JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of B,O,N-Doped Adamantanes and Diamantanes by Condensation of Oximes with Boronic Acids

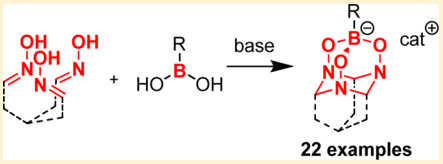
Ivan S. Golovanov,[†] Alexey Yu. Sukhorukov,*[,†] Yulia V. Nelyubina,[‡] Yulia A. Khomutova,[†] Sema L. Ioffe,[†] and Vladimir A. Tartakovsky[†]

[†]N.D. Zelinsky Institute of Organic Chemistry, Leninsky prospect 47, 119991, Moscow, Russia

[‡]A.N. Nesmeyanov Institute of Organoelement Compounds, Vavilov str. 28, 119991, Moscow, Russia

Supporting Information

ABSTRACT: Condensation of oximes with boronic acids $RB(OH)_2$ or $B(OH)_3$ affords remarkably stable 2,4,10-trioxa-1,5,7-triaza-3-boroadamantanes via an unprecedented multicomponent process. The mechanism involves the reversible generation of unstable oxime cyclotrimers, which are readily intercepted by boronic acids.



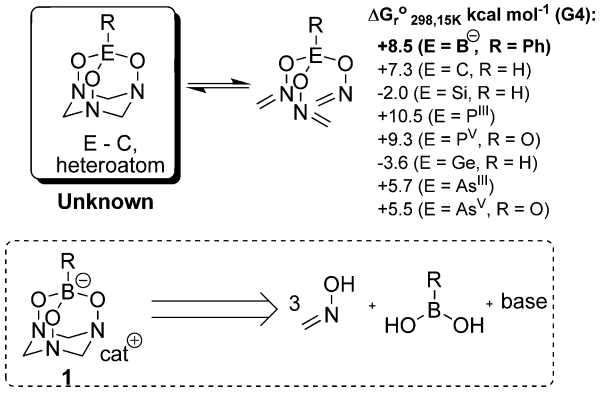
INTRODUCTION

Adamantane derivatives find numerous applications in medicine, material sciences, as well as the rational design of functional molecules and nanosystems.[1] Substitution of carbon atoms for heteroatoms provides vast opportunities for tuning adamatane properties and thus creation of substances and materials with predefined characteristics.[2] Thus, incorporation of heteroatoms such as nitrogen, oxygen, or boron in an adamantane cage results in a significant enhancement of pharmacological activity that led to development of highly potent heteroadamantane-based antiviral drugs.[2a] Some other staggering applications of heteroadamantanes are known. Polyazaadamantanes are used as precursors of high-energy materials[2b] and biodegradable polymers.[2c] Diamondoid molecules doped with oxygen atoms exhibit unusual electronic properties.[2d] Incorporation of boron and nitrogen atoms in the diamond structure produces a superhard and chemically inert material ("heterodiamond") with improved characteristics compared to diamond itself.[2e]

Owing to a significant progress in the synthesis of cage systems in the 1960s to 1980s, heteroadamantanes of various structures became available.[3] However, not any combination of heteroatoms in the adamantane skeleton leads to a stable cage structure.[4] The reasons of extreme stability of some heteroadamantanes and lability of other ones are still not completely understood, being probably a superposition of various factors such as stereoelectronic effects, 3D aromacity, lone electron pair repulsion, electrostatic interactions, etc.[4] In this context, basic studies of structure, stability, and reactivity of heterodiamondoid molecules are of high scientific interest.[4,5]

Unfortunately, traditional approaches to the construction of cage compounds seem to have exhausted themselves, and thus, many challenging heteroadamantane structures still remain inaccessible.[4] Among them are 2,4,10-trioxa-1,5,7-triaza-3-heteroadamantanes (Scheme 1), none of which are known in the literature. Quantum-chemical calculations at the G4 level of theory predict thermodynamic stability of these heterocage

Scheme 1. Suggested Approach to the Synthesis of Heteroadamantanes 1



systems over the corresponding isomeric orthoesters[6] ($R—E(O—N{=}CH_2)_3$) in case atom E is boron, carbon, phosphorus, and some other p-elements. In the present work, the synthesis of 2,4,10-trioxa-1,5,7-triaza-3-boroadamantanes **1** as the first representatives of this unusual class of heteroadamantanes is reported.

We assumed that the assembly of heteroadamantanes **1** can be achieved by a multicomponent condensation of three oxime molecules with a boronic acid involving the formation of three boron−oxygen bonds and cyclotrimerization of oxime groups (Scheme 1). This previously unknown transformation does not have any close analogy in the chemistry of oximes and resembles the one-pot multicomponent synthesis of methenamine from six molecules of formaldehyde and ammonia.[7]

Received: April 21, 2015
Published: June 2, 2015

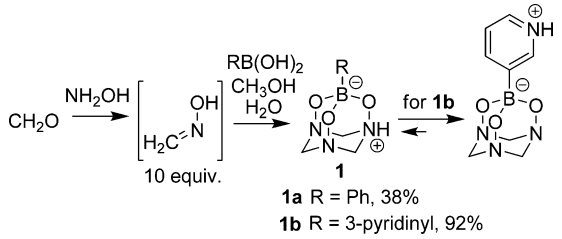
ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736

RESULTS AND DISCUSSION

In our preliminary studies, phenylboronic acid was treated with an excess of formaldoxime generated *in situ* from formaldehyde and hydroxylamine in aqueous methanol (Scheme 2). We were pleased to find that the desired adamantane **1a** did form in moderate yield. However, product **1a** proved to be a labile compound slowly decomposing in solution (DMSO-d_6, see the Supporting Information), forming formaldoxime and an indecipherable product mixture. On the basis of quantum-chemical calculations, we reasoned that the presence of a proton on the nitrogen atom in product **1a** may be the course of the instability of the 2,4,10-trioxa-1,5,7-triaza-3-boroadamantane cage. Indeed, the adduct of 3-pyridinylboronic acid with formaldehyde oxime (product **1b** in Scheme 2) proved to be more stable and formed in higher yield, probably because the proton is localized preferably on the nitrogen atom of the pyridine ring (Scheme 2).

Scheme 2. Interaction of Formaldoxime with Phenyl- and 3-Pyridinylboronic Acids



In a similar fashion, reaction of formaldehyde oxime with $PhB(OH)_2$ in the presence of K_2CO_3 furnished potassium salt of 2,4,10-trioxa-1,5,7-triaza-3-boroadamantane **1c** (entry 1, Table 1), for which X-ray analysis was performed.[8] Product **1c** is stable in air up to 250 °C and unlike **1a** does not undergo any noticeable decomposition upon storage in DMSO-d_6 solution within at least 2 weeks. Treatment of salt **1c** with an excess of HCl results in liberation of phenylboronic acid (73% yield), demonstrating that protonation leads to decomposition of 2,4,10-trioxa-1,5,7-triaza-3-boroadamantane structure.

Using this protocol, several stable potassium salts of heteroadamantanes **1c–h** containing various substituents at the boron atom were obtained (entries 1–6, Table 1). Importantly, $B(OH)_3$ and $B(OCH_3)_3$ also successfully entered the condensation with formaldehyde, hydroxylamine, and K_2CO_3 to yield potassium salts of adamantanes **1g** and **1h** in 86 and 85% yields, respectively (entries 5 and 6, Table 1).

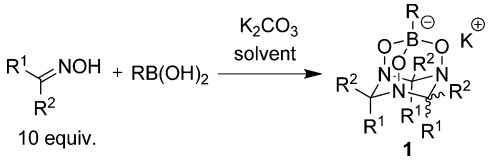
Condensation of acetaldehyde oxime with phenylboronic acid in the presence of K_2CO_3 under solvent-free conditions afforded potassium salt **1i** in 73% yield as a mixture of diastereomers *eq,eq,eq*-**1i** and *eq,eq,ax*-**1i** in 2.0:1.0 ratio (entry 7, Table 1). Reaction with propionaldehyde oxime under the same conditions was less smooth, and the desired adamantane salt **1j** was formed in 10% yield (entry 8, Table 1). In the case of a more bulky isobutyraldehyde oxime (Table 1, entry 9), the corresponding adamantane **1k** was detected only in trace amounts by ESI-HRMS. Benzaldehyde and acetone oximes did not react with phenylboronic acid (entries 10 and 11, Table 1).

These results clearly demonstrate that the presence of substituents at the oxime group complicates the formation of products **1**. We supposed that the formation of heteroadamantane **1** could proceed easier if three oxime groups were tethered together. The only compounds of this type available to date are tris(β-oximinoalkyl)amines **2** (Table 2).[9]

Consequently, we studied the interaction of various symmetrically and unsymmetrically substituted tris-oximes **2a–j** with boronic acids (Table 2). Most of the tris-oximes **2** studied did react with $PhB(OH)_2$ to give in good to high yields stable diamantanes **3** containing 2,4,10-trioxa-1,5,7-triaza-3-boroadamantane fused with the 1,4,6,10-tetraazaadamantane cage (entries 1–5, 8, and 10, Table 2). Since basic tertiary nitrogen is present in tris-oximes **2**, all reactions were performed without an external base.

