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2,4,9-Triazaadamantanes with "Clickable" Groups: Synthesis, Structure and Applications as Tripodal Platforms

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Dedicated to the memory of Professor William A. Smit, a distinguished scientist, lecturer, and our good friend

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Abstract: 2,4,9-Triazaadamantanes (TRIADs) are promising yet scarcely available, conformationally rigid platforms for potential applications in the design of functional molecules and materials. Here, we report a facile synthesis of various *N*- and C7-substituted 2,4,9-triazaadamantanes, starting from amines and 4-allylhepta-1,6-dienes. A focus was placed on the synthesis of 2,4,9-triazaadamantanes bearing reactive groups (NH_2, propargyl, OH) on the bridge nitrogen atoms, which were then used to decorate the 3D scaffold by hydrazone, triazole and boronate linkages. A reversible opening of the adamantane cage to the acyclic tris-oxime form was observed for 2,4,9-triazaadamantanes possessing hydroxy-groups on the nitrogen atoms (TRIAD-triols). This process could be controlled by temperature or by complexation of TRIAD-triol with a boronic acid. The structure of 2,4,9-triazaadamantanes and the stereodynamics at the bridge nitrogen atoms were studied by X-ray analysis and DFT calculations.

Introduction

1,3,5-Trisubstituted cyclohexane derivatives are among the most commonly used synthetic platforms in organic,[1] supramolecular[2] and coordination chemistry.[3] The rigid structure and preorganized spatial disposition of the functional groups at the 1,3,5-axial positions of the six-membered ring have long been recognized and applied in the design of complex molecular architectures,[2c, 4] supramolecular systems,[5] bio-inspired catalysts,[1d, 6] capping ligands,[6a, 7] ion sensors,[8] metallopharmaceuticals,[9] organic superbases[10] and materials.[11] The most widely applied examples of 1,3,5-trisubstituted cyclohexanes include all-*cis*-1,3,5-cyclohexanetricarboxylic acid[5c, 5d, 12] and its trimethyl-substituted analogue (Kemp's acid[1a, 13]), all-*cis*-1,3,5-trihydroxycyclohexane (*cis*-phloroglucitol[5b, 7i-k]) and all-*cis*-1,3,5-triaminocyclohexane (TACH[7a, 7g, 7l, 11a]), as shown in Figure 1. Among the advantages of these platforms are a high stability and the ability to modify functional groups at the periphery. However, the direct derivatization of the six-membered ring backbone is usually not possible, and therefore products bearing additional substituents in the cyclohexane ring have to be prepared independently by multistep synthetic routes.

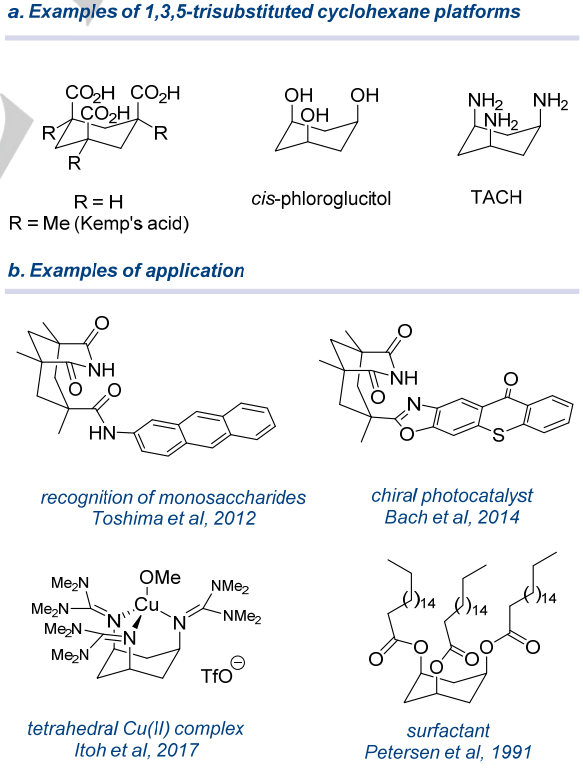
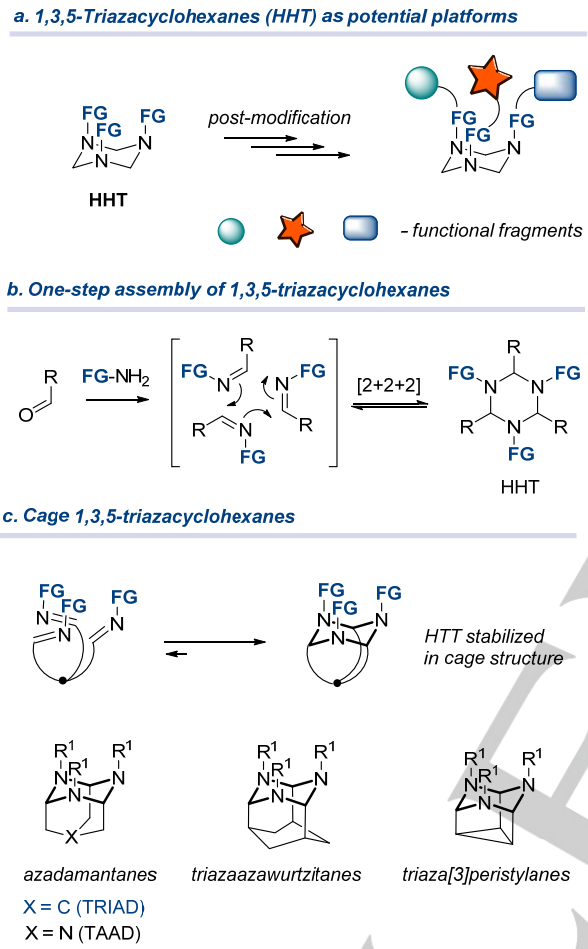


Figure 1. 1,3,5-Trisubstituted cyclohexane-based synthetic platforms

In this regard, 1,3,5-triazacyclohexane (hexahydro-1,3,5-triazine, HHT) can be viewed as a more versatile and easily accessible tripodal scaffold (Scheme 1, chart a).[14] HHT derivatives can be

prepared in a single step by the cyclotrimerization of imines generated *in situ* from aldehydes and amines (Scheme 1, chart b).[15] This synthetic approach may provide access to the large libraries of substituted HHTs, to which functional fragments can be further attached. However, the application of 1,3,5-triazacyclohexane derivatives as synthetic platforms is limited due to the reversible character of imine cyclotrimerization and the lability of the aminal moiety.[15b, 16]



Scheme 1. 1,3,5-Trisubstituted cyclohexane-based synthetic platforms

The stability of a 1,3,5-triazacyclohexane unit can be greatly increased by its incorporation into a cage structure, as demonstrated by several experimental[1b, 17] and theoretical studies.[17d, 18] For this reason, azaadamantanes,[19] triazaazawurtzitanes,[1h] and triaza[3]peristylanes[20] containing nitrogen atoms in bridge positions are considered to be promising molecular platforms for various applications (Scheme 1, chart c). Moreover, the reversible cleavage of a 1,3,5-triazacyclohexane ring in these heterocage systems does not lead to a loss of covalent integrity between the functional units, thus providing a way to control the topology of the scaffold.

Recently, our group introduced 1,4,6,10-tetraazaadamantane (TAAD) as a readily available, stable and easy-to-modify multifunctional platform (Scheme 1, chart c).[17c, 19c, 21] Our group and others have shown the application of TAAD derivatives in the design of fluorophore-labelled natural molecules,[22] biodegradable polymers,[22] polymer-bound organocatalysts,[22] scavengers for boronic acids,[22] water-soluble phthalocyanines,[23] capped metal complexes,[24] and dynamic combinatorial libraries.[22] Surprisingly, 2,4,9-triazaadamantane (TRIAD), which is a simpler analogue of TAAD, has received much less attention and was not considered for applications as a molecular platform (Scheme 1, chart c). Unsubstituted 2,4,9-triazaadamantane is unknown,[18b] and to date only six of its derivatives have been reported in the scientific and patent literature.[25] In this work, we attempted to develop a convenient method for the synthesis of 2,4,9-triazaadamantanes bearing "clickable" groups on nitrogen atoms as potential platforms for the construction of functional molecules. We also performed preliminarily studies on the structure, stability, and transformations of this novel class of heterocage compounds.

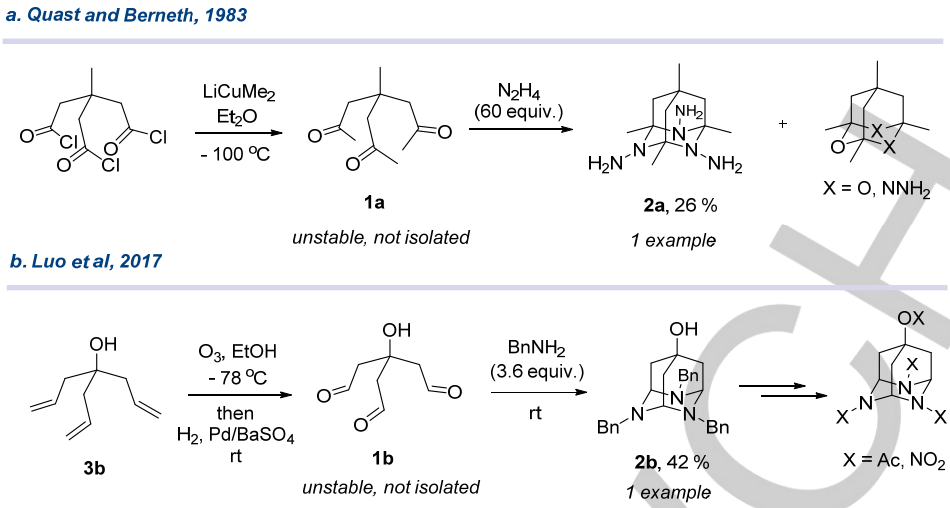
Results and Discussion

Synthesis of TRIADs

Selective synthesis of 2,4,9-triazaadamantanes is challenging and only two reports have dealt with this problem. The first 2,4,9-triazaadamantane derivative (TRIAD **2a**) was obtained by Quast and Berneth[25a] in 1983 by treatment of tris-ketone **1a** with ca. 60 equiv. of hydrazine (Scheme 2, chart a). The required tris-ketone **1a** was generated by the addition of $LiCu(CH_3)_2$ to the corresponding tris-chloroanhydride. Due to an irreversible intramolecular cyclization of the tris-ketone and the intermediate mono- and bis-hydrazones, the yield of the desired triazaadamantane **2a** was only 26%. Recently, Luo and co-workers[25b] reported the synthesis of tris-benzyl TRIAD **2b** via trial **1b**. The later was generated by Stetter's method,[26] which involves ozonolysis of triallylcarbinol **3b** followed by hydrogenolysis of ozonide over $Pd/BaSO_4$ at rt (Scheme 2, chart b). Remarkably, the cyclization of tris-aldehyde **1b** was relatively slow at rt, which allowed for a conversion into the triazaadamantane **2b** by treatment with benzylamine in 42% yield. The resulting *N*,*N*,*N*-tris-benzyl-2,4,9-triazaadamantane **2b** was used to prepare the corresponding *N*-nitro- and *N*-acyl derivatives. However, no attempts to use primary amines other than benzylamine and tris-carbonyl compounds other than trial **1b** were performed in this study. Therefore, it was not evident whether this method could be used to prepare other TRIAD derivatives, especially those containing clickable groups.

