favored process with respect to the starting material (**I** + succinimide radical). From the potential energy surface, it has been observed that **IIIa**, **b**, **c** are found to be stabilized by −7.4, −10.84, and −14.32 kcal/mol, respectively, with respect to starting substances (**I** + succinimimidyl radical) under radical conditions. However, the most important step of this reaction is the formation of the intermediate **VIII**. **VIII** could be obtained from **III** via 1,2-

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120–5127

Scheme 10. Proposed Reaction Mechanism for the Amination Process along with the Free Energy Changes ($\Delta G/\Delta E_a$) Using Quantum Chemical Method (B3LYP/6-311++G(d,p))[a]



[a]The energy values reported in the scheme are with respect to the local reaction step. All the energy values are in kcal/mol. The respective energy values provided in each of the local steps correspond to total energy including all of the reagents and side products. For potential energy surface, refer to Figure 1.

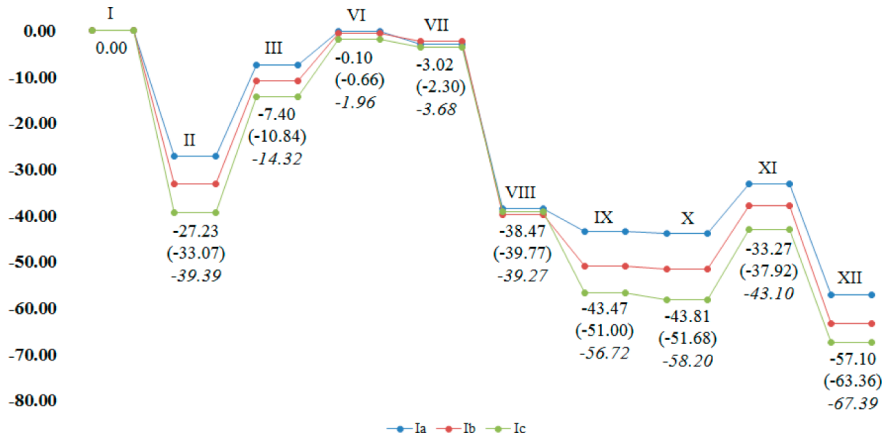


Figure 1. Potential energy surface (based on ΔG values) for the formation of **2b** from **1b** by using cyanamide (**Ia**), methylcyanamide (**Ib**), and phenylcyanamide (**Ic**). *Y*-axis represents the relative free energy changes in kcal/mol.

phenyl migration through a transition state (**TS**, **VI**) (Figure 2) and a metastable intermediate **VII**.

It is pertinent to mention that on the potential energy surface, the energy for the TS structures (**VI**) are found to be lowered by 0.10, 0.66, and 1.96 for **VIa**, **VIb**, and **VIc**, respectively, in comparison to **I**. However, the activation energy for the conversion of **III** to **VIII** was found to be ∼7−12 kcal/mol. The formation of **VII** from **TS VI** is an exergonic process by ∼2−3 kcal/mol, which further loses another ∼35−37 kcal/mol to culminate **VIII**. The "transformation step" from **II** to **III**

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120−5127

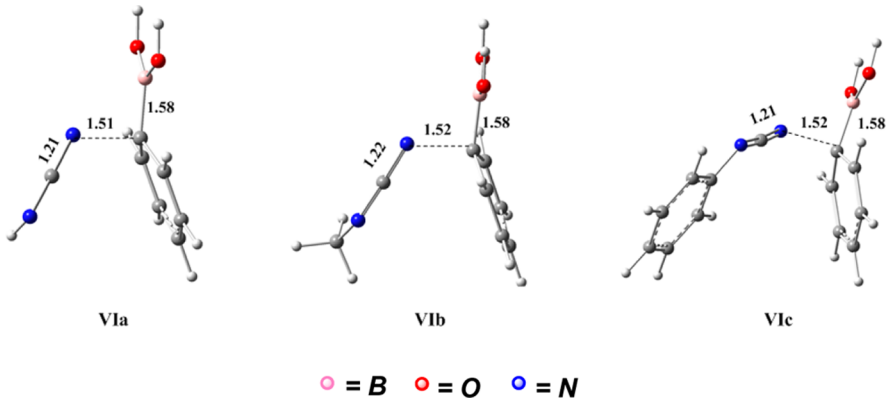


Figure 2. 3D structures of important transition states (**TS VIa–c**) showing the bond distances.