The nature of substituents at oxime groups mainly influenced the time needed for a full conversion of reagents; i.e., more bulky tris-oximes **2** reacted slower (cf. entries 2–5, Table 2). The exceptions were tris-oximes **2f** bearing three phenyl groups

Table 1. Synthesis of Potassium Salts of Heteroadamantanes 1

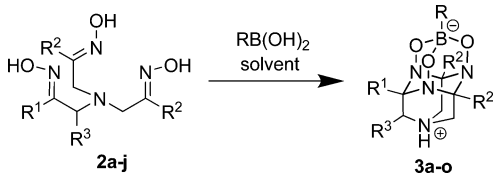


entry	**1**	R	R^1	R^2	solvent	yield[a] (%)
1	**c**	Ph	H	H	CH_3OH/H_2O	99
2	**d**	3-pyridinyl	H	H	CH_3OH/H_2O	92
3	**e**	*trans*-CH=CH—Ph	H	H	CH_3OH/H_2O	79
4	**f**	CH_3	H	H	CH_3OH/H_2O	97
5	**g**	OH	H	H	H_2O	86
6	**h**	OCH_3[b]	H	H	CH_3OH/H_2O	85
7	**i**	Ph	H	CH_3	n.s.[c]	73[d,e]
8	**j**	Ph	H	Et	n.s.	10[d,f,g]
9	**k**	Ph	H	*i*-Pr	n.s.	traces
10	**l**	Ph	H	Ph	n.s.	n.r.[h]
11	**m**	Ph	CH_3	CH_3	CH_3OH	n.r.

[a]Yields calculated on $RB(OH)_2$. [b]$B(OCH_3)_3$ was used. [c]n.s. - no solvent, 5 equiv of H_2O were added. [d]*Eq* and *ax* correspond to positions of substituents R^2 in triazine ring. [e]d.r. *eq,eq,*eq-**1i**/*eq,eq,ax*-**1i** = 2.0:1.0. [f]Determined by ^1H NMR with internal standard. [g]Characterized in a mixture with potassium phenylborate, d.r. *eq,eq,*eq-**1j**/*eq,eq,ax*-**1j** = 1.0:1.4. [h]n.r. - no reaction observed within 24 h.

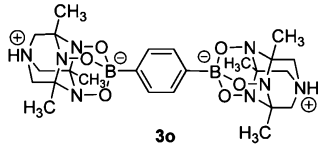
DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728–6736

Table 2. Condensation of Tris-Oximes 2 with Boronic Acids



entry	2	3	R	R^1	R^2	R^3	yield (%)
1	**a**	**a**	Ph	H	H	H	70[a,b]
2	**b**	**b**	Ph	CH_3	CH_3	H	89[b,c]
3	**c**	**c**	Ph	Et	Et	H	83[b,c]
4	**d**	**d**	Ph	$(CH_2)_2CO_2CH_3$	$(CH_2)_2CO_2CH_3$	H	78[a,b]
5	**e**	**e**	Ph	CH_2Ph	CH_2Ph	H	76[b,d]
6	**f**	**f**	Ph	Ph	Ph	H	n.r.[b,e,f]
7	**g**	**g**	Ph	CO_2Et	CO_2Et	H	n.r.[b,e]
8	**h**	**h**	Ph	H	Ph	CH_3	64[a,b]
9	**i**	**i**	Ph	CH_2Ph	Ph	H	n.r.[b,d]
10	**j**	**j**	Ph	$(CH_2)_2CO_2CH_3$	CH_3	H	72[b,c]
11	**b**	**k**	CH_3	CH_3	CH_3	H	93[b,c]
12	**b**	**l**	*trans*-CH=CH—Ph	CH_3	CH_3	H	91[b,c]
13	**b**	**m**	cyclopropyl	CH_3	CH_3	H	91[b,c]
14	**b**	**n**	OH	CH_3	CH_3	H	99[c,g]
15	**b**	**o**	4-$(HO)_2B$—C_6H_4—	CH_3	CH_3	H	83[b,c,h]

[a]48 h. [b]Solvent - CH_3OH. [c]24 h. [d]72 h. [e]96 h. [f]n.r. - no reaction. [g]Solvent - H_2O. [h]2 equiv of **2b** were used. Product:

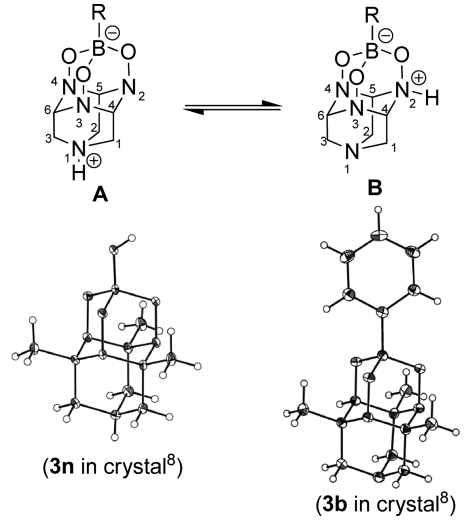


(entry 6, Table 2), **2g** with three CO_2Et substituents (entry 7, Table 2), and **2i** bearing two phenyl and one benzyl group (entry 9, Table 2). No conversion of these tris-oximes was observed. On the contrary, condensation of $PhB(OH)_2$ with tris-oxime **2h** possessing two phenyl groups and a hydrogen at the oxime groups produced the desired unsymmetrically substituted diamantane **3h** in moderate yield (entry 8, Table 2). Therefore, reaction of tris-oximes **2** with boronic acids proved to be much less sensitive to the substitution at oxime groups as compared to mono-oximes. In particular, aldoximes as well as ketoximes **2** bearing relatively bulky benzyl and phenyl groups afforded the corresponding diamantanes **3** efficiently.

Various boronic acids were well-tolerated in the reaction with tris-oximes **2** (entries 11−15, Table 2). In addition to $PhB(OH)_2$, diamantane adducts of tris-oxime **2b** with methyl-, cyclopropyl-, and *trans*-styrylboronic acids as well as with $B(OH)_3$ were prepared in excellent yields (entries 11−14, Table 2). 1,4-Phenylenediboronic acid in reaction with 2 equiv of tris-oxime **2b** selectively produced a 1:2 adduct **3o** in high yield (entry 15, Table 2).

Structures of diamantanes **3b** and **3n** were secured by single-crystal X-ray analysis (Scheme 3).[8] Interestingly, in the crystal of **3n**, the acidic proton is localized on nitrogen atom N(1) (form **A**), while in **3b** nitrogen N(2) is protonated (form **B**) (Scheme 3). As a result, a considerable distortion of the triazine ring is observed in **3b** due to the elongation of bonds C(4)−N(2) and C(5)−N(2) (by 0.02−0.04 Å) and shortening of bonds C(4)−N(3) and C(5)−N(4) (by 0.02−0.03 Å) as compared to analogous bonds in **3n**. Such distortion results from strong lp(N) → $\sigma^*_{C-N(2)}$ interactions in structure **B**,

Scheme 3. Structures of Diamantanes 3n and 3b[a]



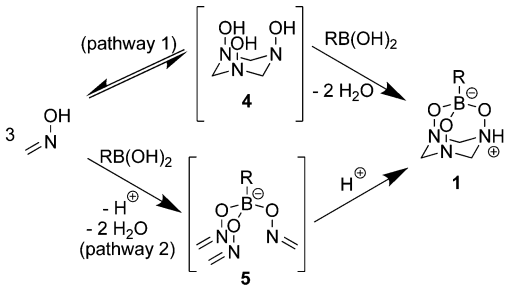
[a]Methyl groups are omitted for clarity.

leading to charge transfer from lone electron pairs of nitrogens N(3) and N(4) to the σ^* orbitals of C−N(2) bonds as confirmed by NBO analysis for **3b** (Supporting Information). Furthermore, the presence of a positive charge on nitrogen N(2) in diamantane **3b** leads to the expected shortening of the $N(2)^+$−O(1) bond (by 0.03 Å) and elongation of the B−O(1) bond (by 0.02−0.03 Å) as compared to the corresponding bonds with N(3) and N(4). It is likely that there is equilibrium between zwitterionic forms **A** and **B** in solution, leading to the observed widening of signals in NMR spectra in products **3**.

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736

Two mechanisms can be proposed for the discovered condensation of oximes with boronic acids (Scheme 4). The

Scheme 4. Possible Mechanisms for the Formation of Heteroadamantanes 1



Calculated free energies of oxime cyclotrimerization in gas-phase:

Intermolecular (3 oximes ⇌ **4**) Intramolecular (tris-oxime **2** ⇌ **6**)

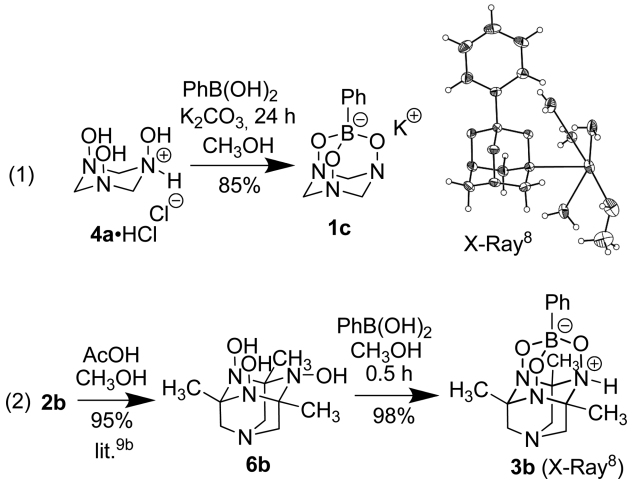
Oxime	$\Delta G_r°_{298,15K}$ kcal mol^{-1} (method)	Tris-oxime	$\Delta G_r°_{298,15K}$ kcal mol^{-1} (method)
H_2C=NOH	+4.6 (G4)	**2a**	-3.8 (G4MP2)
CH_3HC=NOH	+7.6 (G4)	**2b**	-0.7 (G4MP2)
EtHC=NOH	+8.2 (G4MP2)		
$(CH_3)_2C$=NOH	+27.2 (G4MP2)		

first pathway involves oxime cyclotrimerization furnishing all-*cis*-1,3,5-trihydroxy-hexahydro-1,3,5-triazines **4**,[10] which serve as the matrix for the assembly of adamantanes **1** in reaction with $RB(OH)_2$. The second pathway starts with condensation of three oxime molecules with a boronic acid furnishing boronates **5**, which then cyclize to adamantane **1**. Both routes involve as a key stage the cyclotrimerization of C═N—O fragments, which is nontypical for oximes.