From these studies it can be concluded that the intramolecular cyclization of tris-carbonyl compounds **1** and transient mono- and bis-imines are major side-processes, which substantially decrease the yield of triazaadamantanes **2**. We assumed that this issue might be solved by performing the reaction of tris-carbonyl compounds with amines at low temperatures. To validate this, we performed a series of experiments on the interaction of tris-carbonyl compounds **1** with *N*-nucleophiles (Scheme 3, Table 1).

The required tris-carbonyls **1b**-**e** were generated *in situ* by ozonolysis of the corresponding trienes – triallylcarbinol **3b**, trimethallylcarbinol **3c**, triallylphenylmethane **3d** and triallylcarbinol benzyl ether **3e**.



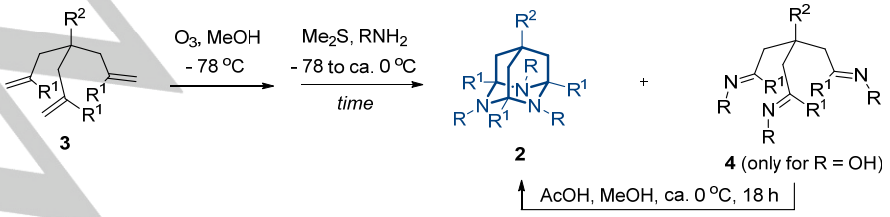
Scheme 2. Previously reported syntheses of 2,4,9-triazaadamantanes

Unlike the procedures of Stetter[26] and Luo,[25b] in which ozonide was cleaved by catalytic hydrogenation at room temperature, we used reduction with Me_2S to generate tris-carbonyl compounds **1b**-**e** at -78 °C. Furthermore, *N*-nucleophile was added together with the Me_2S to ensure a maximum conversion of the tris-carbonyl compound into the corresponding tris-imine (Scheme 3). These modifications resulted in much better yields of triazaadamantanes **2** compared to the previous procedures by Quast[25a] and Luo[25b] (*vide infra*). In all cases, an excess of the *N*-nucleophile was needed, as it also reacted with formaldehyde, which was formed as a by-product from the alkene ozonolysis.[27] Table 1 summarizes some illustrative results obtained with each *N*-nucleophile. As seen from these data, the desired triazaadamantane derivatives **2** were isolated in moderate to high yields with hydrazine, acethydrazide, *tert*-butyl carbazate, benzyl carbazate and propargylamine (entries 1, 3-6). In the case of hydrazine, 50 equiv. were required to achieve an acceptable yield of the corresponding *N*,*N*,*N*-triaminotriazaadamantane **2c** (entry 1, Table 1). A reduction in the amount of hydrazine to 20 equiv. resulted in a drop of the yield to 17% (entry 2, Table 1). To our delight, reactions with acethydrazide and carbazates afforded corresponding triazaadamantanes **2d**-**f** in high yields, even with a nearly stoichiometric amount of the nucleophile (by taking into account the presence of 3 equiv. of formaldehyde in the reaction mixture, entries 4-6, Table 1).[28]

Remarkably, the reaction with hydroxylamine gave the non-cyclized tris-oxime **4h** as the major product after 18 h (entry 7, Table 1). Extension of the reaction time to 5 days resulted in the cyclization of tris-oxime **4h** to the desired *N*,*N*,*N*-trihydroxytriazaadamantane **2h**, which was isolated by crystallization from the reaction mixture in a 66% yield (entry 8, Table 1). Due to its low solubility, product **2h** was characterized in the form of hydrochloride salt (**2h**•HCl).

Given our interest in *N*,*N*,*N*-trihydroxy-derivatives of type **2h** as potential partners for boronate-triol coupling,[22] we attempted to prepare these products by ozonolysis/oximation of trimethallylcarbinol **3c**, triallylphenylmethane **3d** and triallylcarbinol benzyl ether **3e**. Similar to **3b**, mixtures of tris-oximes **4** and triazaadamantanes **2** were obtained after 18 h in these experiments (e.g., entry 9, Table 1).[29] In the case of triallylcarbinol benzyl ether **3e**, prolongation of the reaction time to 72 h resulted in the conversion of tris-oxime **4k** to the corresponding adamantane **2k** (entry 12 in Table 1). Remarkably, benzoyl ester **2l**, as a result of the oxidation of benzyl ether moiety, was formed as a side-product (11%) in this experiment.

Importantly, tris-oximes **4** could be cyclized to corresponding adamantanes **2** upon the action of protic acids. Complete conversion of tris-oxime **4h** to adamantane **2h** was observed in the presence of 3 equiv. of AcOH in methanol after 3 h (rt). A reaction with 1 equiv. of HCl quantitatively gave the corresponding hydrochloride salt **2h**•HCl within a few minutes. Thus, an optimal procedure for the synthesis of *N*,*N*,*N*-trishydroxytriazaadamantanes **2i**,**j** consisted in the treatment of the crude mixtures of **2** and **4** with acetic acid and subsequent crystallization of the product (entries 10, 11 in Table 1).



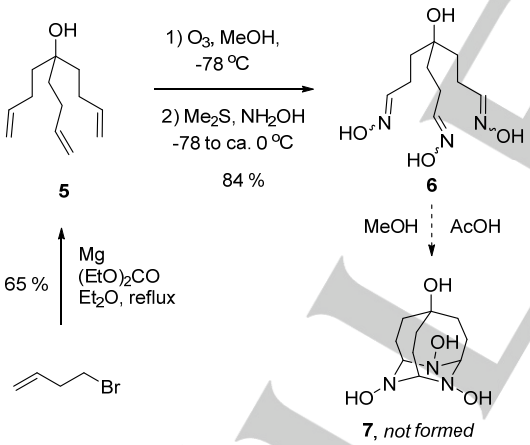
Scheme 3. Optimized scheme for the synthesis of 2,4,9-triazaadamantanes **2** from trienes **3**

Table 1. Synthesis of C- and N-substituted 2,4,9-triazaadamantanes **2** from triallylmethane derivatives **3**.

Entry	product	triene	R	R^1	R^2	RNH_2 equiv.[a]	*time*	Yield, %[b]	
								2	**4**
1	**2c**	**3b**	NH_2	H	OH	50	72 h	43	n.o.
2	**2c**	**3b**	NH_2	H	OH	20	72 h	17	n.o.
3	**2d**	**3b**	NHAc	H	OH	7.5	72 h	56	n.o.
4	**2e**	**3b**	NHBoc	H	OH	7.5	72 h	77	n.o.
5	**2f**	**3b**	NHCbz	H	OH	7.5	72 h	76	n.o.
6	**2g**	**3b**	$CH_2C{\equiv}CH$	H	OH	10	18 h	44	n.o.
7	**4h**	**3b**	OH	H	OH	10	18 h	n.d.	45
8	**2h**	**3b**	OH	H	OH	10	120 h	66	traces
9	**2i** + **4i**	**3c**	OH	Me	OH	10	18 h	21	33
10	**2i**	**3c**	OH	Me	OH	10	18 h + 18 h[c]	51	traces
11	**2j**	**3d**	OH	H	Ph	10	18 h + 18 h[c]	31	n.o.
12	**2k** + **2l**[d]	**3e**	OH	H	OBn (**2k**) OBz (**2l**)	10	72 h	61 11	n.o. n.o.

[a] Per 1 equiv. of triene **3**. [b] Isolated yields. [c] Crude product (mixture of **2** and **4**) was treated with 3 equiv. of AcOH in MeOH for 18 h. [d] A mixture of **2k** and **2l** (ratio 86 : 14) was isolated as a single crystal phase (see experimental section). n.o. – not observed. n.d. – not determined.

Ozonolysis of the homologous triene **5** followed by treatment with hydroxylamine afforded only the tris-oxime product **6**, which was stable and did not cyclize to the corresponding homoadamantane derivative **7** (Scheme 4).

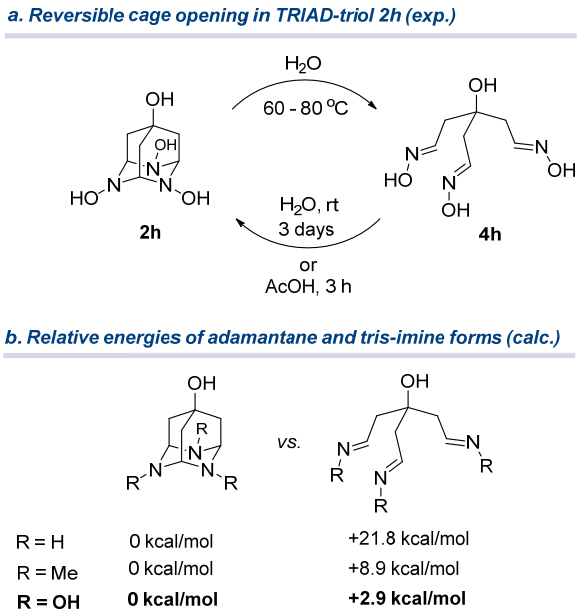


Scheme 4. Attempted synthesis of tris-homoazaadamantane **7**

Stability of TRIADs

In previous reports by Quast[25a] and Luo,[25b] no studies on the stability of 2,4,9-triazaadamantanes **2** were performed, since very few representatives of this class were prepared. Therefore, it was not known whether TRIADs **2** could undergo a retro-[2+2+2]-annulation reaction to give tris-imines **4**, which is characteristic for compounds having a 1,3,5-triazacyclohexane ring.[17c] As this may limit the thermal stability of a triazaadamantane scaffold, the retro-[2+2+2]-annulation process has to be taken into account when performing chemical modifications of these molecules. On the other hand, the opening of the adamantane unit provides an interesting way to change the topology of the scaffold from cage to an open chain. Such a process, if reversible while controllable, may be useful for applications in molecular switches.