is found to be rate limiting step for the *ipso* amination process presented herein. The formation of final product **2b** from **VIII** proceeds through three more stages via formations of **IX**, **X**, and **XI**. Transformation from **VIII** to **IX** is interesting. **VIII** would take up the hydrogen from the cyanamide itself regenerating the cyanamidyl radical and the reaction continues. This is also supported by the quntum calculations, as the relative energy change for the aforementioned transformation is found to be exergonic by ∼5−17 kcal/mol. From the study, it could be indicated that the chemoselective formation of aniline (**2b**) from cyanamidyl and substituted cyanamidyl radicals through specific interaction of their nitrile-N centres is found to be highly exothermic process by ∼30−39 kcal/mol, which clearly suggests the spontaneous nature of this chemoselective amination process presented in the report.

CONCLUSIONS

In conclusion, we have developed a novel metal and base free method for chemoselective synthesis of primary amines via *ipso* amination of boronic acids using a combination of PIFA-NBS as acidic hydrogen radical abstractor and cyanamides as the aminating agent. The reaction conditions employed in the protocol exhibited a wide range of functional groups compatibility especially to the carbonyl, nitrile, and ester. The method is applicable for both aryl- and heteroarylboronic acids and produces amino compounds at ambient temperature in 1 h. Furthermore, computational studies utilizing Density Functional Theory (DFT) have been performed to understand the mechanism of the reaction in depth. To the best of our knowledge, it is the first example of using cyanamide as the aminating reagent for *ipso* amination of arylboronic acid. Additionally, use of ambident cyanamidyl radical and its exclusive specificity to utilize the nitrile-N center toward the arylboronic acids for the amination to take place is a unique phenomenon and has not been reported so far. The use of cyanamide radical and its ambidency for other reactions are currently under progress.

EXPERIMENTAL SECTION

Experimental Details. *General Information.* Chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous acetonitrile obtained from supplier was used for the reactions. Column chromatography was performed using silica gel 60 (100−200 mesh). NMR spectra were recorded in $CDCl_3$ at operating frequencies of 400 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (chloroform, δ = 7.26 for ^{1}H and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quartet, dd for doublet of doublet, dt for doublet of triplet, and m for multiplet.

Preparation[21] of Arylcyanamides, 3b, 3d–f. To a solution of cyanogen bromide (5.0 mmol, 1.0 equiv) in THF/Et_2O (12 mL; 3:1 v/v), were added the primary amines, **2b**, **2d–f** (8.0 mmol, 1.6 equiv) slowly at 0 °C. After some time, solid amine salt started to separate out. Under this circumstance, the reaction mixture was stirred at room temperature for 12 h. Then, the solvent was evaporated carefully under reduced pressure and washed with water. After it was dried over anhydrous Na_2SO_4, the crude mixture was further purified by a short column chromatography to give the desired arylcyanamides. The spectroscopic data for the substrate **3b**,[22] **3d–e**,[22] and **3f**[23] were identical to those reported in the literature.

General Procedure for Synthesis of the Amino Compounds. To a stirred solution of appropriate boronic acids (2.0 mmol, 1.0 equiv), PIFA (4.0 mmol, 2.0 equiv), and NBS (4.0 mmol, 2.0 equiv) in CH_3CN (6 mL) was added the solution of cyanamide or arylcyanamides (2.2 mmol, 1.1 equiv) in CH_3CN (8 mL), and the mixture was stirred for 1−2 h. After completion of the reaction (checked by TLC), the solvent was evaporated under reduced pressure. A solid mass was obtained which was then dissolved to its optimum extent, in minimum volume of water. The solution was made completely alkaline with saturated aq NaOH solution under ice-cold condition and the aq solution was extracted with ethyl acetate (5 × 20 mL). The combined organic phase was washed with distilled water (3 × 7 mL) and was dried over anhydrous Na_2SO_4. After the solvent was evaporated, the residue was purified by column chromatography over silica gel using hexane/EtOAc as eluent to provide the pure target product.

*3-Methylaniline (**2a**).*[7] Light yellow liquid (89%, 190.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (t, J = 7.8 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 6.52−6.54 (m, 2H), 3.54 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 139.1, 129.0, 119.5, 116.0, 112.3, 21.8.

*Aniline (**2b**).*[7] Pale yellow liquid (80%, 148.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19−7.23 (m, 2H), 6.80−6.84 (m, 1H), 6.71−6.73 (m, 2H), 3.58 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 129.3, 118.3, 115.2.

*2-Methylaniline (**2c**).*[7] Pale yellow liquid (86%, 184.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07−7.10 (m, 2H), 6.76 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 3.61 (s, br, 2H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 131.2, 127.0, 121.8, 118.6, 114.6, 17.4.