In our experiments, we never observed the formation of open-chain oxime ethers **5** neither in methanol/H_2O nor in toluene solutions. In those cases, when adamantanes **1** or **3** were not formed, the initial oximes and boronic acids remained unchanged (according to ^{1}H NMR, see the Supporting Information). On the other hand, stable 1,3,5-trihydroxy-1,3,5-triazines **4a**·HCl[10] and **6b** (prepared from **2b**[9b]) readily reacted with phenylboronic acid to give the corresponding adamantanes **1c** and **3b** in quantitative yield (Scheme 5). Furthermore, strong correlation between oxime cyclotrimerization and the formation of corresponding boradamantanes is observed: tris-oximes **2f,g,i**, which did not enter the intramolecular oxime cyclotrimerization,[9b] did not react with boronic acids (entries 6, 7, and 9, Table 2). These data suggest that pathway (1) involving oxime trimers **4** or **6** as key intermediates is likely to be involved (Scheme 4). However, pathway (2) cannot be completely ruled out as a competitive route considering that boronate **5** cyclization to heteroadamantane **1** should be thermodynamically favored according to G4 theory level calculations (see Scheme 1 and the Supporting Information).

Pathway (1) explains why the formation of heteroadamantanes **1** from substituted oximes is difficult (Table 1). Evidently, the reason is thermodynamic instability of oxime cyclotrimers **4**.[9b,10] In contrast to azomethines and carbonyl compounds,[11] the intermolecular cyclotrimerization of oximes has been reported only for formaldoxime.[10] The resulting trimer **4a** is a kinetic product and decomposes to a monomer and polymer.[10] Substitution at the oxime group hampers its

Scheme 5. Reaction of 1,3,5-Trihydroxy-1,3,5-triazines 4a·HCl and 6b with $PhB(OH)_2$

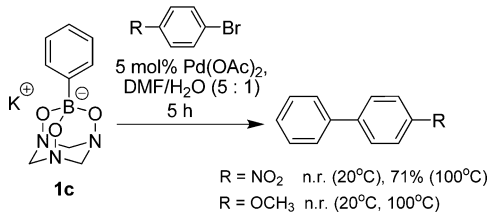


cyclotrimerization both in inter- and intramolecular variants, which is well-illustrated by high-level quantum-chemical calculations (see the table in Scheme 4). Thus, we failed to observe cyclotrimerization of acetaldehyde oxime by ^{1}H NMR in a broad concentration range (0.2−10 M in $CDCl_3$), indicating that the equilibrium concentration of the corresponding trimer **2** is very low. Apparently, cyclotrimerization of simple aldoximes takes place only to a very small extent; however, the trimer **4** still can be intercepted by a boronic acid to give a stable heteroadamantane anion **1**. Therefore, reactions with boronic acids may serve as a convenient tool to study the oxime cyclotrimerization process.

The suggested strategy for the synthesis of B,O,N-doped adamantanes may be useful in the construction of pH responsible boronate linear polymers, dendrimers, and supramolecular systems.[12] 2,4,10-Trioxa-1,5,7-triaza-3-boroadamantanes of types **1** and **3** represent interest as potential antiviral agents considering their structural similarity to bananins.[2a,13] Furthermore, boradamantane salts **1**, which are readily prepared by mixing $RB(OH)_2$ with formaldehyde, hydroxylamine, and K_2CO_3, may be considered as convenient thermo- and air-stable forms of boronic acids. Interestingly, unlike other boronates,[14] adamantane **1c** proved to be unreactive in Suzuki−Miyaura (SM) coupling with 1-bromo-4-nitrobenzene and 1-bromo-4-methoxybenzene at ambient temperature. The formation of coupling product (4-nitrobiphenyl) was observed only at elevated temperatures and led to complete decomposition of heteroadamantane (Scheme 6).

Similar behavior was recently reported by Kuno[15] for adamantane-like boronates derived from *scyllo*-inosytol, which thus was suggested as an effective protective group for arylboronic acids.[14] In this context, boradamantanes **1** may be

Scheme 6. SM Coupling with Boradamantane 1c



DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736

considered as an alternative to *scyllo*-inosytol complexes of boronic acids. Further studies on application of 2,4,10-trioxa-1,5,7-triaza-3-boroadamantanes **1** and **3** in other transition-metal-catalyzed cross-coupling reactions are currently underway.

CONCLUSIONS

In summary, a straightforward synthesis of hitherto unknown 2,4,10-trioxa-1,5,7-triaza-3-boroadamantanes and their fused derivatives has been achieved by an unprecedented multicomponent condensation of oximes with boronic acids. The discovered process involves uncommon cyclotrimerization of oximes to unstable 1,3,5-trihydroxy-1,3,5-triazaadamantanes, which react with boronic acids to give the desired heteroadamantanes.

EXPERIMENTAL SECTION

All reactions were performed in oven-dried (150 °C) glassware. 1D and 2D NMR spectra were recorded at room temperature on a 300 MHz spectrometer with residual solvents peaks as an internal standard.[16] Chemical shifts in ^{11}B are given relative to $BF_3{\cdot}Et_2O$. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), and br (broad). *W* values correspond to the full width at half-maximum of signal in Hz. Peaks in FT-IR-spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), and sh (shoulder). HRMS were measured on an electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light and solution of ninhydrine/acetic acid in ethanol. CH_3OH, EtOH, and ethyl acetate were distilled without drying agents. All inorganic reagents and boronic acids were commercial grade and were used as received. Tris-oximes **2a,c,d,g**,[9b] **2b,e,f**,[9a] **2i,j**,[9c] and 1,4,6,10-tetraazaadamantane **6b**[9b] were synthesized according to previously published protocols. Quantum-chemical calculations were performed with the Gaussian 09 program.

Synthesis of 3-Boro-2,4,10-trioxa-1,5,7-triazaadamantanes 1a–g. To a stirred solution of boronic acid or $B(OH)_3$ (1.0 mmol) in 1.8 mL of CH_3OH (for **1a–f**) or water (for **1g**) at 0 °C was added a 37% aqueous solution of formaldehyde (0.75 mL, 10 mmol) followed by a 50% aqueous solution of hydroxylamine (0.61 mL, 10 mmol). The mixture was stirred for 10 min at 0 °C, warmed up to room temperature, and stirred for 18 h followed by addition of potassium carbonate (69 mg, 0.5 mmol, for the synthesis of **1c–g**). After stirring for an additional 5 h, the reaction mixture was diluted with water (5 mL) and the precipitate was centrifuged off and washed with water (5 mL) and CH_3OH (5 mL) in centrifuge cups. Combined solutions were evaporated in a vacuum at 45–50 °C, and the residue was dried in a vacuum at 0.1 Torr until constant weight (unstable products **1a,b** were dried at room temperature, and products **1c–g** were dried at 100 °C).

*3-Phenyl-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo[3.3.1.1^{3,7}]-decan-1-ium-3-uide (**1a**).* 0.084 g (yield 38%). White solid, decomposes upon storage at r.t. or heating. Undergoes decomposition at 149–150 °C to give crystalline triphenyl boroxine (Mp = 208–212 °C, lit.[17] 213–214 °C). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 4.62 (d, *J* = 12.2 Hz, 3 H), 4.85 (d, *J* = 12.2 Hz, 3 H), 7.12 (m, 3 H), 7.32 (d, *J* = 5.4 Hz, 2 H), 8.59 (br, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6): σ = 72.6, 126.1, 126.4 and 130.9, 146.1. ^{11}B NMR (96 MHz, DMSO-d_6): σ = 6.6 (br, *W* = 480 Hz). FT-IR: 3406 (w, br), 3181 (m, br), 3013 (s), 2997 (s), 2936 (s, sh), 2759 (s, br), 2091 (w, br), 1633 (m), 1533 (w), 1434 (m), 1372 (w), 1297 (w), 1237 (s, sh), 1164 (s), 991 (m, sh), 945 (s), 932 (s), 909 (m), 877 (m), 844 (s), 809 (s), 744 (s), 710 (m), 680 (s), 537 (m), 438 (m, sh). ESI-HRMS *m/z*: $[M - H]^-$ Calcd for $C_9H_{11}BN_3O_3$ 220.0901; Found 220.0908.