Most of the obtained triazaadamantanes **2** were found to be stable upon heating (reflux in methanol) and did not undergo cage opening. However, the *N*,*N*,*N*-trihydroxy-triazaadamantane **2h** was an exception. Upon heating to 60-80 °C in water, it was converted to the corresponding tris-oxime **4h** within a few minutes (Scheme 5, chart a). Remarkably, the reaction proved to be reversible and the cyclization of **4h** back to the adamantane **2h** took 3 days at rt (or 3 h in the presence of acetic acid). This result demonstrates that the open-chain and adamantane forms have similar thermodynamic stabilities and the position of equilibrium is controlled by the entropy factor.[17c] This is confirmed by DFT calculations at the B3LYP/6-311G** level of theory, which predict adamantane **2h** to be more stable than the isomeric tris-oxime **4h** by only 2.9 kcal/mol (Scheme 5, chart b). For TRIAD derivatives bearing hydrogen or methyl group at the nitrogen atoms, the calculated energetic preference of the adamantane structure *vs*. the open-chain form is much higher (21.8 and 8.9 kcal/mol, respectively). Reduced thermodynamic stability of the triazaadamantane moiety in trihydroxy-derivatives (compared to other *N*-substituted TRIADs) may be attributed to the lability of the *N*,*N*,*N*-trihydroxy-triazaacyclohexane ring.[17c, 30] This is in line with the fact that oximes are known to have the least tendency to form cyclotrimers among other azomethines.[17d]



Scheme 5. Stability of TRIAD derivatives towards cage opening. DFT calculations: B3LYP/6-311G** level of theory (E_0 + ZPE). Values are given relative to the most stable invertomer of TRIAD **2**

Structure of TRIADs

The structure of the 2,4,9-triazaadamantane cage has not received much attention in previous studies.[31] For applications in molecular design, understanding the geometry of the scaffold and the associated stereodynamics is needed. We were able to perform X-ray diffraction analyses for the tris-propargyl-TRIAD **2g**, TRIAD-triols **2k**, **2l** and TRIAD-triol salt **2h**•HCl, which provided the structures of free and protonated 2,4,9-triazaadamantane skeletons (Figures 2, 3). The neutral TRIAD structures **2g**, **2k** and **2l** have distorted triazaadamantane skeletons, in which C–C and C–N bonds are within a relatively narrow range of 1.524–1.538 Å and 1.462–1.490 Å, respectively (Figure 2). These values are close to those observed in adamantane (C–C 1.54 Å[32]) and 1,3,5-triazaadamantane (C–N 1.468–1.478 Å[33]). Remarkably, in structures **2g**, **2k** and **2l**, the nitrogen atom N(2) with an equatorial substituent is more deviated from the mean plane formed by bridgehead atoms C(1), C(3) and C(5) (deviation ca. 0.58 Å) compared to the N(4) and N(9) atoms bearing axial groups (deviations ca. 0.4–0.42 Å). Propargyl groups at the N(4) and N(9) atoms in **2g** are not ideally axial, most likely due to a steric repulsion (diaxial torsion angles are 162.2° and 165.5°). In TRIAD-triols **2k** and **2l**, these angles lie in the range 171.9–177.6°, and the nitrogen atoms are more pyramidal. Generally, despite having different substitutions at N- and O-atoms, the geometrical parameters of the triazaadamantane skeleton in structures **2g**, **2k** and **2l** are very similar.

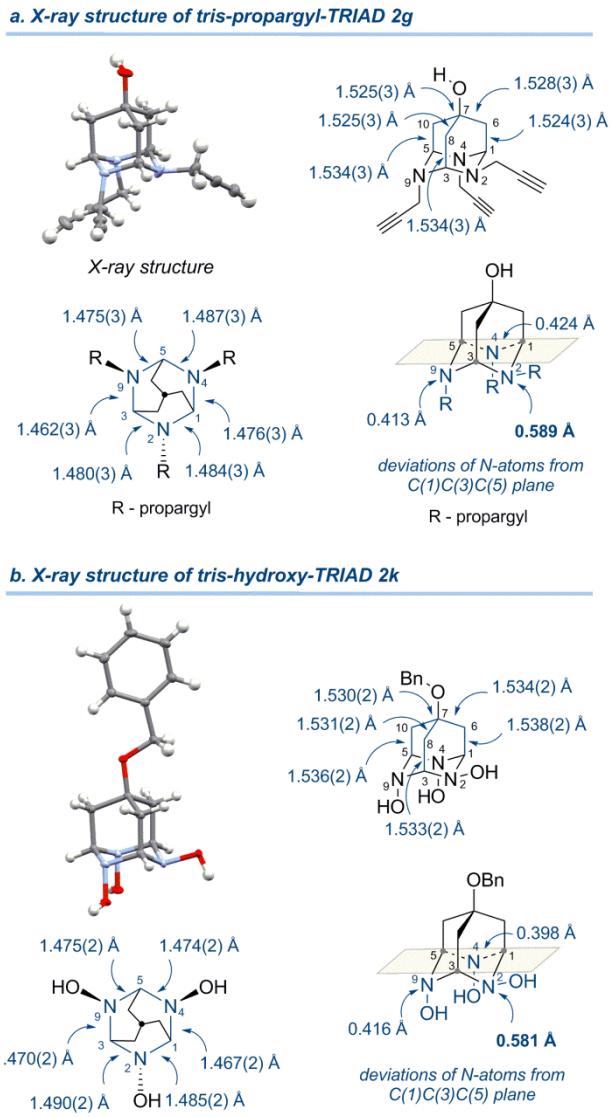


Figure 2. X-ray data for TRIADs **2g** and **2k**. Structural parameters of benzoyl ester **2l** (not shown) are very similar to benzyl ether **2k**.

The cationic 2,4,9-triazaadamantanium skeleton in salt **2h**•HCl (Figure 3) has a nearly C_s symmetrical structure with the length of the C–C bonds (1.523(2)–1.533(2) Å) close to those observed in the neutral 2,4,9-triazaadamantane cage in **2g**,**k**,**l** (cf. with data in Figure 2). The range of the C–N bonds length is expectedly wider (1.441(3)–1.528(3) Å) due to the presence of a tetravalent nitrogen atom N(2). Notably, the C(1)–N(4) and C(3)–N(9) bonds are shortened (1.441(2)–1.446(2) Å) compared to the C(5)–N(4) and C(5)–N(9) bonds (1.466(2)–1.470(2) Å). This may be attributed to the strong anomeric interactions between the equatorial lone electron pair of N(4) and N(9) and the antibonding orbitals of the C–N(2)$^+$ bonds. Similar to **2g**, **2k** and **2l**, the N(2) nitrogen atom shows the highest deviation from the mean plane formed by bridgehead atoms C(1), C(3) and C(5). The crystal structure of **2h**•HCl displays a complex network of hydrogen bonds between the HO/NH-groups of individual 2,4,9-triazaadamantanium cations and chloride anions. The formation of a 3D-framework is completed by weak H…H interactions between the bridge CH_2-groups of neighbouring adamantane units (distance c.a. 2.5 Å).[34]

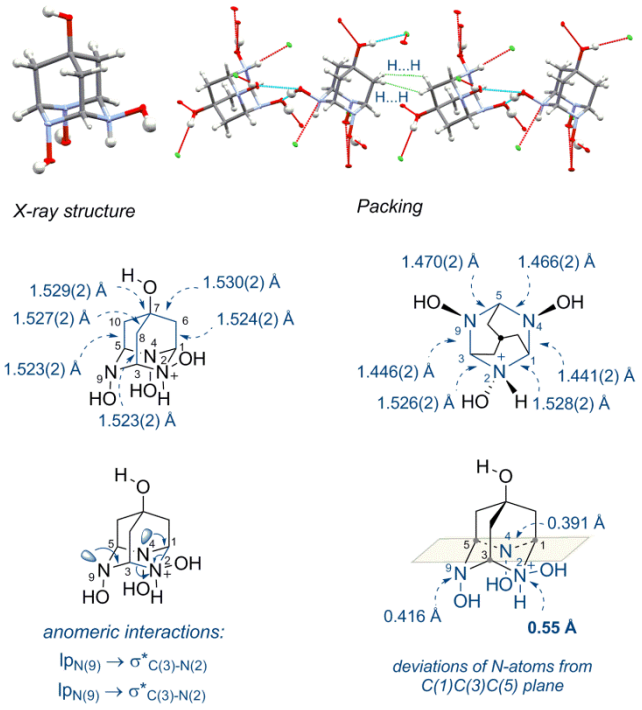


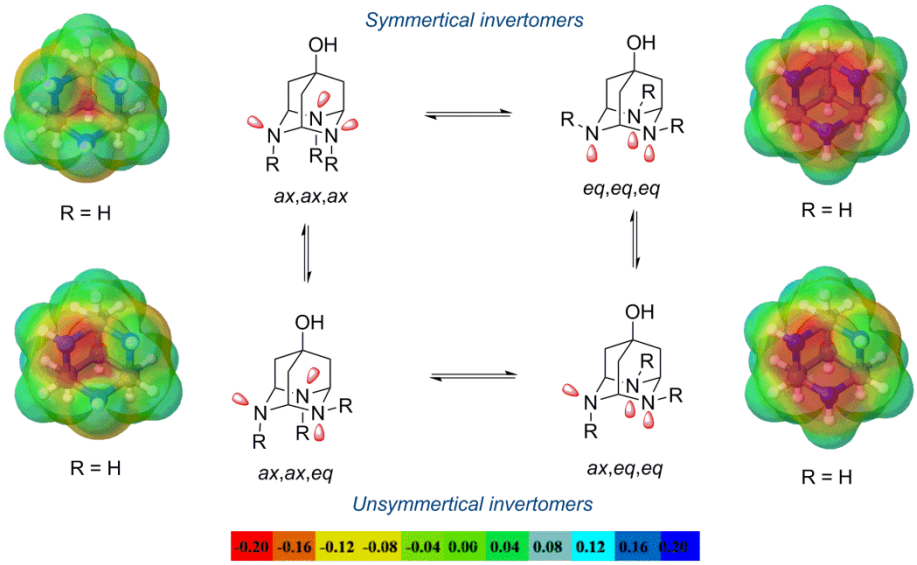
Figure 3. X-ray data for hydrochloride **2h**•HCl