*4-Methylaniline (**2d**).*[6] Off-white semisolid (90%, 192.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97−6.99 (m, 2H), 6.61−6.64 (m, 2H), 3.39 (s, br, 2H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 129.8, 127.9, 115.3, 20.5.

*2-Methoxyaniline (**2e**).*[6] Light yellow liquid (88%, 216.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73−6.83 (m, 4H), 3.86 (s, 3H), 3.69 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 136.1, 121.2, 118.2, 115.3, 110.4, 55.4.

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120−5127

*4-Methoxyaniline (**2f**)*.[6] Pale off-white solid (91%, 223.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (dd, J = 8.6 Hz, 2.3 Hz, 2H), 6.65 (dd, J = 8.7 Hz, 2.3 Hz, 2H), 3.74 (s, 3H), 3.19 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 139.8, 116.5, 114.7, 55.7.

*4-Cyanoaniline (**2g**)*.[7] Pale yellowish solid (85%, 200.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J = 8.7 Hz, 1.8 Hz, 2H), 6.64 (dd, J = 8.6 Hz, 2.3 Hz, 2H), 4.17 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 133.9, 120.1, 114.5, 100.1.

*Ethyl 4-Aminobenzoate (**2h**)*.[6] Off-white solid (83%, 273.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 8.7 Hz, 2.3 Hz, 2H), 6.63 (dd, J = 8.7 Hz, 2.3 Hz, 2H), 4.31 (q, J = 7.3 Hz, 2H), 4.05 (s, br, 2H), 1.35 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 150.7, 131.6, 120.1, 113.9, 60.1, 14.8.

*4-Nitroaniline (**2i**)*.[24a] Brown solid (80%, 220.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 9.2 Hz, 2H), 4.39 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 126.3, 122.0, 113.4.

*3-Aminoacetophenone (**2j**)*.[24b] Brownish solid (87%, 234.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.26 (m, 1H), 7.14−7.19 (m, 2H), 6.78−6.81 (m, 1H), 3.66 (s, br, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 146.8, 138.1, 129.5, 119.9, 119.0, 113.8, 26.8.

*3-Trifluoromethylaniline (**2k**)*.[24c] Light yellow liquid (71%, 228.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 7.15 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.79 (m, 1H), 6.70−6.73 (m, 1H), 3.72 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 131.7, 131.5, 131.1, 129,8, 128.3, 125.6, 122.9, 118.0, 115.1, 115.0, 111.4, 111.3.

*4-Fluoroaniline (**2l**)*.[7] Brown liquid (78%, 173.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83−6.87 (m, 2H), 6.59−6.63 (m, 2H), 3.45 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 155.3, 142.4, 116.2, 116.1, 115.8, 115.6.

*4-Bromoaniline (**2m**)*.[7] Off-white solid (93%, 319.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (dd, J = 6.8 Hz, 1.8 Hz, 2H), 6.55 (dd, J = 6.4 Hz, 2.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 132.1, 116.8, 110.1.

*3,4-Dichloroaniline (**2n**)*.[24a] Gray solid (85%, 275.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.48−6.51 (m, 1H), 3.71 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 132.7, 130.6, 121.2, 116.9, 114.9.

*1-Aminonapthaline (**2o**)*.[24b] Gray solid (79%, 235.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 7.81−7.84 (m, 2H), 7.46−7.48 (m, 2H), 7.29−7.35 (m, 2H), 6.80 (d, J = 6.8 Hz, 1H), 4.03 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 134.4, 128.6, 126.4, 125.9, 124.9, 123.7, 120.8, 119.0, 109.7.

*2-Aminopyridine (**2p**)*.[24a] Light yellow solid (77%, 217.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8.03−8.05 (m, 1H), 7.37−7.46 (m, 1H), 6.59−6.62 (m, 1H), 6.46 (d, J = 8.2 Hz, 1H), 4.52 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 148.1, 137.8, 114.0, 108.2.

*3-Aminoquinoline (**2q**)*.[24a] Brownish solid (82%, 354.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.94−7.96 (m, 1H), 7.55−7.58 (m, 1H), 7.39−7.44 (m, 2H), 7.21 (m, 1H), 3.65 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 142.6, 139.9, 129.2, 128.9, 127.0, 125.9, 125.7, 115.1.