*3-(Pyridin-3-yl)-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo-[3.3.1.1^{3,7}]decan-1-ium-3-uide (**1b**).* 0.204 g (yield 92%). For analytical purposes, the product was recrystallized from CH_3OH–AcOEt–Et_2O = 1:1:1 to give **1b** as colorless needles. Mp 152–157 °C (with decomposition). ^{1}H NMR (300 MHz, D_2O): σ = 4.70 (d, *J* = 13.0 Hz, 3 H), 4.74 (br s, N*H* and H_2O), 5.05 (d, *J* = 13.0 Hz, 3 H), 7.95 (t, *J* = 6.8 Hz, 1 H), 8.52 (d, *J* = 6.8 Hz, 1 H), 8.54 (s, 1 H), 8.61 (d, *J* = 6.8 Hz, 1 H). ^{13}C NMR (75 MHz, DEPT, D_2O): σ = 72.5 (*C*H$_2$), 126.6 and 140.0 (*C*H), 142.2 and 149.0 (*C*H) (*C*-B not observed). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 5.6 (br, *W* = 96 Hz). FT-IR: 3461 (s, br), 3122 (m), 3050 (m), 2997 (m), 2925 (m), 2526 (s, br), 2155 (s, br), 1649 (s, sh), 1467 (s), 1423 (m, sh), 1372 (s), 1252 (s), 1233 (s), 1164 (s, sh), 1058 (m), 999 (s), 959 (s), 944 (s), 902 (m), 816 (m), 786 (s), 691 (s, sh), 614 (s), 526 (w), 511 (w), 443 (s, sh). ESI-HRMS *m/z*: $[M - H]^-$ Calcd for $C_8H_{10}BN_4O_3$ 221.0853; Found 221.0857; $[M + H]^+$ Calcd for $C_8H_{12}BN_4O_3$ 223.0998; Found 223.0994.

*Potassium 3-Phenyl-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo-[3.3.1.1^{3,7}]decan-3-uide (**1c**).* 0.256 g (yield 99%). White solid. Dec. 280 °C (without melting). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 4.32 (d, *J* = 12.1 Hz, 3 H), 4.75 (d, *J* = 12.1 Hz, 3 H), 7.02 (m, 3 H), 7.29 (d, *J* = 6.8 Hz, 2 H). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 73.9 (*C*H$_2$), 125.2, 125.9, and 131.2 (*C*H) (*C*-B not observed). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 6.3 (br, *W* = 288 Hz). FT-IR: 3420 (s, br), 3075 (w, sh), 3015 (w), 2978 (m), 2937 (m), 2230 (w, br), 1639 (m), 1441 (m, sh), 1420 (m), 1364 (m), 1259 (m), 1232 (s), 1159 (s), 1040 (m), 1026 (m), 993 (s), 940 (s, sh), 914 (m), 894 (m), 814 (m), 799 (w), 737 (m), 710 (m), 696 (s), 635 (m, br), 580 (s, br), 490 (w), 446 (w), 430 (w). ESI-HRMS *m/z*: $[M - K]^-$ Calcd for $C_9H_{11}BN_3O_3$ 220.0901; Found 220.0901. Anal. Calcd for $C_9H_{11}BKN_3O_3$: C, 41.72; H, 4.28; N, 16.22. Found: C, 41.54; H, 4.48; N, 16.12.

For X-ray diffraction analysis, the compound was crystallized from a CH_3OH/H_2O = 10:1 mixture to give crystal solvate **1c**·3.25H_2O·CH_3OH.

*Potassium 3-(Pyridin-3-yl)-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo[3.3.1.1^{3,7}]decan-3-uide Hydrate (**1d**).* 0.247 g (yield 92%). White hydroscopic solid. Dec. 240 °C (without melting). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 4.38 (d, *J* = 11.9 Hz, 3 H), 4.77 (d, *J* = 11.9 Hz, 3 H), 7.04 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1 H), 7.57 (ddd, *J* = 7.4, 1.8, 1.8 Hz, 1 H), 8.21 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.40 (dd, *J* = 1.8, 0.9 Hz, 1 H). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 74.0 (*C*H$_2$), 122.1 and 138.6 (*C*H), 146.4 and 152.4 (*C*H) (*C*-B not observed). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 6.0 (br, *W* = 192 Hz). ESI-HRMS *m/z*: $[M - K]^-$ Calcd for $C_8H_{10}BKN_4O_3$ 221.0853; Found 221.0851. Anal. Calcd for $2C_8H_{10}BKN_4O_3{\cdot}H_2O$: C, 35.71; H, 4.12; N, 20.82. Found: C, 35.95; H, 4.32; N, 21.11.

*Potassium 3-[(E)-2-Phenylethenyl]-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo[3.3.1.1^{3,7}]decan-3-uide (**1e**).* 0.225 g (yield 79%). White solid. Dec. > 290 °C (without melting). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 4.23 (d, *J* = 12.0 Hz, 3 H), 4.67 (d, *J* = 12.0 Hz, 3 H), 5.92 (d, *J* = 18.4 Hz, 1 H), 6.37 (d, *J* = 18.4 Hz, 1 H), 7.10 (m, 1 H), 7.23 (m, 4 H). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 74.0 (*C*H$_2$), 125.3, 125.8, 128.2 (*C*H), 133.8 (*C*H), 139.1 (*C*), 140.3 (*C*H). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 5.8 (br, *W* = 288 Hz). FT-IR: 3420 (s, br), 3076 (m), 3022 (m), 2994 (m, sh), 2932 (m), 1638 (s, sh), 1493 (m), 1447 (s), 1422 (s), 1377 (s, sh), 1301 (m), 1242 (m), 1154 (s, sh), 1125 (s), 996 (m), 959 (s, sh), 931 (s), 883 (s), 823 (s), 783 (s), 733 (m), 691 (s), 670 (m), 554 (m), 521 (m), 495 (m), 451 (m). ESI-HRMS *m/z*: $[M - K]^-$ Calcd for $C_{11}H_{13}BN_3O_3$ 246.1057; Found 246.1060. Anal. Calcd for $C_{11}H_{13}BKN_3O_3$: C, 46.33; H, 4.60; N, 14.74. Found: C, 45.64; H, 4.54; N, 14.51.

*Potassium 3-Methyl-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo-[3.3.1.1^{3,7}]decan-3-uide (**1f**).* 0.191 g (yield 97%). White solid. Dec. > 290 °C (without melting). ^{1}H NMR (300 MHz, D_2O): σ = −0.39 (s, 3 H), 4.60 (d, *J* = 13.1 Hz, 3 H), 4.94 (d, *J* = 13.1 Hz, 3 H). ^{13}C NMR (75 MHz, D_2O): σ = 2.8 (*C*H$_3$), 72.2 (*C*H$_2$). ^{11}B NMR (96 MHz, D_2O): σ = 8.1 (br, *W* = 192 Hz). FT-IR: 3343 (s, br), 3236 (m, br), 3017 (w), 2965 (s), 2942 (s), 2929 (s), 1701 (w, br), 1604 (w, br), 1447 (m), 1432 (m), 1367 (m), 1307 (s), 1296 (s), 1163 (s, sh), 1105 (s), 997 (s), 982 (s), 967 (s), 930 (s), 889 (m), 814 (s), 743 (s), 687 (s), 617 (w, br), 564 (w), 482 (w), 430 (w). ESI-HRMS *m/z*: $[M - K]^-$ Calcd for $C_4H_9BN_3O_3$ 158.0732; Found 158.0735. Anal. Calcd

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728–6736

for $C_4H_9BKN_3O_3$: C, 24.38; H, 4.60; N, 21.33. Found: C, 24.35; H, 4.62; N, 21.22.

*Potassium 3-Hydroxy-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo-[3.3.1.1^{3,7}]decan-3-uide (**1g**).* 0.171 g (yield 86%). White solid. Dec. > 220 °C (without melting). ^{1}H NMR (300 MHz, D_2O): σ = 4.54 (d, J = 13.2 Hz, 3 H), 4.72 (d, J = 13.2 Hz, 3 H), 4.79 (br, O*H*). ^{13}C NMR (75 MHz, DEPT, D_2O): σ = 71.2 (CH_2). ^{11}B NMR (96 MHz, D_2O): σ = 2.1. FT-IR: 3407 (s, br), 2992 (m), 2940 (m), 1663 (m, sh), 1431 (m, sh), 1365 (m), 1267 (s, sh), 1160 (s), 945 (s), 911 (s), 890 (s), 818 (s), 796 (s), 692 (s), 563 (w), 483 (w), 437 (w). ESI-HRMS m/z: [M − K]$^-$ Calcd for $C_3H_7BN_3O_4$ 160.0536; Found 160.0539. Anal. Calcd for $C_3H_7BKN_3O_4$: C, 18.11; H, 3.55; N, 21.11. Found: C, 18.24; H, 3.56; N, 21.25.