An interesting feature of all 2,4,9-triazaadamantanes, **2g**, **2k**, **2l** and **2h**•HCl, is the *ax*,*ax*,*eq*-disposition of substituents at the nitrogen atoms in the crystal phase. In the solution, different isomeric forms may exist, which easily interconvert through the fast inversion of the nitrogen atoms (Scheme 6, Table 2).[35] As an indication of this, the broadening of signals is observed in the NMR spectra of *N*,*N*,*N*-trihydroxy-2,4,9-triazaadamantanes **2h-l** due to dynamic exchange processes. For the application of TRIAD as a synthetic platform, it is important for the symmetrical isomers (ideally, the all-axial isomer) to be thermodynamically achievable. To reveal the relative stability of the invertomers, DFT calculations were performed. As seen from data given in Table 2, the all-axial isomer is predicted to be the most stable for TRIADs bearing hydrogen or NH_2-group on nitrogen atoms (R = H, NH_2), yet the isomer having one equatorial hydrogen nearly has the same energy. For TRIADs with R = OH or Me, the relative stability changes, and the *ax*,*eq*,*eq*-isomer becomes more stable that is in agreement with the X-ray data for **2g**, **2k** and **2l**. Nevertheless, for all calculated TRIAD derivatives**,** the all-axial invertomer is expected to be present in substantial amounts, and thus can be involved in chemical reactions (*vide infra*). In contrast, in all cases the all-equatorial isomer is the least stable among four invertomers due to a repulsion between the three lone electron pairs in the 1,3-diaxial positions (for accumulation of the electron density see the molecular electrostatic potential surfaces in Scheme 6).

Table 2. Calculated relative stability of invertomers

R	Relative energy of invertomer, kcal/mol[a]				ΔE*, kcal/mol[b]
	ax,*ax*,*ax*	*ax*,*ax*,*eq*	*ax*,*eq*,*eq*	*eq*,*eq*,*eq*	
H	0	0.3	3.8	10.0	4.8
OH	1.6	0	1.1	8.2	13.1
NH_2	0	0.4	3.0	12.3	8.6
Me	3.0	0	1.2	8.0	5.0

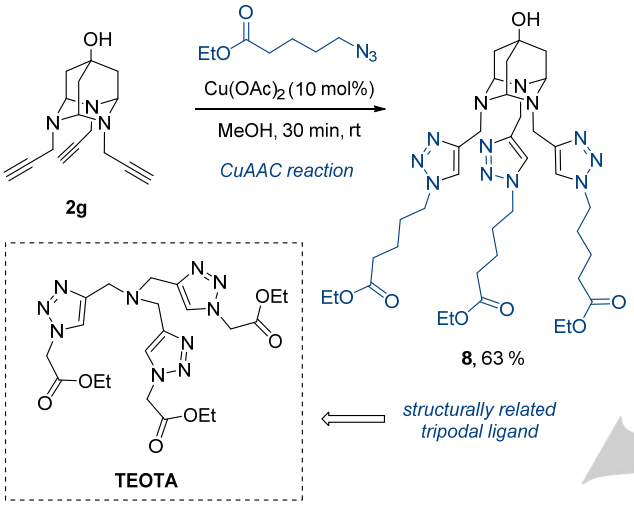
[a] Calculated at B3LYP/6-311G** level of theory (E_0 + ZPE). Values are given relative to the most stable isomer. [b] Conversion of *eq*,*ax*,*ax* invertomer to *ax*,*ax*,*ax* invertomer.



Scheme 6. Inversion of nitrogen atoms in TRIAD derivatives and molecular electrostatic potential (MESP) surfaces for R = H (view on the triazine ring, B3LYP/6-311G**)

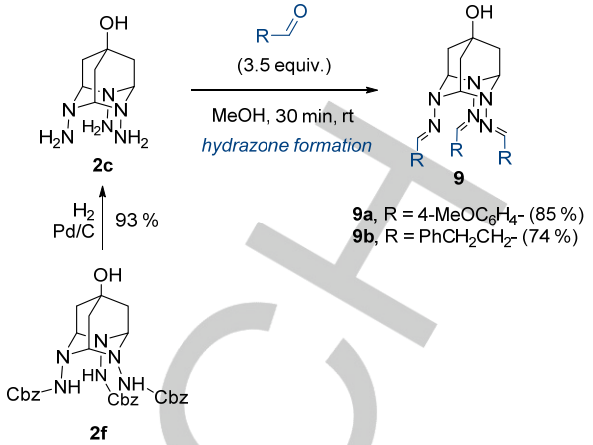
Modification of TRIADs using click-reactions

Having prepared a series of 2,4,9-triazaadamantanes **2** bearing reactive groups at the nitrogen atoms, we studied the synthetic potential of these products, in particular the possibility of using them in click-like reactions (Scheme 7). Thus, adamantane **2g** possessing three propargyl groups enters the Cu-catalysed azide-alkyne coupling (CuAAC) reaction with ethyl 5-azidovalerate, giving the corresponding tris-adduct in 63% yield. This product is structurally related to tris(triazolylmethyl)amines (such as TEOTA[36]), which are efficient tripodal ligands in Cu-catalysed reactions.



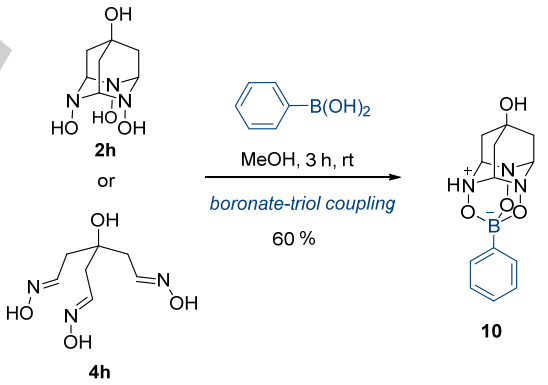
Scheme 7. Modification of TRIADs using CuAAC reaction

Apart from the CuAAC process, the formation of hydrazones from aldehydes (hydrazone ligation) is a well-established click-like reaction, which is widely used as a synthetic tool in conjugation chemistry. Tris-amino-substituted 2,4,9-triazaadamantane **2c** reacts smoothly with aromatic and aliphatic aldehydes to give stable tris-hydrazones **9a**,**b** in high yields (Scheme 8). These tris-hydrazone adducts can be viewed as interesting tripodal capping ligands for transition metals.
The initial 2,4,9-triazaadamantane **2c** can be prepared from hydrazine, as shown in Table 1. However, a more efficient procedure was found to be deprotection of the corresponding Cbz-derivative **2f** by mild hydrogenolysis over Pd/C (70% for two steps from triene **3b**). This experiment also demonstrates that the aminal units in the triazaadamantane cage and the N–N bonds are resistant towards catalytic hydrogenation.



Scheme 8. Modification of TRIADs using hydrazone ligation

Recently, condensation of boronic acids with triols (boronate-triol coupling) was introduced as a perspective and efficient technique for reversible click-chemistry (the formation of degradable polymers, dynamic combinatorial libraries, etc.).[22, 37] We have shown that tri-hydroxy-substituted TRIAD **2h** reacts smoothly with phenylboronic acid to form the corresponding boronate adduct **10** with a betaine structure (Scheme 9). Diamantane **10** is very stable and undergoes decomposition at ca. 200 °C. Facile formation of the diamantane skeleton demonstrates that substituents at the nitrogen atoms in 2,4,9-triazaadamantane can occupy all axial positions, as predicted by the DFT calculations (see Table 2).



Scheme 9. Modification of TRIADs using boronate-triol coupling

Notably, diamantane **10** could also be prepared by the reaction of phenylboronic acid with tris-oxime **4h**. Thus, the equilibrium between open-chain **4h** and cage **2h** forms can be irreversibly shifted to the later by complexation with boronic acids.
The aforementioned examples illustrate that TRIAD derivatives **2** can be easily modified at the nitrogen atoms using different click strategies without any problems associated with the opening of the triazaadamantane cage.

Conclusion

In conclusion, we developed an optimized method for the synthesis of 2,4,9-triazaadamantanes, which were scarcely known in previous literature. Modifying the procedures previously reported by Quast and Luo allowed us to prepare a series of substituted 2,4,9-triazaadamantanes from various amines (propargylamine, hydrazine, acethydrazide, carbazates and hydroxylamine) and 4-allylhepta-1,6-dienes in moderate to high yields. The structure of 2,4,9-triazaadamantanes and the stereochemistry at the bridge nitrogen atoms were studied by X-ray analysis and DFT calculations. A reversible but controllable opening of the 2,4,9-triazaadamantane cage to open-chain tris-imines was observed for the *N*,*N*,*N*-trihydroxy-substituted derivatives for the first time. This process results in a substantial change in the scaffold geometry, and thus can be considered for applications in molecular switches. Modification of the bridge N-positions in 2,4,9-triazaadamantanes through three different click-strategies was successfully performed, demonstrating the versatile characteristics of this new 3D scaffold.

Experimental Section

All reactions were performed in oven-dried (150°C) glassware. The NMR spectra were recorded on a Bruker AM 300 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) at 297 K (if not stated otherwise), with residual solvents peaks as an internal standard. The multiplicities are indicated by s (singlet), d (doublet), t (triplet), dd (doublet of doublets), q (quartet), ddt (doublet of doublets of triplets), m (multiplet), or br (broad). Coupling constants (*J*) are given in Hz. The HRMS were measured on the electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector (Bruker MicroTOF). The FTIR spectra were recorded on a FT-801 spectrometer (SIMEX). Peaks in the FT-IR spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), or sh (shoulder). Thermogravimetric analyses (TGA) were recorded on a Discovery SDT 650 (TA Instrument). X-ray analysis was performed on Bruker APEX2 DUO CCD and Bruker Quest D8 diffractometers. Elemental analyses were performed at the Analytical Center of the N.D. Zelinsky Institute of Organic Chemistry. Melting points (uncorrected) were determined on a Kofler hot-stage microscope. Column chromatography was performed using Kieselgel 40-60 μm 60A. Analytical thin-layer chromatography was performed on silica gel plates with QF 254. Visualization was accomplished with UV light and staining with iodine or a solution of ninhydrin in methanol. All reagents were commercial grade and used as received. The diethyl ether and dichloroethane for the reactions were distilled over CaH_2 prior to the experiments. MeOH, hexane, and ethyl acetate were distilled without drying agents. The ozone/oxygen mixture was generated from dry oxygen (dried by Drierite column) using a laboratory-made ozone generator (ozone output 8-12 mmol/h).