*4-Aminopyridine (**2r**)*.[24a] White solid (85%, 239.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, J = 6.4 Hz, 1.4 Hz, 2H), 6.51 (dd, J = 6.4 Hz, 1.4 Hz, 2H), 4.14 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 150.4, 109.7.

*2-Phenylethylamine (**2s**)*.[24b] Light brown liquid (89%, 215.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.32 (m, 2H), 7.19−7.23 (m, 3H), 2.96 (t, J = 6.9 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 1.24 (s, br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 128.9, 128.4, 126.0, 43.8, 40.0.

*Benzylamine (**2t**)*.[24b] Light yellow liquid (84%, 179.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−7.27 (m, 5H), 3.77 (s, 2H), 1.43 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 128.5, 127.1, 126.8, 46.5.

*4- Methylbenzylamine (**2u**)*.[24b] Brownish oil (87%, 210.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16−7.21 (m, 4H), 3.81 (s, 2H), 2.34 (s, 3H), 1.49 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 136.2, 129.1, 127.0, 46.2, 21.0.

*Cyclohexylamine (**2v**)*.[24b] Pale yellow liquid (74%, 219.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53−2.60 (m, 1H), 1.74−1.78 (m, 2H), 1.63−1.68 (m, 2H), 1.52−1.57 (m, 1H), 1.34 (s, br, 2H), 0.94−1.26 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.5, 36.9, 25.7, 25.2.

*Hexylamine (**2w**)*.[24b] Light brown oil (72%, 218.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (t, J = 7.3 Hz, 2H), 1.36−1.41 (m, 2H), 1.21−1.31 (m, 6H), 1.16 (s, br, 2H), 0.85 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.3, 39.9, 31.6, 26.4, 22.7, 14.0.

Quantum Chemical Analysis. Quantum chemical calculations were carried out using Gaussian09 suite[18] of programs on a cluster computer with intel octacore processors. Complete geometry optimizations were performed on all the structures without any symmetry constraints using B3LYP/6-311++G(d,p)[19] levels of quantum chemistry. Vibrational frequencies were computed analytically for all optimized species on the reaction pathways at the same levels to characterize them as either minima or transition states.[20] Transition states on different cyclization pathways were characterized to be first order saddle points with one negative imaginary vibrational mode. The energy values discussed in the manuscript are based on the free energy (ΔG) changes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00671.

^{1}H and ^{13}C NMR spectra of the amines **2a**−**2w**; GC−MS spectra of the crude amine salts (**1a′** and **1m′**) in the reaction mixtures; GC−MS spectra of the radical scavenging experiment; computational method, Cartesian coordinates, Gibbs-free energies, important bond lengths, relevant imaginary frequencies, 3D structures of T.S. and other conformers (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: agoswami@iitrpr.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to SERB, DST (File No. SB/S1/OC-29/2013), New Delhi, India for its generous financial support. The authors would like to thank IIT Ropar and NIPER Mohali for infrastructural facilities and other support.

■ REFERENCES

(1) (a) Lawrence, S. A., Ed.; *Amines: Synthesis, Properties, and Applications*; Cambridge University Press: Cambridge, 2004. (b) Ricci, A., Ed.; *Amino Group Chemistry: From Synthesis to Life Sciences*; Wiley-VCH: Weinheim, 2008. (c) Rappoport, Z. *The Chemistry of Anilines, Parts 1 and 2*; John Wiley & Sons: New York, 2007. (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (e) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190. (f) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(2) (a) Bhunia, S.; Ghosh, S.; Dey, D.; Bisai, A. *Org. Lett.* **2013**, *15*, 2426. (b) Ghosh, S.; Bhunia, S.; Kakde, B. N.; De, S.; Bisai, A. *Chem. Commun.* **2014**, *50*, 2434. (c) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11895. (d) Jaiswal, P. K.; Biswas, S.; Singh, S.; Samanta, S. *Org. Biomol. Chem.* **2013**, *11*, 8410. (e) Santhanam, V.; Ramesh, N. G. *Eur. J. Org. Chem.* **2014**, *2014*, 6992. (f) Kumar, V.; Ramesh, N. G. *Chem. Commun.* **2006**, 4952.