Synthesis of 3-Boro-2,4,10-trioxa-1,5,7-triazaadamantane 1h. To a stirred solution of $B(OCH_3)_3$ (0.112 mL, 1.0 mmol) in 1.8 mL of CH_3OH at 0 °C was added a 37% aqueous solution of formaldehyde (0.75 mL, 10 mmol) followed by a 50% aqueous solution of hydroxylamine (0.61 mL, 10 mmol). The mixture was stirred for 10 min at 0 °C, warmed up to room temperature, and stirred for 18 h followed by addition of potassium carbonate (69 mg, 0.5 mmol). After stirring for an additional 5 h, the reaction mixture was diluted with CH_3OH (5 mL) and the precipitate was centrifuged off and washed with CH_3OH (2 × 5 mL) in centrifuge cups. Combined solutions were evaporated in a vacuum at 45−50 °C to give a mixture of **1g** and **1h** (ratio 1.6:1.0). The residue was dissolved in CH_3OH (10 mL) and refluxed for 1 h to convert **1g** to **1h** and evaporated in a vacuum. The product was dried in a vacuum at 0.1 Torr and 100 °C until constant weight to give analytically pure **1h** as white solid (0.181 g, 85%). Dec. 230 °C (without melting). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 3.07 (s, 3 H), 4.14 (d, J = 12.1 Hz, 3 H), 4.41 (d, J = 12.1 Hz, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): σ = 47.9, 72.7. ^{11}B NMR (96 MHz, DMSO-d_6): σ = 2.7. ESI-HRMS m/z: [M − K]$^-$ Calcd for $C_4H_9BN_3O_4$ 174.0694; Found 174.0692. Anal. Calcd for $C_4H_9BKN_3O_4$: C, 22.55; H, 4.26; N, 19.72. Found: C, 22.52; H, 4.32; N, 19.65.

Synthesis of 3-Boro-2,4,10-trioxa-1,5,7-triazaadamantanes 1i,j. Phenylboronic acid (122 mg, 1.0 mmol) and oxime (10 mmol) were placed in a vial, water (0.09 mL, 5.0 mmol) was added, and the resulting slurry was stirred for 5 min followed by addition of potassium carbonate (69 mg, 0.5 mmol). After stirring for 24 h at room temperature, the reaction mixture was diluted with Et_2O (3 mL) and water (3 mL). The organic layer was separated, the aqueous layer was washed with Et_2O (3 × 2 mL), and the combined organic extracts were washed with water (2 mL). The combined aqueous solutions were evaporated in a vacuum at 45−50 °C, and the residue was dried in a vacuum at 0.1 Torr and 100 °C until constant weight.

*Potassium 6,8,9-Trimethyl-3-phenyl-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo[3.3.1.1^{3,7}]decan-3-uide Hydrate (**1i**).* 0.233 g (yield 73%). White hydroscopic solid. Dec. 250 °C (without melting). Mixture of *eq,eq,eq*-**1i** and *eq,eq,ax*-**1i** isomers (ratio 2.0:1.0). ^{1}H NMR (300 MHz, DMSO-d_6, COSY, HSQC, NOESY, *eq,eq,eq*-**1i**): σ = 1.49 (d, J = 6.3 Hz, 9 H, CH_3), 3.88 (q, J = 6.3 Hz, 3 H, C*H*), 6.96−7.06 (m, 3 H, *m*-, *p*-C_6H_5), 7.30 (d, J = 7.7 Hz, 2 H, *o*-C_6H_5). ^{13}C NMR (75 MHz, DMSO-d_6, HSQC, *eq,eq,eq*-**1i**): σ = 18.2 (CH_3), 76.5 (*C*H), 124.8, 125.7, and 131.1 (*o*, *m*, *p*-C_6H_5), 150.7 (*C*-B). ^{1}H NMR (300 MHz, DMSO-d_6, COSY, HSQC, NOESY, *eq,eq,ax*-**1i**): σ = 1.16 (d, J = 7.3 Hz, 3 H, *ax*-CH_3), 1.47 (d, J = 6.3 Hz, 6 H, *eq*-CH_3), 4.03 (q, J = 6.3 Hz, 2 H, *ax*-C*H*), 5.00 (q, J = 7.3 Hz, 1 H, *eq*-C*H*), 6.96−7.06 (m, 3 H, *m*-, *p*-C_6H_5), 7.29 (d, J = 6.2 Hz, 2 H, *o*-C_6H_5). ^{13}C NMR (75 MHz, DMSO-d_6, HSQC, *eq,eq,ax*-**1i**): σ = 16.3 (*eq*-CH_3), 18.2 (*ax*-CH_3), 69.2 (*ax*-CH), 78.3 (*eq*-CH), 124.8, 125.7, and 131.2 (*o*, *m*, *p*-C_6H_5), 150.7 (*C*-B). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 4.6 (br, W = 288 Hz). Characteristic 2D-NOESY correlations in *eq,eq,ax*-**1i**: *ax*-C*H*/*ax*-CH_3. FT-IR: 3332 (s, br), 3067 (s), 3005 (s, sh), 2935 (s), 1648 (m, sh), 1432 (m, sh), 1369 (s), 1318 (m), 1244 (m, sh), 1225 (s), 1163 (s), 1120 (m), 1085 (w), 1044 (s), 1002 (s, sh), 932 (s, sh), 914 (s, sh), 766 (s), 752 (s), 737 (s), 704 (s), 654 (w), 590 (w), 534 (w, sh), 409 (m). ESI-HRMS m/z: [M − K]$^-$ Calcd for $C_{12}H_{17}BN_3O_3$ 262.1360; Found 262.1374. Anal. Calcd for $C_{12}H_{17}BKN_3O_3{\cdot}H_2O$: C, 45.15; H, 6.00; N, 13.16. Found: C, 44.60; H, 6.49; N, 12.73.

*Potassium 6,8,9-Triethyl-3-phenyl-2,4,10-trioxa-1,5,7-triaza-3-boratricyclo[3.3.1.1^{3,7}]decan-3-uide (**1j**).* Obtained and characterized in mixture with potassium phenylborate.[18] Mixture of *eq,eq,eq*-**1j** and *eq,eq,ax*-**1j** isomers (ratio 1.0:1.4). White hydroscopic solid. ^{1}H NMR (300 MHz, D_2O, COSY, HSQC, NOESY, *eq,eq,eq*-**1j**): σ = 1.07 (t, J = 7.6 Hz, 9 H, CH_2CH_3), 2.24 (m, 6 H, CH_2CH_3), 3.96 (t, J = 6.3 Hz, 3 H, C*H*), 7.30−7.40 (m, 3 H, *m*-, *p*-C_6H_5), 7.49 (br d, J = 6.7 Hz, 2 H, *o*-C_6H_5). ^{13}C NMR (75 MHz, D_2O, HSQC, *eq,eq,eq*-**1j**): σ = 10.2 (CH_3), 23.8 (CH_2), 82.7 (*C*H), 127.1, 127.6, and 131.0 (*o*, *m*, *p*-C_6H_5) (*C*-B not observed). ^{1}H NMR (300 MHz, D_2O, COSY, HSQC, NOESY, *eq,eq,ax*-**1j**): σ = 1.07 (t, J = 7.3 Hz, 3 H, *ax*-CH_2CH_3), 1.12 (t, J = 7.6 Hz, 6 H, *eq*-CH_2CH_3), 1.78 (m, 2 H, *ax*-CH_2CH_3), 2.09 and 2.29 (2 m, 4 H, *eq*-CH_2CH_3), 4.12 (t, J = 6.3 Hz, 2 H, *ax*-C*H*), 5.06 (t, J = 6.8 Hz, 1 H, *eq*-C*H*), 7.30−7.40 (m, 3 H, *m*-, *p*-C_6H_5), 7.49 (br d, J = 6.7 Hz, 2 H, *o*-C_6H_5). ^{13}C NMR (75 MHz, D_2O, HSQC, *eq,eq,ax*-**1j**): σ = 9.8 (*eq*-CH_2CH_3), 10.6 (*ax*-CH_2CH_3), 23.0 (*ax*-CH_2CH_3), 23.6 (*eq*-CH_2CH_3), 75.8 (*ax*-CH), 84.1 (*eq*-CH), 127.1, 127.6, and 131.9 (*o*, *m*, *p*-C_6H_5) (*C*-B not observed). Characteristic 2D-NOESY correlations in *eq,eq,ax*-**1j**:*ax*-C*H*/*ax*-CH_2CH_3. ESI-HRMS m/z: [M − K]$^-$ Calcd for $C_{15}H_{23}BN_3O_3$ 304.1833; Found 304.1841.

Synthesis of 3-Boro-2,4,10-trioxa-1,5,7-triazaadamantanes 3a−e,h,j−o from Tris-Oximes 2a−e,h. To a stirred solution of tris-oxime **2a−e,h,j** (1.0 mmol) in 8 mL of CH_3OH (for **3a−e,h,j−m,o**) or water (for **3n**) was added boronic acid (1.0 mmol for **3a−e,h,j−n**, 0.5 mmol for **3o**). The solution was kept at room temperature for the time indicated in Table 2 and evaporated in a vacuum. The residue was triturated with AcOEt and dried in a vacuum (0.1 Torr and 100 °C) until constant weight.

*9-Phenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo-[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (**3a**).* 192 mg (yield 70%). White solid. Dec. ca. 200 °C (without melting). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 3.21 (s, 6 H), 3.27 (br, *H*N), 4.83 (s, 3H), 7.09−7.15 (m, 3 H), 7.33 (br d, J = 7.9 Hz, 2 H). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 53.2 (CH_2), 72.3 (CH), 126.3, 126.4, and 131.0 (CH), 144.8 (*C*). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 4.3 (br W = 384 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{12}H_{14}BN_4O_3$ 273.1167; Found 273.1168; [M + H]$^+$ Calcd for $C_{12}H_{16}BN_4O_3$ 275.1312; Found 275.1322. Anal. Calcd for $C_{12}H_{15}BN_4O_3$: C, 52.59; H, 5.52; N, 20.44. Found: C, 52.28; H, 5.69; N, 20.12.