The DFT calculations were performed using the GAMESS Computational Chemistry Program with a Web-Based Job Submission Interface[38] and the Gaussian 16 Rev A.03 program. For all calculations (geometry optimization, IR frequencies, thermochemistry, MESP) the B3LYP/6-311G** level of theory was used. Cartesian coordinates are given in angstroms, and absolute energies are given in Hartrees (see supporting information). Analysis of the vibrational frequencies was performed for all optimized structures. All structures except for transition-states were characterized by only real vibrational frequencies, and the transition-states had one imaginary frequency. Visualization of MESP was performed using the Web-Based Interface of the Chem Compute website.

Synthesis of triallylcarbinol 3b and trimethallylcarbinol 3c. Magnesium turnings (12 g, 500 mmol) and dry Et_2O (100 ml) were placed in a 2-neck round bottom flask equipped with a high-efficient Dimroth condenser with an argon inlet. The dropping funnel was charged with a mixture of diethylcarbonate (11.8 g, 100 mmol), corresponding haloalkene (350 mmol, 30 ml of allyl bromide and 35 ml for methallyl chloride) and Et_2O (70 ml). A small amount of haloalkene (0.5-1 ml) was added to the magnesium and the reaction was initiated by gentle heating. Then, the heating was stopped and the mixture from the dropping funnel was slowly added with the rate to maintain vigorous refluxing. After completion of the addition, the reaction mixture was refluxed for 3 h, kept overnight at rt, and the supernatant was poured into a large beaker with ice-cold water (300 ml) and hexane (100 ml). The solid residue, which remained in the flask, was washed with 50 ml of Et_2O. Citric acid was added to the organic-aqueous mixture until the dissolution of the precipitate; the organic phase was separated in a funnel, washed with brine, dried with anhydrous sodium sulphate and concentrated in vacuo. The oily residue was subjected to vacuum distillation in a Hickman apparatus (~5 Torr, oil bath temperature 75-85 °C (triallylmethanol[26]) and 80-110 °C (trimethallylmethanol[26]). The yields were 12.3 g (81%) for **3b** and 14.0 g (72%) for **3c**. The NMR spectra of triallylcarbinol **3b** are in accordance with literature data.[39]

2,6-Dimethyl-4-(2-methylprop-2-en-1-yl)hepta-1,6-dien-4-ol (trimethallylcarbinol 3c). Colourless liquid. ^{1}H NMR ($CDCl_3$): δ = 1.89 (s, 10 H, 3 C*H*$_3$ and O*H*), 2.24 (s, 6 H, 3 C*H*$_2$), 4.76 and 4.93 (2 d, *J* = 2.5, 6 H, C=C*H*$_2$). ^{13}C NMR ($CDCl_3$): δ = 25.0 (3 *C*H$_3$), 47.9 (3 *C*H$_2$), 73.5 (*C*OH), 114.8 (3 C=*C*H$_2$), 143.1 (3 *C*=CH$_2$). HRMS: calculated for $C_{13}H_{22}ONa$ [M+Na$^+$] 217.1563; found 217.1565.

(4-Allylhepta-1,6-dien-4-yl)benzene (triallylphenylmethane 3d). Allyltrimethylsilane (1.7 g, 14.9 mmol) under an argon atmosphere was added to a solution of 4-phenylhepta-1,6-dien-4-ol[40] (900 mg, 4.8 mmol) in freshly distilled 1,2-dichloroethane (5 ml). The reaction mixture was cooled to the temperature of an ice-bath and scandium triflate (50 mg, 0.1 mmol) was added. After full conversion of the starting material (TLC control), the reaction mixture was poured into a mixture of water (25 ml) and hexane (25 ml). The organic phase was separated, and the water phase was washed with hexane (25 ml). Combined organic extracts were washed with brine, dried with anhydrous sodium sulphate, and concentrated in vacuo. The residue contained a crude mixture of triallylphenylmethane **3d** and (hepta-1,3,6-trien-4-yl)benzene (^{1}H NMR analysis, formed by a competitive dehydration of starting alcohol). The mixture was dissolved in Et_2O (20 ml) and 1 drop of boron trifluoride diethyl etherate was added. The resulting solution was concentrated in vacuo. During this operation, (hepta-1,3,6-trien-4-yl)benzene underwent spontaneous tarring. The residue was subjected to column chromatography on silica gel (eluent – hexane) to afford **3d** as a colourless liquid (260 mg, 26%). The NMR spectra is in accordance with the literature data.[41]

({[4-(Prop-2-en-1-yl)hepta-1,6-dien-4-yl]oxy}methyl)benzene (O-benzyl triallylmethanol 3e). Sodium hydride (1.6 g of 60% suspension in mineral oil, 39 mmol) was washed with anhydrous THF (3x10 ml) under an argon atmosphere, and THF (5 ml) and DMPU (5 ml) were added. The mixture was cooled on an ice bath and triallylmethanol (2.0 g, 13.2 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred for 2 h. Then, benzyl bromide (2.6 ml, 22 mmol) was added and the reaction mixture was refluxed for 2 h. The resulting mixture was poured in cold water (50 ml) and hexane (30 ml). The organic phase was separated, and the water phase was washed with hexane (30 ml). Combined organic extracts were washed with brine, dried with anhydrous sodium sulphate, and concentrated in vacuo. The oily residue was subjected to vacuum distillation in a Hickman still apparatus (~0.5 Torr, oil bath temperature 150-170 °C) to afford 2.42 g of **3e** (76%). Colourless liquid. ^{1}H ($CDCl_3$): δ = 2.46 (d, J = 7.3, 6 H, 3 C*H*$_2$), 4.57 (s, 2 H, C*H*$_2$Ph), 5.19 (m, 6 H, C=C*H*$_2$), 5.98 (m, 3 H, 3 C=C*H*), 7.27-7.49 (m, 5 H, *Ph*). ^{13}C NMR (DEPT135, $CDCl_3$): δ = 39.9 (3 *C*H$_2$),

63.2 (CH_2Ph), 78.3 (*C*-O), 118.0 (3 HC=CH_2), 127.3, 127.5 and 128.4 (*o*,*m*,*p-Ph*), 133.9 (3 H*C*=CH_2), 139.3 (*i-Ph*). HRMS: calculated for $C_{17}H_{22}ONa$ [M+Na^+]: 265.1563; found 265.1565.

5-(But-3-en-1-yl)nona-1,8-dien-5-ol (5). Magnesium turnings (2.4 g, 100 mmol) and dry Et_2O (50 ml) were placed in a 2-neck round bottom flask equipped with a high-efficient Dimroth condenser with an argon inlet. 4-Bromo-1-butene (0.5 ml) was added to the magnesium and the reaction was initiated by gentle heating. A mixture of diethylcarbonate (2.5 g, 20.7 mmol) and 4-bromo-1-butene (10 g, 74 mmol) was slowly added (portionwise) from a disposable syringe via rubber septum. After the addition, the reaction mixture was refluxed for 3 h, kept overnight, and the supernatant was poured into a large beaker with ice-cold water (100 ml) and hexane (50 ml). Citric acid was added until the dissolution of the precipitate. The organic phase was separated, washed with brine, dried with anhydrous sodium sulphate and concentrated in vacuo. The oily residue was subjected to vacuum distillation in a Hickman apparatus (90-120 °C) to afford 2.6 g of **5** (65%). Colourless liquid. ^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 1 H, CO*H*), 1.55 and 2.09 (2 m, 12 H, 3 CH_2CH_2), 4.96 (dd, J_1 = 10.1, J_2 = 1.7, 3 H, 3 C=CH*H*), 5.04 (dd, J_1 = 16.8, J_2 = 1.7, 3 H, 3 C=C*H*H), 5.84 (ddt, J_1 = 16.8, J_2 = 10.1, J_3 = 6.5, 3 H, 3 C=C*H*). ^{13}C NMR (DEPT135, $CDCl_3$): δ = 28.1 and 38.3 (3 CH_2CH_2), 74.3 (*C*OH), 114.6 (3 HC=CH_2), 138.9 (3 HC=CH_2). HRMS: calculated for $C_{13}H_{22}ONa$ [M+Na^+] 217.1563; found 217.1562.

General procedure for preparation of triazaadamantanes 2c-m and tris-oximes 4h-j, 6. A solution of the corresponding triene **3** or **5** (3.0 mmol) in MeOH (15 ml) was cooled to the temperature of the dry ice-acetone bath. The ozone was bubbled through the solution until an intensive blue colour appeared. Then, argon was bubbled through the solution until the blue colour disappeared. Me_2S (3 ml) and amine were successively added, and the dry ice-acetone bath was changed to an ice bath. The reaction mixture was stirred for 1-2 h and then kept at 2-4 °C (fridge) with occasional shaking for the time period indicated below. Details on the amount of amine, reaction time and isolation procedures are given below for each product. *CAUTION! Operations should be performed in a well-operated fume hood and precautions should be taken to avoid the formation of explosive oxygen-organic vapor mixtures.*

Tris(2,4,9-triamino-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-7-ol) hydrate (2c×1/3H_2O). Product **2c** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: 7.5 ml (150 mmol) of hydrazine hydrate was used. The reaction mixture was kept for 3 days, then concentrated in vacuo to dryness (bath temperature 60 °C). Methanol (25 ml) was added to the residue, and the resulting precipitate was collected by filtration, washed with methanol and dried in vacuo. Yield 265 mg (43%). White cryst., mp = 172-176 °C (with dec.). Thermogravimetric analysis: 3.8% weight loss before melting (water desorption), fast decomposition upon melting. ^{1}H NMR (D_2O): δ = 1.96 (d, *J* = 2.9, 3 CH_2), 4.06 (t, *J* = 2.9, 3 C*H*) (OH and NH_2 hydrogens are not observed). ^{13}C NMR (DEPT135, D_2O): δ = 34.3 (3 CH_2), 63.5 (*C*OH), 78.5 (3 *C*H). FT-IR (KBr): ν = 3275 (s), 3250 (s, sh), 3162 (s, br), 2957 (s), 2925 (s, sh), 1634 (s, sh), 1478 (m), 1461 (m), 1341 (m, sh), 1323 (s), 1211 (m), 1160 (m), 1131 (s, sh), 1024 (m, sh), 967 (m), 938 (w), 918 (m), 896 (m), 808 (m), 776 (m), 723 (m), 644 (m), 619 (w) cm^{-1}. Elemental analysis: calculated for $C_{21}H_{50}N_{18}O_4$ (**2c**×1/3H_2O) C (40.76), H (8.15), N (40.75); found C (40.62), H (8.60), N (41.03).