(3) (a) Demare, P.; Regla, I. *J. Chem. Educ.* **2012**, *89*, 147. (b) Seifert, J.; Mostecka, H.; Kolar, G. F. *Toxicology* **1993**, *83*, 49. (c) Martinez-Montero, S. M.; Fernandez, S.; Sanghvi, Y. S.; Chattopadhyaya, J.;

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120−5127

Ganesan, M.; Ramesh, N. G.; Gotor, V.; Ferrero, M. *J. Org. Chem.* **2012**, *77*, 4671.
(4) (a) Mallat, T.; Baiker, A.; Kleist, W.; Koehler, K. *Handb. Heterog. Catal.* **2008**, *7*, 3548. (b) Blaser, H. U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210.
(5) (a) Molander, G. A. *J. Org. Chem.* **2015**, *80*, 7837. (b) Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013**, *78*, 12837. (c) Molander, G. A.; Siddiqui, S. Z.; Fleury, B. N. *Org. Synth.* **2013**, *90*, 153. (d) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maity, D. *Org. Lett.* **2012**, *14*, 1736. (e) Zhu, C.; Falck, J. R. *Adv. Synth. Catal.* **2014**, *356*, 2395.
(6) Voth, S.; Hollett, J. W.; McCubbin, J. A. *J. Org. Chem.* **2015**, *80*, 2545.
(7) Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253.
(8) (a) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (b) Chatterjee, N.; Goswami, A. *Org. Biomol. Chem.* **2015**, *13*, 7940.
(9) For, hypervalent iodine or iodine promoted other reactions, see: (a) Zhdankin, V. V. *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*; John Wiley & Sons, Ltd., West Sussex, United Kingdom, 2014. (b) Chatterjee, N.; Chowdhury, H.; Sneh, K.; Goswami, A. *Tetrahedron Lett.* **2015**, *56*, 172. (c) Chatterjee, N.; Goswami, A. *Tetrahedron Lett.* **2015**, *56*, 1524. (d) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469. (e) Ghosh, S.; Chaudhuri, S.; Bisai, A. *Org. Lett.* **2015**, *17*, 1373.
(10) Chatterjee, N.; Bhatt, D.; Goswami, A. *Org. Biomol. Chem.* **2015**, *13*, 4828.
(11) Kulbitski, K.; Nisnevich, G.; Gandelman, M. *Adv. Synth. Catal.* **2011**, *353*, 1438.
(12) Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pKa Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981.
(13) (a) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415. (b) Yan, G.; Yang, M.; Wu, X. *Org. Biomol. Chem.* **2013**, *11*, 7999. (c) Duret, G.; Quinlan, R.; Bisseret, P.; Blanchard, N. *Chem. Sci.* **2015**, *6*, 5366.
(14) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.
(15) Griller, D.; Ingold, K. U.; Patterson, L. K.; Scaiano, J. C.; Small, R. D., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 3780.
(16) Baba, H.; Moriyama, K.; Togo, H. *Tetrahedron Lett.* **2011**, *52*, 4303.
(17) Selected reports of DFT studies on organic reaction mechanisms: (a) Hioe, J.; Sakic, D.; Vrcek, V.; Zipse, H. *Org. Biomol. Chem.* **2015**, *13*, 157. (b) Wagner, A.; Hampel, N.; Zipse, H.; Ofial, A. R. *Org. Lett.* **2015**, *17*, 4770. (c) Patschinski, P.; Zhang, C.; Zipse, H. *J. Org. Chem.* **2014**, *79*, 8348. (d) Kessar, S. V.; Singh, P.; Singh, K. N.; Venugopalan, P.; Kaur, A.; Bharatam, P. V.; Sharma, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 4506. (e) Kessar, S. V.; Singh, P.; Singh, K. N.; Bharatam, P. V.; Sharma, A. K.; Lata, S.; Kaur, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4703. (f) Abbat, S.; Dhaked, D.; Arfeen, M.; Bharatam, P. V. *RSC Adv.* **2015**, *5*, 88353.
(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, EM64L-G09RevB.01; Gaussian, Inc.: Wallingford, CT, 2010.
(19) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785. (b) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press; New York, 1989. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(20) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.
(21) Rao, B.; Zeng, X. *Org. Lett.* **2014**, *16*, 314.
(22) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 6124.
(23) Nath, J.; Patel, B. K.; Jamir, L.; Sinha, U. B.; Satyanarayana, K. V. V. V. *Green Chem.* **2009**, *11*, 1503.
(24) (a) Damodara, D.; Arundhathi, R.; Ramesh Babu, T. V.; Legan, M. K.; Kumpaty, H. J.; Likhar, P. R. *RSC Adv.* **2014**, *4*, 22567. (b) Yadav, A. K.; Yadav, L. D. S. *RSC Adv.* **2014**, *4*, 34764. (c) Cheung, C. W.; Surry, D. S.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3734.

DOI: 10.1021/acs.joc.6b00671
J. Org. Chem. 2016, 81, 5120−5127