*2,6,12-Trimethyl-9-phenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide Dihydrate (**3b**).* 313 mg (yield 89%). White hydroscopic solid. For analytical purposes and X-ray diffraction analysis, the sample was crystallized from H_2O−MeOH (1:1). Mp = 138−144 °C (melting with dec.). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 1.60 (s, 9 H), 3.05 (s, 6 H), 3.80−5.20 (br, H_2O and *H*N), 7.09−7.20 (m, 3 H), 7.31−7.39 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): σ = 19.3, 59.1, 74.9, 126.5, 126.6, 130.0, 144.1. ^{11}B NMR (96 MHz, DMSO-d_6): σ = 4.0 (br, W = 451 Hz). FT-IR: 3387 (s, br), 3075 (w), 3021 (w), 2942 (m), 2602 (m), 2550 (m), 1639 (w, br), 1439 (m), 1377 (m), 1328 (w), 1233 (s, sh), 1202 (w), 1179 (w), 1081 (s), 1011 (s, sh), 948 (s, sh), 892 (w), 849 (s), 775 (w), 745 (s), 706 (m), 626 (br), 563 (w), 526 (w), 496 (w), 462 (w), 420 (w). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{15}H_{20}BN_4O_3$ 315.1637; Found 315.1631; [M + H]$^+$ Calcd for $C_{15}H_{22}BN_4O_3$ 317.1782; Found 317.1785. Anal. Calcd for $C_{15}H_{21}BN_4O_3{\cdot}2H_2O$: C, 51.15; H, 7.16; N, 15.91. Found: C, 50.90; H, 7.08; N, 15.86.

*2,6,12-Triethyl-9-phenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (**3c**).* 297 mg (yield 83%). White solid. Mp = 140−147 °C (melting with dec.). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 0.92 (t, J = 6.8 Hz, 9 H), 2.11−2.43 (br, 7 H), 3.05 (s, 6 H), 7.10−7.20 (m, 3 H), 7.26−7.42 (m, 2 H). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 6.8 (CH_3), 24.3 (CH_2), 56.2 (CH_2), 77.3 (*C*), 126.3, 126.4, and 131.0 (CH), 145.3 (*C*). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.6 (br, W = 576 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{18}H_{26}BN_4O_3$ 357.2107; Found 357.2092; [M + H]$^+$ Calcd for $C_{18}H_{28}BN_4O_3$ 359.2252; Found 359.2243. Anal. Calcd for $C_{18}H_{27}BN_4O_3$: C, 60.35; H, 7.60; N, 15.64. Found: C, 60.37; H, 7.76; N, 15.51.

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736

2,6,12-Tris(3-methoxy-3-oxopropyl)-9-phenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (**3d**). 415 mg (yield 78%). White solid. Mp = 153−155 °C (melting with dec.). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 2.41−2.55 (br, 12 H), 3.07 (br, 7 H), 3.59 (s, 9 H), 7.09−7.17 (m, 3 H), 7.28 (br d, J = 7.0 Hz, 2 H). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 26.5 and 26.9 (CH_2), 51.3 (CH_3), 56.1 (CH_2), 76.3 (C), 126.4, 126.5, and 130.9 (CH), 144.7 (br, C), 173.5 (C). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 4.0 (br, W = 96 Hz). FT-IR: 3422 (m, br), 3008 (m, br), 2362 (m, br), 1638 (w, br), 1426 (m, sh), 1359 (m, sh), 1315 (m), 1233 (s, sh), 1186 (m), 1151 (w), 1102 (m, sh), 1044 (s), 1005 (s, sh), 972 (s), 939 (s, sh), 841 (s, sh), 806 (m), 781 (s), 729 (s, sh), 703 (s), 656 (m), 619 (w), 527 (m, sh), 474 (m), 425 (m, sh). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{24}H_{32}BN_4O_9$ 531.2261; Found 531.2265; [M + H]$^+$ Calcd for $C_{24}H_{34}BN_4O_9$ 533.2418; Found 533.2410. Anal. Calcd for $C_{24}H_{33}BN_4O_9$: C, 54.15; H, 6.25; N, 10.52. Found C, 54.14; H, 6.25; N, 10.43.

2,6,12-Tribenzyl-9-phenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (**3e**). 413 mg (yield 76%). White solid. Mp = 141−142 °C (melting with dec.). ^{1}H NMR (300 MHz, HSQC, DMSO-d_6): σ = 2.69 (s, 6 H, CH_2N), 3.59 (br s, 7 H, CH_2Ph and NH), 7.13−7.32 (m, 12 H, 4 m and p-C_6H_5), 7.42 (d, J = 6.9 Hz, 6 H, 3 o-C_6H_5), 7.61 (d, J = 7.7 Hz, 2 H, o-C_6H_5-B). ^{13}C NMR (75 MHz, DEPT, HSQC, DMSO-d_6): σ = 37.4 (CH_2Ph), 56.0 (CH_2N), 77.0 (br, C), 126.4, 126.5, 126.8, 127.6, 130.9, and 131.1 (o, m, p-C_6H_5), 135.0 (i-C_6H_5), 145.1 (br, C-B). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.9 (br, W = 864 Hz). ESI-HRMS m/z: [M + H]$^+$ Calcd for $C_{33}H_{34}BN_4O_3$ 545.2719; Found 545.2727; [M + Na]$^+$ Calcd for $C_{33}H_{33}BN_4O_3Na$ 567.2538; Found 567.2537. Anal. Calcd for $C_{33}H_{33}BN_4O_3$: C, 72.80; H, 6.11; N, 10.29. Found C, 72.91; H, 6.20; N, 10.28.

5-Methyl-2,9,12-triphenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide Hydrate (**3h**). 293 mg (yield 64%). White hydroscopic solid. Mp = 146−152 °C (melting with dec.). ^{1}H NMR (300 MHz, HSQC, DMSO-d_6): σ = 1.48 (d, J = 6.4 Hz, 3 H, CH_3), 3.08−3.55 (br m, CH_2N, NH and H_2O), 3.76 (br m, 1 H, CHCH$_3$), 5.38 (br m, 1 H, CH-N), 6.81−6.96, 7.19−7.51, and 7.80−7.91 (3 m, 5 H, 6 and 4 H, o, m, p-C_6H_5). ^{13}C (75 MHz, HSQC, DMSO-d_6): σ = 14.4 (CH_3), 55.6 (CH_2N), 57.1 (CHCH$_3$), 62.0 (br, C), 78.1 (CH-N), 125.8, 126.6, 127.2, 127.4, 127.6, and 130.9 (o, m, p-C_6H_5), 133.9 (i-C_6H_5), 141.2 (br, C-B). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.7 (br, W = 1824 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{25}H_{24}BN_4O_3$ 439.1951; Found 439.1926; [M + H]$^+$ Calcd for $C_{25}H_{26}BN_4O_3$ 441.2097; Found 441.2080; [M+K]$^+$ Calcd for $C_{25}H_{25}BN_4O_3K$ 479.1656; Found 479.1646. Anal. Calcd for $C_{25}H_{25}BN_4O_3\cdot H_2O$: C, 65.52; H, 5.94; N, 12.22. Found C, 65.12; H, 5.75; N, 12.47.

2-(3-Methoxy-3-oxopropyl)-6,12-dimethyl-9-phenyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (**3j**). 279 mg (yield 72%). White solid. Mp = 148−152 °C (melting with dec.). ^{1}H NMR (300 MHz, HSQC, DMSO-d_6): σ = 1.64 (s, 6 H, CH_3), 2.36−2.60 (m, 4 H, CH_2−CH_2), 2.98−3.23 (m, 6 H, 3 CH_2N), 3.60 (s, 3 H, CO_2CH_3), 3.90−5.46 (br, 1 H, NH), 7.12−7.21 (m, 3 H, m and p-C_6H_5), 7.30−7.37 (br d, J = 7.0 Hz, 2 H, o-C_6H_5). ^{13}C NMR (75 MHz, HSQC, DMSO-d_6): σ = 19.1 (CH_3), 26.6 and 27.1 (CH_2−CH_2), 51.2 (CO_2CH_3), 56.8 (1 CH_2N), 58.7 (2 CH_2N), 75.1 and 75.5 (C), 126.4, 126.5, and 130.9 (o, m, p-C_6H_5), 145.0 (C-B), 173.4 (CO_2CH_3). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.9 (br, W = 960 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{18}H_{24}BN_4O_5$ 387.1848; Found 387.1848; [M + H]$^+$ Calcd for $C_{18}H_{26}BN_4O_5$ 389.1994; Found 389.1990. Anal. Calcd for $C_{18}H_{25}BN_4O_5$: C, 55.69; H, 6.49; N, 14.43. Found C, 55.16; H, 6.91; N, 14.10.

2,6,9,12-Tetramethyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide Hydrate (**3k**). 245 mg (yield 93%). White hydroscopic solid, oxidizes upon exposure to air. Mp = 147−150 °C (melting with dec.). ^{1}H NMR (300 MHz, HSQC, DMSO-d_6): σ = −0.61 (s, 3 H, CH_3B), 1.51 (s, 9 H, CH_3), 2.98 (s, 6 H, CH_2N), 4.6−6.2 (br, NH and H_2O). ^{13}C NMR (75 MHz, DEPT, HSQC, DMSO-d_6): σ = 2.3 (CH_3B), 19.3 (CH_3), 59.0 (CH_2N), 74.4 (C). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 5.5 (br, W = 336 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{10}H_{18}BN_4O_3$ 253.1479; Found 253.1487; [M + H]$^+$ Calcd for $C_{10}H_{20}BN_4O_3$ 255.1625; Found 255.1623. Anal. Calcd for $2C_{10}H_{19}BN_4O_3\cdot H_2O$: C, 45.65; H, 7.66; N, 21.29. Found C, 45.31; H, 7.98; N, 20.83.