Synthesis of 3c by hydrogenolysis of 3f. Palladium on activated charcoal (10% Pd, 50 mg) under an argon atmosphere was added to a suspension of **3f** (150 mg, 0.25 mmol) in methanol (7.5 ml). The reaction vessel was evacuated and filled with hydrogen 3 times (rubber balloon), and hydrogenation was conducted for 1 h with vigorous stirring (magnetic stirring bar). The reaction mixture was centrifuged, and the supernatant was evaporated. Methanol (ca. 2 ml) was added to the residue methanol, and the resulting precipitate was collected by filtration and dried in vacuo to afford 47 mg (93%) of product **3c**.

1-{4,9-Diacetyl-7-hydroxy-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-2-yl}ethan-1-one (2d). Product **2d** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: a solution of $AcNHNH_2$ (1.7 g, 23 mmol) in methanol (15 ml) was used. The reaction mixture was kept for 3 days, and then concentrated in vacuo. Methanol (5-10 ml) and diethyl ether (until clouding) were added to the residue and the mixture was kept in the refrigerator for 3-4 days. The resulting precipitate was collected by filtration, washed with diethyl ether and dried in vacuo. Yield: 547 mg (56%). White cryst., mp = 270-276 °C (with dec.). Thermogravimetric analysis: weight loss starts at 250 °C. ^{1}H NMR (D_2O): δ = 2.03 (s, 9 H, 3 CH_3), 2.18 (d, *J* = 2.6, 6 H, 3 CH_2), 4.16 (s, 3 H, 3 C*H*) (OH and NH hydrogens are not observed). ^{13}C NMR (D_2O): δ = 20.2 (3 CH_3), 36.6 (3 CH_2), 63.5 (*C*OH), 75.0 (3 *C*H), 172.4 (3 *C*=O). HRMS: for $C_{13}H_{22}N_6O_4Na$ [M+Na^+] calculated 349.1595; found 349.1589.

2,4,9-Tri-tert-butyl 7-hydroxy-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decane-2,4,9-tricarboxylate (2e). Product **2e** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: a solution of $BocNHNH_2$ (3.0 g, 22.7 mmol) in methanol (15 ml) was used. The reaction mixture was kept for 3 days, and then concentrated in vacuo. Methanol (5-10 ml) and diethyl ether (until clouding) were added to the residue and the mixture was kept in the refrigerator for 3-4 days. The resulting precipitate was collected by filtration, washed with diethyl ether and dried in vacuo. Yield: 1.15 g (77%). White cryst., mp = 248-253 °C (with dec., darkening starts at 240 °C). ^{1}H NMR (DMSO-d_6): δ = 1.40 (s, 27 H, 3 C(CH_3)$_3$), 1.83 (s, 6 H, 3 CH_2), 3.74 (s, 3 H, 3 C*H*), 4.82 (s, 1 H, CO*H*), 7.9-8.1 (s br, 3 H, 3 NN*H*). ^{13}C NMR (DMSO-d_6): δ = 28.1 (3 C(*C*H_3)$_3$), 37.1 (3 CH_2), 62.5 (*C*OH), 76.8 (3 *C*(CH$_3$)$_3$), 78.8 (3 *C*H), 154.4 (3 *C*=O). FT-IR (KBr): ν = 3295 (s, sh, br), 2978 (s), 2934 (m), 1742 (m), 1705 (s), 1682 (s), 1529 (m), 1476 (m), 1457 (m), 1392 (m), 1366 (m), 1327 (m), 1278 (m), 1252 (m), 1156 (s, sh), 1057 (m), 1020 (m), 930 (w), 873 (w), 821 (m), 756 (w, sh) cm^{-1}.HRMS: calculated for $C_{22}H_{40}N_6O_7Na$ [M+Na^+] 523.2851; found 523.2849.

2,4,9-Tribenzyl 7-hydroxy-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decane-2,4,9-tricarboxylate (2f). Product **2f** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: a solution of $CbzNHNH_2$ (3.75 g, 22.6 mmol) in methanol (15 ml) was used. The reaction mixture was kept for 3 days, and then concentrated in vacuo. Methanol (5-10 ml) and diethyl ether (until clouding) were added to the residue and the mixture was kept in the refrigerator for 3-4 days. The resulting precipitate was collected by filtration, washed with diethyl ether and dried in vacuo. Yield: 1.37 g (76%). White cryst., mp = 216-220 °C (with dec.). ^{1}H NMR (DMSO-d_6): δ = 1.90 (s, 6 H, 3 CH_2), 3.4-3.5 and 4.91 (2 m, 1 H, CO*H*), 3.83 (s, 3 H, 3 C*H*), 5.06 (s, 6 H, 3 CH_2Ph), 7.2-7.4 (m, 15 H, 3 *o*,*m*,*p-Ph*), 8.80 (s, 3 H, 3 NN*H*). ^{13}C NMR (DMSO-d_6): δ = 37.7 (3 CH_2), 62.5 (*C*OH), 65.6 (3 CH_2Ph), 77.2 (3 *C*H), 127.6, 127.8 and 128.3 (3 *o*,*m*,*p-Ph*), 136.9 (3 *i-Ph*), 155.3 (3 *C*=O). FT-IR (KBr): ν = 3364 (m), 3264 (s, br), 3222 (s, br), 3030 (m), 2956 (w, sh), 1737 (s), 1713 (s), 1563 (m), 1510 (s), 1453 (m), 1326 (m), 1250 (s), 1153 (m), 1134 (m), 1044 (m, sh), 1027 (m), 972 (w, sh), 824 (m), 750 (s), 700 (s), 602 (m, sh) cm^{-1}. HRMS: calculated for $C_{31}H_{34}N_6O_7Na$ [M+Na^+] 625.2381; found 625.2372.

2,4,9-Tris(prop-2-yn-1-yl)-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-7-ol (2g). Product **2g** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: 1.9 ml (30 mmol) of propargyl amine was used. The reaction mixture was kept overnight, concentrated in vacuo, and then subjected for aqueous work-up (EtOAc-brine), the organic phase was dried with anhydrous sodium sulphate and concentrated in vacuo. The residue was subjected to a column chromatography on silica gel (eluent hexane-EtOAc (3:1) → EtOAc) to give crude adamantane **2g** and 458 mg (76%) of 1,3,5-tris(prop-2-yn-1-yl)-1,3,5-triazinane by-product (NMR spectra in accordance with the literature data[42]). Crude adamantane **2g** was additionally recrystallized from diethyl ether and dried in vacuo. Yield: 355 mg (44%). White cryst., mp = 128-134 °C (with dec.). ^{1}H NMR (DMSO-d_6): δ = 1.68 (s, 6 H, 3

CH_2), 3.06 (s, 3 H, 3 C≡CH), 3.51 (d, J = 2.5, 6 H, 3 CH_2C≡C), 3.99 (s, 3 H, 3 CH). 4.76 (s, 1 H, COH). ^{13}C NMR (DEPT135, DMSO-d_6): δ = 37.9 and 41.0 (6 CH_2), 64.1 (*C*OH), 71.0, 74.1 and 81.5 (3 *C*H and 3 *C*≡*C*H). FT-IR (KBr): ν = 3289 (s), 3238 (s), 2960 (m), 2938 (m, sh), 2871 (w), 2115 (w), 1438 (m, sh), 1334 (s, sh), 1154 (s, sh), 1110 (s), 1085 (s), 1025 (m), 1000 (m), 906 (w), 789 (s, sh), 717 (s), 698 (s), 673 (s), 641 (s, sh) cm^{-1}. HRMS: calculated for $C_{16}H_{19}N_3ONa$ [M+Na$^+$] 292.1420; found 292.1419. Crystals for the X-ray diffraction analysis were obtained by crystallization using vapor diffusion of diethyl ether into the methanol solution of **2g**. CCDC 1987350 contains the supplementary crystallographic information for **2g**.

2,4,9-Triazatricyclo[3.3.1.1^{3,7}]decane-2,4,7,9-tetrol (2h). Product **2h** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept for 5 days, the resulting white precipitate was collected by filtration, washed with methanol and dried in vacuo. Yield 402 mg (66%). White cryst., mp = 119-123 °C. Thermogravimetric analysis: 8% weight loss upon melting, decomposition at 177 °C. It was observed that the product is almost insoluble in common NMR solvents ($CDCl_3$, D_2O, DMSO-d_6, CD_3OD, CD_3CN). Upon heating conversion to tris-oxime **4h** was observed. ^{1}H NMR ($CDCl_3$): δ = 1.9-2.0 (s br, 6 H, 3 CH_2), 3.7-3.8 (s br, 3 H, 3 CH). FT-IR (KBr): ν = 3539 (s), 3283 (s, br), 3218 (s, br), 2924 (s), 2879 (s), 1666 (m), 1468 (m), 1405 (s), 1379 (s), 1348 (s), 1310 (m), 1285 (m), 1143 (s), 1115 (s), 1039 (s), 1003 (m), 951 (m, sh), 906 (w), 865 (s, sh), 800 (w), 703 (w, sh), 625 (m, sh), 571 (w) cm^{-1}. HRMS: for $C_7H_{13}N_3O_4Na$ [M+Na$^+$] calculated 226.0798; found 226.0796.

Hydrochloride 2h•HCl. 4M solution of HCl in dioxane (0.25 ml, 1 mmol) was added to a suspension of adamantane **2h** (203 mg, 1 mmol) in methanol (5 ml). Immediate dissolution of the precipitate was observed. The resulting solution was concentrated, and the residual solid was washed with diethyl ether, rinsed with a small amount of methanol, and dried in vacuo. Yield 225 mg (94%). White cryst., mp = 147-152 °C (with dec.). ^{1}H NMR (D_2O): δ = 3.04 (s, 6 H, 3 CH_2), 4.54 (s, 3 CH) (OH and NH hydrogens are not observed). ^{13}C NMR (DEPT135, D_2O): δ = 35.9 (3 CH_2), 62.8 (*C*OH), 78.0 (3 *C*H). Crystals for X-ray diffraction analysis were obtained by crystallization using vapor diffusion of diethyl ether into the reaction mixture. CCDC 1987938 contains the supplementary crystallographic information for **2h•HCl**.