2,6,12-Trimethyl-9-[(E)-2-phenylethenyl]-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (**3l**). 311 mg (yield 91%). White solid. Mp = 160−163 °C (melting with dec.). ^{1}H NMR (300 MHz, HSQC, DMSO-d_6): σ = 1.56 (s, 9 H, CH_3), 3.02 (s, 6 H, CH_2N), 3.3−3.9 (br, NH), 5.93 (d, J = 18.4 Hz, 1 H, CH=CH), 6.53 (d, J = 18.4 Hz, 1 H, CH=CH), 7.16 (t, J = 7.0 Hz, 1 H, p-C_6H_5), 7.27 (dd, J = 7.6, 7.0 Hz, 2 H, m-C_6H_5), 7.35 (d, J = 7.6 Hz, 2 H, m-C_6H_5). ^{13}C NMR (75 MHz, HSQC, DMSO-d_6): σ = 19.4 (CH_3), 59.1 (CH_2N), 74.7 (C), 125.6, 126.6, and 128.3 (o, m, p-C_6H_5), 133.4 (br, HC-B), 136.1 (=CH), 139.2 (i-C_6H_5). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.5 (br, W = 672 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{17}H_{22}BN_4O_3$ 341.1794; Found 341.1791; [M + H]$^+$ Calcd for $C_{17}H_{24}BN_4O_3$ 343.1939; Found 343.1938. Anal. Calcd for $C_{17}H_{23}BN_4O_3$: C, 59.67; H, 6.77; N, 16.37. Found C, 59.45; H, 6.90; N, 16.48.

9-Cyclopropyl-2,6,12-trimethyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide Hydrate (**3m**). 271 mg (yield 91%). White hydroscopic solid. For analytical purposes, the sample was crystallized from H_2O−MeOH. Mp = 142−145 °C (melting with dec.). ^{1}H NMR (300 MHz, DMSO-d_6): σ = −0.85 (quint, J = 7.2 Hz, 1H), −0.03 (m, 4 H), 1.47 (s, 9 H), 2.95 (s, 6 H), 4.7−6.3 (br, NH and H_2O). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = −0.9 (CH), 0.0 (CH_2), 19.1 (CH_3), 59.0 (CH_2), 74.5 (C). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.8 (br, W = 336 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{12}H_{20}BN_4O_3$ 279.1636; Found 279.1633; [M + H]$^+$ Calcd for $C_{12}H_{22}BN_4O_3$ 281.1782; Found 281.1790. Anal. Calcd for $C_{12}H_{21}BN_4O_3\cdot H_2O$: C, 48.34; H, 7.78; N, 18.79. Found: C, 48.30; H, 8.37; N, 18.93.

9-Hydroxy-2,6,12-trimethyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-4-ium-9-uide Hydrate (**3n**). 271 mg (yield 99%). White hydroscopic solid. For analytical purposes and X-ray diffraction analysis, the sample was crystallized from H_2O. Mp = 158 °C (melting with dec.). ^{1}H NMR (300 MHz, D_2O): σ = 1.77 (s, 9 H), 3.57 (s, 6 H), 4.79 (br s, NH, OH and H_2O). ^{13}C NMR (75 MHz, DEPT, D_2O): σ = 19.6 (CH_3), 57.4 (CH_2), 72.6 (C). ^{11}B NMR (96 MHz, D_2O): σ = −0.13. FT-IR: 3193 (s, br), 2343 (w, sh), 1444 (w, sh), 1405 (w, sh), 1366 (w), 1270 (w), 1176 (br, sh), 1057 (w), 1009 (s), 946 (m, sh), 903 (m, sh), 766 (s), 714 (w), 649 (s), 570 (m), 463 (m), 423 (w). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_9H_{16}BN_4O_4$ 255.1272; Found 255.1269; [M + H]$^+$ Calcd for $C_9H_{18}BN_4O_4$ 257.1417; Found 257.1406. Anal. Calcd for $C_9H_{17}BN_4O_4\cdot H_2O$: C, 39.44; H, 6.99; N, 20.44. Found C, 39.11; H, 7.36; N, 20.49.

2,6,12-Trimethyl-9-(4-{2,6,12-trimethyl-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uid-9-yl}phenyl)-8,10,13-trioxa-1,4,7,11-tetraaza-9-borapentacyclo-[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetadecan-1-ium-9-uide Trihydrate (**3o**). 505 mg (yield 83%). White hydroscopic solid. For analytical purposes, the sample was crystallized from H_2O−MeOH. Mp = 166−176 °C (melting with dec.). ^{1}H NMR (300 MHz, DMSO-d_6): σ = 1.59 (s, 18 H), 3.04 (s, 12 H), 3.32 (s, H_2O), 7.14 (s, 4 H), 10.1−11.7 (br, 2 H, NH). ^{13}C NMR (75 MHz, DEPT, DMSO-d_6): σ = 19.3 (CH_3), 59.1 (CH_2), 74.6 (br, C), 129.4 (CH), 142.4 (C). ^{11}B NMR (96 MHz, DMSO-d_6): σ = 3.7 (br, W = 960 Hz). ESI-HRMS m/z: [M − H]$^-$ Calcd for $C_{24}H_{35}B_2N_8O_6$ 553.2880; Found 553.2880. Anal. Calcd for $C_{24}H_{36}B_2N_8O_6\cdot 3H_2O$: C, 47.39; H, 6.96; N, 18.42. Found C, 47.28; H, 7.07; N, 18.14.

Synthesis of 3-Boro-2,4,10-trioxa-1,5,7-triazaadamantane 1c from Formaldoxime Trimer Hydrochloride 4a·HCl. A solution of hydrochloride **4a·HCl** (172 mg, 1.0 mmol) and phenylboronic acid (122 mg, 1.0 mmol) in CH_3OH (7.5 mL) was stirred for 18 h. Then, K_2CO_3 (69 mg, 0.5 mmol) was added and the mixture was stirred for an additional 5 h. The resulting mixture was filtered through a syringe filter and evaporated in a vacuum. The residue was dried in a vacuum until constant weight to give 221 mg (85%) of boradamantane **1c** as white solid.

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736

Synthesis of 3-Boro-2,4,10-trioxa-1,5,7-triazaadamantane 3b from adamantane 6b. To a stirred solution of adamantane **6b** (115 mg, 0.5 mmol) in CH_3OH (3.8 mL) was added phenylboronic acid (61 mg, 0.5 mmol). The solution was stirred at room temperature until full consumption of starting material (0.5 h, TLC control) and evaporated in a vacuum. The residue was triturated with AcOEt and dried in a vacuum (0.1 Torr and 100 °C) until constant weight to give 155 mg (98%) of boroadamantane **3b** as a white solid.

Decomposition of Boradamantane Salt 1c under Acidic Conditions. To a solution of boradamantane salt **1c** (115 mg, 0.44 mmol) in 1 mL of water was added concentrated aqueous solution of HCl (36% in water, 0.2 mL). The mixture was kept for 1 h and then extracted with $CHCl_3$ (8 × 5 mL). Combined organic extracts were dried (Na_2SO_4) and evaporated in a vacuum to give 39 mg (73%) of phenylboronic acid (Mp 212−214 °C, lit. 214−219 °C (Alfa Aesar)).

SM Coupling of Boradamantane Salt 1c with 1-Bromo-4-nitrobenzene. To a solution of $Pd(OAc)_2$ (2 mg, 0.009 mmol) in 0.6 mL of DMF/H_2O mixture (5:1) was added boradamantane salt **1c** (52 mg, 0.2 mmol) and 1-bromo-4-nitrobenzene (36 mg, 0.18 mmol) under an argon atmosphere. The mixture was stirred at 100 °C for 5 h. After cooling, the organic products were extracted with Et_2O (3 × 3 mL). Combined organic layers were washed with water, dried ($MgSO_4$), and evaporated in a vacuum. Flash-chromatography (pentane−Et_2O = 10:1) of the residue provided 26 mg (71%) of 4-nitrobiphenyl (GC-MS) as white crystals (Mp 111−114 °C, lit.[19] 112−114 °C).