1,3,5-Trimethyl-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decane-2,4,7,9-tetrol (2i). Product **2i** was prepared from trimethallylcarbinol **3c** according to the general procedure with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept overnight, then concentrated in vacuo and poured into an EtOAc (100 ml)/water (50 ml) mixture. The organic phase was separated and the water phase was washed with EtOAc (30 ml). Combined organic extracts were washed with brine and concentrated in vacuo. The residue was dissolved in methanol (5 ml) and acetic acid (0.5 ml) was added. The solution was kept in the refrigerator (0 – 5 °C) overnight and concentrated in vacuo. The residual solid was washed with diethyl ether, rinsed with a small amount of methanol and dried in vacuo to give 375 mg (51%) of triazaadamantane **2i**. White cryst., mp = 145-148 °C. ^{1}H NMR (DMSO-d_6, 322 K): δ = 1.27 (s, 9 H, 3 CH_3), 1.61 (s, 6 H, 3 CH_2), 4.4-4.6 (s br, 1 H, COH), 7.3-7.5 (s br, 3 H, 3 NOH). ^{13}C NMR (DMSO-d_6, 322 K): δ = 23.8 (3 CH_3), 41-44 (br, 3 CH_2), 63.8 (*C*OH), 78.7 (3 *C*). HRMS: calculated for $C_{10}H_{19}N_3O_4Na$ [M+Na$^+$] 268.1268; found 268.1266.

7-Phenyl-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decane-2,4,9-triol (2j). Product **2j** was prepared from triallylphenylmethane **3d** according to the general procedure with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept overnight, then concentrated in vacuo and poured into an EtOAc (100 ml)/water (50 ml) mixture. The organic phase was separated; the water phase was washed with EtOAc (30 ml). Combined organic extracts were washed with brine and concentrated in vacuo. The residue was dissolved in methanol (5 ml) and acetic acid (0.5 ml) was added. The solution was kept in a refrigerator (0 – 5 °C) overnight and concentrated in vacuo. The residual solid was washed with diethyl ether, rinsed with a small amount of methanol, and dried in vacuo to give 244 mg (31%) of triazaadamantane **2j**. White cryst., mp = 209-212 °C (with dec.). ^{1}H NMR (DMSO-d_6): δ = 1.5-2.5 (s br, 6 H, 3 CH_2), 4.31 (s, 3 H, 3 CH), 7.1-7.4 (2 m, 5 H, *o*,*m*,*p*-*Ph*), 8.59 (s, 3 H, 3 NOH). ^{13}C NMR (DMSO-d_6): δ = 32.0 (*C*Ph), 30-37 (br, 3 CH_2), 74-78 (br, 3 *C*H), 124.7, 126.3 and 128.4 (*o*,*m*,*p*-*Ph*), 147.0 (*i*-*Ph*). FT-IR (KBr): ν = 3380 (s, br), 3179 (s, br), 2965 (s), 2933 (s), 1600 (w), 1497 (m), 1450 (m), 1410 (s, sh), 1346 (m), 1317 (m), 1299 (w), 1264 (m), 1164 (s, sh), 1084 (s), 1047 (m), 1016 (m), 983 (m), 957 (m), 932 (m), 910 (m), 811 (m), 789 (m), 764 (s), 727 (w), 702 (s), 627 (m) cm^{-1}. HRMS: calculated for $C_{13}H_{17}N_3O_3Na$ [M+Na$^+$] 286.1162; found 286.1161.

7-Benzyloxy-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decane-2,4,9-triol (2k) and 2,4,9-trihydroxy-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-7-yl benzoate (2l). An inseparable mixture of **2k** and **2l** was obtained from O-benzyl triallylmethanol **3e** according to the general procedure with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept for 3 days, concentrated in vacuo and water (15 ml) was added. The oil was precipitated, which solidified after some time. The precipitate was collected by filtration, washed with water, rinsed with a small portion of methanol (2-3 ml) and dried in vacuo to give 637 mg of a mixture of **2k** (61%) and **2l** (11%), which could not be separated by crystallization. White crystals. ^{1}H NMR (DMSO-d_6): δ = 1.5-2.4 (s br, 6 H, 3 CH_2), 4.31 (s, 3 H, 3 CH), 4.42 (s, 2 H, PhCH_2), 7.3 (m, 5 H, *o*,*m*,*p*-*Ph*), 8.3-8.7 (s br, 3 H, 3 NOH). ^{13}C NMR (DMSO-d_6): δ = 30-36 (br, 3 CH_2), 62.4 (PhCH_2), 68.0 (*C*OCH_2), 78-82 (br, 3 *C*H), 127.2, 127.5 and 128.2 (*o*,*m*,*p*-*Ph*), 139.3 (*i*-*Ph*). Selected signals of benzoate **2l**: ^{1}H NMR (DMSO-d_6): δ = 7.50, 7.60 and 7.91 (3 m, 5 H, *o*,*m*,*p*-*Ph*). ^{13}C NMR (DMSO-d_6): δ = 74.9 (*C*OBz), 128.7, 129.2, 133.3 (*o*,*m*,*p*-*Ph*), 164.6 (C=O). Crystals for X-ray analysis were obtained by crystallization from methanol. A mixture of **2k** and **2l** (ratio 86 : 14) was obtained as a single crystal phase. CCDC 1999152 contains the supplementary crystallographic information for the single crystal mixture **2k+2l**.

1,5-Bis(hydroxyimino)-3-[2-(hydroxyimino)ethyl]pentan-3-ol (4h). Product **4h** was prepared from triallylmethanol **3b** according to the general procedure with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept overnight, and then concentrated in vacuo. The residue was subjected to a column chromatography on silica gel (eluent EtOAc) to give 274 mg (45%) of tris-oxime **4h**. Viscous oil. R_f = 0.35 (EtOAc). Mixture of (*E*,*E*,*E*)-, (*E*,*E*,*Z*)-, (*E*,*Z*,*Z*)- and (*Z*,*Z*,*Z*)-isomers with *E*/*Z* fragments ratio ~1 : 1.5. ^{1}H NMR (D_2O): δ = 2.52 (*E*-fragments) and 2.71 (*Z*-fragments) (2 m, 6 H, 3 CH_2), 7.03 (*Z*-fragments) and 7.59 (*E*-fragments) (2 m, 3 H, 3 *C*H) (OH hydrogens are not observed). ^{13}C NMR (DEPT135, D_2O): δ = 34.4, 34.6, 37.1, 39.0, 39.2 and 39.3 (3 CH_2), 72.2 and 72.7 (*C*OH), 148.6, 148.8, 148.9, 149.7, 149.8, 149.9 (3 *C*=N). FT-IR (thin layer): ν = 3280 (s, br), 2901 (s), 1658 (m), 1433 (s), 1334 (m), 1137 (m), 1035 (m, sh), 941 (s, sh), 863 (m), 781 (w, sh), 684 (w, sh) cm^{-1}. HRMS: for $C_7H_{14}N_3O_4$ [M+H$^+$] calculated 204.0982; found 204.0979.

2,6-Bis(hydroxyimino)-4-[2-(hydroxyimino)propyl]heptan-4-ol (4i). Product **4i** was prepared from trimethallylcarbinol **3c** according to the general procedure with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept overnight, and then concentrated in vacuo. The residue was subjected to a column chromatography on silica gel (eluent EtOAc) to give 242 mg (33%) of tris-oxime **4i**. Elution of the column with EtOAc–MeOH (1:1) afforded 154 mg (21%) of triazaadamantane **2i**. Pale yellow oil, R_f = 0.6 (EtOAc). Mixture of (*E*,*E*,*E*)- and (*E*,*E*,*Z*)-isomers (ratio 1.5 : 1). (*E*,*E*,*E*)-**4i**: ^{1}H NMR (DMSO-d_6): δ = 1.80 (s, 9 H, 3 CH_3), 2.30 (s, 6 H, 3 CH_2), 4.69 (s, 1 H, OH), 10.43 (s, 3 H, 3 NOH). ^{13}C NMR (DMSO-d_6): δ = 15.7 (3 CH_3), 44.8 (3 CH_2), 73.8 (*C*), 154.3 (3 *C*=N). (*E*,*E*,*Z*)-**4i**: ^{1}H NMR (DMSO-d_6): δ = 1.81 (s, 3 H, CH_3, *Z*-fragment), 1.87 (s, 6 H, 2

C*H*$_3$, *E*-fragments), 2.27 (s, 4 H, 2 C*H*$_2$, *E*-fragments), 2.47 (s, 2 H, C*H*$_2$, *Z*-fragment), 4.76 (s, 1 H, O*H*), 10.41 (s, 1 H, NO*H*, *Z*-fragment), 10.45 (s, 2 H, NO*H*, *E*-fragments). ^{13}C NMR (DMSO-d$_6$): δ = 15.6 (2 *C*H$_3$, *E*-fragments), 22.2 (*C*H$_3$, *Z*-fragment), 40.8 (*C*H$_2$, *Z*-fragment), 45.2 (2 CH$_2$, *E*-fragments), 74.2 (*C*), 154.1 (*C*=N, *Z*-fragment) and 154.4 (2 *C*=N, *E*-fragments). HRMS: calculated for $C_{10}H_{20}N_3O_4$ [M+H$^+$] 246.1448; found 246.1448.

1,7-Bis(hydroxyimino)-4-[3-(hydroxyimino)propyl]heptan-4-ol (6). Product **6** was prepared according to the general procedure from triene **5** with the following additions: 1.85 ml (30 mmol) of 50% aqueous hydroxylamine solution was used. The reaction mixture was kept overnight, and then concentrated in vacuo. The residue was subjected to a column chromatography on silica gel (eluent EtOAc → EtOAc-MeOH (3:1)). Crude tris-oxime **6** was additionally recrystallized from the diethyl ether/methanol mixture and dried in vacuo. Yield: 617 mg (84%). White cryst., mp = 106-112 °C. Mixture of (*E*,*E*,*E*)-, (*E*,*E*,*Z*)-, (*E*,*Z*,*Z*)- and (*Z*,*Z*,*Z*)-isomers with *E*/*Z* fragments ratio ~1 : 1. ^{1}H NMR (CD$_3$OD): δ = 1.65 (m, 6 H, 3 C*H*$_2$CH), 2.23 and 2.40 (2 m, 6 H, 3 C*H*$_2$CH$_2$), 6.71 and 7.39 (2 t, J = 5.4 and 5.9, 3 H, 3 *H*C=N), 10.35 and 10.70 (2 s, ~30% of integral intensively, 3 NO*H*). ^{13}C NMR (DEPT135, CD$_3$OD): δ = 20.6 and 24.9 (3 *C*H$_2$CH), 35.4 and 36.2 (3 *C*H$_2$CH$_2$), 73.9, 74.0, 74.2, 74.4 (*C*OH), 152.25, 152.31, 152.34, 152.68, 152.74 and 152.78 (3 *C*=N). HRMS: calculated for $C_{10}H_{19}N_3O_4Na$ [M+Na$^+$] 268.1288; found 268.1272.

Ethyl 5-(4-{[4,9-bis({[1-(5-ethoxy-5-oxopentyl)-1H-1,2,3-triazol-4-yl]methyl})-7-hydroxy-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-2-yl]methyl}-1H-1,2,3-triazol-1-yl)pentanoate (8). Cu(OAc)$_2$•H$_2$O (3 mg, 0.015 mmol) was added to a stirred solution of triazaadamantane **2g** (35 mg, 0.13 mmol) and ethyl 5-azidopentanoate (132 mg, 0.77 mmol) in methanol (3 ml). After 30 min, the reaction mixture was concentrated in vacuo. The residue was subjected to a column chromatography on silica gel (eluent EtOAc → EtOAc-MeOH (3:1)) to afford 64 mg (63%) of tris-triazole **8**. White amorphous solid. R$_f$ = 0.2 (EtOAc-MeOH (3:1)). ^{1}H NMR (HSQC, HMBC, CDCl$_3$): δ = 1.22 (t, J = 7.1, 9 H, 3 C*H*$_3$), 1.62 and 1.93 (2 m, 18 H, 3 CH$_2$C*H*$_2$C*H*$_2$CH$_2$ and 3 C*H*$_2$), 2.33 (t, J = 7.2, 6 H, 3 C*H*$_2$C=O), 2.5-3.0 (br s, 1 H, O*H*), 3.91 (s, 3 H, 3 C*H*), 4.10 (q, J = 7.1, 6 H, 3 C*H*$_2$CH$_3$), 4.14 (s, 6 H, 3 NC*H*$_2$C), 4.32 (t, J = 7.5, 6 H, 3 CH$_2$C*H*$_2$N), 7.57 (s br, 3 H, 3 C=C*H*). ^{13}C NMR (HSQC, HMBC, CDCl$_3$): δ = 14.3 (3 *C*H$_3$), 21.9 and 29.7 (3 CH$_2$*C*H$_2$*C*H$_2$CH$_2$), 33.5 (3 *C*H$_2$C=O), 38.7 (3 *C*H$_2$), 48.4 (3 NCH$_2$C), 50.0 (3 NCH$_2$CH$_2$), 60.5 (3 *C*H$_2$CH$_3$), 66.1 (*C*OH), 72.6 (3 *C*H), 122.3 (3 *C*=CH), 146.7 (3 C=CH), 173.1 (3 *C*=O). HRMS: calculated for $C_{37}H_{59}N_{12}O_7$ [M+H$^+$] 783.4624; found 783.4619.

2,4,9-Tris({[(4-methoxyphenyl)methylidene]amino})-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-7-ol (9a). *p*-Anisaldehyde (250 μl, 2.03 mmol) was added to a stirred suspension of triazaadamantane **2c** (120 mg, 0.58 mmol) in methanol (2.5 ml). The starting material immediately dissolved, and a yellow precipitate was formed within 10-15 min. After 30 min, the precipitate was collected by filtration, washed with methanol, and dried in vacuo. Yield: 272 mg (85%). Pale yellow cryst., mp = 185-189 °C (with dec., darkening starts at 160 °C). ^{1}H NMR (DMSO-d$_6$): δ = 1.97 (s, 6 H, 3 C*H*$_2$), 3.31 and 5.10 (2 s, 1 H, CO*H*), 3.77 (s, 9 H, 3 OC*H*$_3$), 5.68 (s, 3 H, 3 C*H*), 6.85 and 7.49 (2 d, J = 8.7, 12 H, 3 C$_6$*H*$_4$), 7.88 (s, 3 H, 3 *H*C=N). ^{13}C NMR (DEPT135, DMSO-d$_6$): δ = 38.2 (3 *C*H$_2$), 55.1 (3 OCH$_3$), 64.45 and 64.54 (*C*OH), 71.2 (3 *C*H), 113.8 (3 *m*-*C*$_6$H$_4$OCH$_3$), 127.3 (3 *o*-*C*$_6$H$_4$OCH$_3$), 128.8 (3 *i*-*C*$_6$H$_4$OCH$_3$), 138.0 (3 *C*=N), 160.3 (3 =*C*-O). FT-IR (KBr): ν = 3419 (s, br), 2999 (w), 2956 (m), 2932 (m, sh), 2835 (w), 1608 (s), 1512 (s), 1462 (m, sh), 1350 (m, sh), 1305 (m), 1250 (s), 1168 (s), 1063 (m), 1031 (m), 1002 (m), 901 (w), 878 (w), 830 (m), 765 (m, sh), 728 (w), 611 (w) cm^{-1}. HRMS: calculated for $C_{31}H_{35}N_6O_4$ [M+H$^+$] 555.2714; found 555.2725.

2,4,9-Tris[(3-phenylpropylidene)amino]-2,4,9-triazatricyclo[3.3.1.1^{3,7}]decan-7-ol (9b). 3-Phenylpropanal (70 mg, 0.52 mmol) was added to a stirred suspension of triazaadamantane **2c** (30 mg, 0.15 mmol) in methanol (1.5 ml). The starting material dissolved within 30 min. After an additional 1 h of stirring, the reaction mixture was concentrated in vacuo. The residue was subjected to a column chromatography on silica gel (eluent EtOAc) to give 61 mg (74%) of tris-imine **9b**. Yellow oil. R$_f$ = 0.4 (EtOAc). ^{1}H NMR (DMSO-d$_6$): δ = 1.74 (s, 6 H, 3 C*H*$_2$), 2.42 and 2.73 (2 m, 6 H and 6 H, 3 C*H*$_2$C*H*$_2$), 3.34 and 4.93 (2 s, 1 H, CO*H*), 5.20 (s, 3 H, 3 C*H*), 7.02 (t, J = 5.0, 3 H, 3 *H*C=N), 7.1-7.3 (m, 15 H, 3 *o*,*m*,*p*-*Ph*). ^{13}C NMR (DMSO-d$_6$): δ = 32.8 and 34.4 (3 *C*H$_2$CH$_2$), 37.5 (3 CH$_2$), 64.5 and 64.6 (*C*OH), 70.3 (3 CH), 125.8, 128.27 and 128.31 (3 *o*,*m*,*p*-*Ph*), 140.2 and 141.4 (3 *i*-*Ph* and 3 *C*=N). FT-IR (KBr): ν = 3166 (s, br), 2962 (s), 2676 (s, br), 1620 (m, sh), 1530 (m), 1434 (m), 1351 (s), 1319 (m), 1230 (s, sh), 1160 (s, sh), 1087 (m, sh), 1023 (w), 981 (s), 958 (m), 927 (m), 917 (m), 888 (s), 783 (s), 745 (s), 708 (s), 673 (m), 647 (m) cm^{-1}. HRMS: calculated for $C_{34}H_{40}N_6ONa$ [M+Na$^+$] 571.3156; found 571.3145.

4-Hydroxy-9-phenyl-1,7,11-triaza-9-borapentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecan-1-ium-9-uide (10). Phenylboronic acid (122 mg, 1 mmol) was added to a suspension of triazaadamantane **2h** (203 mg, 1 mmol) in methanol (5 ml). The starting compound dissolved within 10 min, and the precipitation of product **10** was observed. After 3 h, the precipitate was collected by filtration and dried in vacuo. Yield: 172 mg (60%). White cryst., mp = 272-274 °C (with dec., darkening starts at 200 °C). ^{1}H NMR (D$_2$O): δ = 2.17 (s, 6 H, 3 C*H*$_2$), 5.03 (s, 3 H, 3 C*H*), 7.3-7.4 and 7.4-7.5 (2 m, 3 H and 2 H, *o*,*m*,*p*-*Ph*) (OH and NH hydrogens are not observed). ^{13}C NMR (DEPT135, D$_2$O): δ = 39.8 (3 *C*H$_2$), 62.9 (*C*OH), 74.4 (3 *C*H), 127.6, 127.8 and 130.9 (*o*,*m*,*p*-*Ph*) (*C*-B signal is not observed). HRMS: for $C_{13}H_{15}BN_3O_4$ [M-H$^+$] calculated 288.1163; found 288.1169.

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[27] In the case of propargylamine (entry 6 in Table 1), the trimer of the corresponding formaldehyde imine was isolated in 76 % yield (see Experimental section).

[28] With propargylamine (entry 6 in Table 1), trace amounts of the oxaazaadamantanes, resulting from the cyclization of mono- and bis-imines of aldehyde **1b**, were detected by NMR and HRMS in the reaction mixture.

[29] Tris-oximes **4j** and **4k** were detected in reaction mixtures by NMR and were not isolated.

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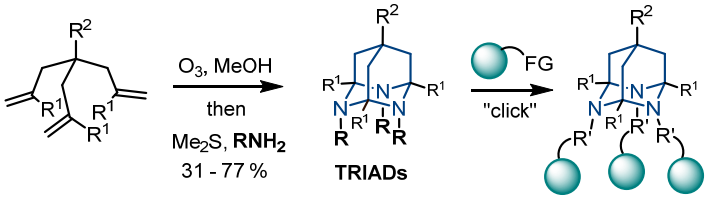

2,4,9-Triazaadamantanes (TRIADs) are a poorly investigated class of hetrocage molecules, which have the potential for applications as synthetic platforms. Here, comprehensive studies on the synthesis, structure and stability of TRIADs were performed. Facile modification of bridge *N*-positions in TRIADs through different click-strategies demonstrates the versatile characteristics of this new 3D scaffold.

Key Topic: Adamantane chemistry

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