Synthesis of *N*-(2-{[2-(Hydroxyimino)-2-phenylethyl][1-(hydroxyimino)propan-2-yl]amino}-1-phenylethylidene)-hydroxylamine (2h) (synthesized according to the procedure used for 2i[9c]). To a stirred solution of *N*-(2-aminopropylidene)-hydroxylamine[9c] (176 mg, 2.0 mmol) in 8 mL of dioxane was added a 1 M solution of 2,2,6,6-tetramethyl-4-(1-phenylethenyl)-3,5-dioxa-4-aza-2,6-disilaheptane[20] in dry CH_2Cl_2 (4.4 mL, 4.4 mmol). After 24 h at room temperature, 20 mL of CH_3OH was added and the mixture was kept for an additional 5 h with stirring. Then, the mixture was evaporated in a vacuum at 37 °C. The residue was preadsorbed on silica gel and purified by flash chromatography (silica gel; EtOAc−hexane, 1:1 then EtOAc and EtOAc−CH_3OH, 3:1). The residue was triturated with $CHCl_3$ and dried in a vacuum (0.1 Torr, room temperature) until constant weight to give 438 mg (61%) of oxime **2h** as a yellowish solid. Mixture of three isomers (ratio **2h′**:**2h″**:**2h‴** = 5.2:3.8:1.0). ^{1}H NMR (300 MHz, DMSO-d_6, HSQC, isomer **2h′**): 1.05 (d, J = 6.5 Hz, 3 H, CH_3), 3.34 (m, 1 H, CH), 3.68 (d, J = 13.5 Hz, 2 H, CH_2), 3.85 (d, J = 13.5, 3.4 Hz, 2 H, CH_2), 7.11−7.46 (m, 11 H, 2 C_6H_5 and N=CH), 10.69, 10.96, and 11.45 (3 s, 3 H, 3 NOH). ^{1}H NMR (300 MHz, DMSO-d_6, HSQC, isomer **2h″**): 1.11 (d, J = 7.6 Hz, 3 H, CH_3), 3.34 (m, 3 H, CH and CH_2), 3.59 (d, J = 13.2 Hz, 2 H, CH_2), 7.11−7.46 (m, 11 H, 2 C_6H_5 and N=CH), 10.73, 10.85, and 11.50 (3 s, 3 H, 3 NOH). ^{1}H NMR (300 MHz, DMSO-d_6, HSQC, isomer **2h‴**): 0.97 (d, J = 6.6 Hz, 3 H, CH_3), 3.19 (m, 1 H, CH), 3.46 (s, 4 H, CH_2), 6.72 (d, J = 5.9 Hz, 1 H, N=CH), 7.11−7.46 (m, 10 H, 2 C_6H_5), 10.64, 10.94, and 11.41 (3 s, 3 H, 3 NOH). ^{13}C NMR (75 MHz, DMSO-d_6, HSQC, **2h′** and **2h″**): 11.8 and 12.0 (CH_3), 42.8, 53.0, 53.2, 53.4, 53.9 (CH and CH_2), 126.4, 127.4, 127.7, 127.8, 128.2, 128.3, 128.5 (o, m, p-C_6H_5), 135.5 (i-C_6H_5), 150.1 and 154.1 (C=N). ^{13}C NMR (75 MHz, DMSO-d_6, HSQC, characteristic signals of **2h‴**): 152.8 (C=N). ESI-HRMS m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}N_4O_3$ 355.1765; Found 355.1758. $[M + Na]^+$ Calcd for $C_{19}H_{22}N_4O_3$ 377.1584; Found 377.1576.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for all new compounds, NMR and GC-MS for known compounds, X-ray data, Cartesian coordinates, absolute energies for all optimized geometries, and NBO analysis summary. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00892.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sukhorukov@ioc.ac.ru.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The support from Russian Foundation for Basic Research (grant no. 14-03-00933-a) and Russian President's Council for Grants (grant MK-5957.2015.3) is greatly acknowledged.

■ REFERENCES

(1) (a) Mansoori, G. A.; de Araujo, P. L. B.; de Araujo, E. S. *Diamondoid Molecules: With Applications in Biomedicine, Materials Science, Nanotechnology and Petroleum Science*; World Scientific: Hackensack, NJ, 2012. (b) Schwertfeger, H.; Fokin, A. A.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 1022. (c) Wanka, L.; Iqbal, K.; Schreiner, P. R. *Chem. Rev.* **2013**, *113*, 3516. (d) Grillaud, M.; Russier, J.; Bianco, A. *J. Am. Chem. Soc.* **2014**, *136*, 810. (e) Chu, P.-L. E.; Wang, L.-Y.; Khatua, S.; Kolomeisky, A. B.; Link, S.; Tour, J. M. *ACS Nano* **2013**, *7*, 35.

(2) (a) Kessel, A. J. *Anti-Infect. Agents* **2013**, *11*, 1. (b) Nielsen, A. T.; Chafin, A. P.; Christian, S. L.; Moore, D. W.; Nadler, M. P.; Nissan, R. A.; Vanderah, D. J. *Tetrahedron* **1998**, *54*, 11793. (c) Balija, A. M.; Kohman, R. E.; Zimmerman, S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8072. (d) Fokin, A. A.; Zhuk, T. S.; Pashenko, A. E.; Dral, P. O.; Guchenko, P. A.; Dahl, J. E. P.; Carlson, R. M. K.; Koso, T. V.; Serafin, M.; Schreiner, P. R. *Org. Lett.* **2009**, *11*, 3068. (e) Vel, L.; Demazeau, G.; Etourneau, J. *Mater. Sci. Eng., B* **1991**, *10*, 149.

(3) (a) Stetter, H. *Angew. Chem., Int. Ed.* **1962**, *1*, 286. (b) Averina, N. V.; Zefirov, N. S. *Russ. Chem. Rev.* **1976**, *45*, 544. (c) Vittal, J. J. *Polyhedron* **1996**, *15*, 1585.

(4) Wang, Y.; Wu, J. I-C.; Li, Q.; Schleyer, P. v. R. *Org. Lett.* **2010**, *12*, 1320.

(5) (a) Fischer, J.; Baumgartner, J.; Marschner, C. *Science* **2005**, *310*, 825. (b) Schreiner, P. R.; Chernish, L. V.; Gunchenko, P. A.; Tikhonchuk, E. Y.; Hausmann, H.; Serafin, M.; Schlecht, S.; Dahl, J. E. P.; Carlson, R. M. K.; Fokin, A. A. *Nature* **2011**, *477*, 308. (c) Semakin, A. N.; Sukhorukov, A. Yu.; Nelyubina, Y. V.; Khomutova, Yu. A.; Ioffe, S. L.; Tartakovsky, V. A. *J. Org. Chem.* **2014**, *79*, 6079. (d) For a review on inorganic and organometallic heteroadamantanes, see: Vittal, J. J. *Polyhedron* **1996**, *15*, 1585.

(6) For some stable ortho esters R—E(O—N=CR'_2)$_3$, see: (a) Singh, A.; Mehrotra, R. C. *Synth. React. Inorg. Met.-Org. Chem.* **1974**, *4*, 557. (b) Singh, A.; Mehrotra, R. C. *Indian J. Chem.* **1975**, *13*, 1197.

(7) Nielsen, A. T.; Moore, D. W.; Ogan, M. D.; Atkins, R. L. *J. Org. Chem.* **1979**, *44*, 1678.

(8) CCDC 1048296 (**1c**·3.25H_2O·CH_3OH, Scheme 5), 1048293 (**3b**·2H_2O, Scheme 3), 1048295 (**3n**·H_2O, Scheme 3).

(9) (a) Semakin, A. N.; Sukhorukov, A. Yu.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L. *Synthesis* **2007**, 2862. (b) Semakin, A. N.; Sukhorukov, A. Yu.; Lesiv, A. V.; Ioffe, S. L.; Lyssenko, K. A.; Nelyubina, Y. V.; Tartakovsky, V. A. *Org. Lett.* **2009**, *11*, 4072. (c) Semakin, A. N.; Sukhorukov, A. Yu.; Ioffe, S. L.; Tartakovsky, V. A. *Synthesis* **2011**, 1403.

(10) Jensen, K. A.; Holm, A. *K. Dan. Vidensk. Selsk. Math.−Fys. Medd.* **1978**, *40*, 1. For the calculated ΔΔG° of triazine **4a** invertomers and the activation barrier of nitrogen inversion in **4a**, see the Supporting information.

(11) (a) Jones, G. O.; García, J. M.; Horn, H. W.; Hedrick, J. L. *Org. Lett.* **2014**, *16*, 5502. (b) Carta, M.; Malpass-Evans, R.; Croad, M.; Rogan, Y.; Jansen, J. C.; Bernardo, P.; Bazzarelli, F.; McKeown, N. B. *Science* **2013**, *339*, 303. (c) Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. *J. Org. Chem.* **1973**, *38*, 3288.

(12) (a) Kubo, Y.; Nishiyabua, R.; James, T. D. *Chem. Commun.* **2015**, *51*, 2005. (b) He, L.; Fullenkamp, D. E.; Riveraa, J. G.;

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736

Messersmith, P. B. *Chem. Commun.* **2011**, *47*, 7497. (c) Guan, Y.; Zhang, Y. *Chem. Soc. Rev.* **2013**, *42*, 8106.
(13) Tanner, J. A.; Zheng, B.-J.; Zhou, J.; Watt, R. M.; Jiang, J.-Q.; Wong, K.-L.; Lin, Y.-P.; Lu, L.-Y.; He, M.-L.; Kung, H.-F.; Kesel, A. J.; Huang, J.-D. *Chem. Biol.* **2005**, *12*, 303.
(14) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412.
(15) Kuno, S.; Kimura, T.; Yamaguchi, M. *Tetrahedron Lett.* **2014**, *55*, 720.
(16) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176.
(17) Crampton, R.; Woodward, S.; Fox, M. *Adv. Synth. Catal.* **2011**, *353*, 903.
(18) (a) Rao, G. S. S.; Pillai, S. M.; Gupta, V. K. (Reliance Industries Ltd.) U.S. Patent 289632 A1, Nov 15, 2012. (b) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. *Org. Lett.* **2006**, *8*, 4071.
(19) Siphamandla, S.; Robinson, R. S. *Beilstein J. Org. Chem.* **2014**, *10*, 1107.
(20) Dilman, A. D.; Ioffe, S. L.; Mayr, H. *J. Org. Chem.* **2001**, *66*, 3196.

DOI: 10.1021/acs.joc.5b00892
J. Org. Chem. 2015, 80, 6728−6736