ISSN 1070-4280, Russian Journal of Organic Chemistry, 2024, Vol. 60, No. 10, pp. 1831–1891. © Pleiades Publishing, Ltd., 2024.

REVIEW

Dedicated to the Memory of Full Member of the Academy of Sciences of the USSR B.A. Kazanskii (April 23, 1891—April 5, 1973)

Adamantane: On the 90th Anniversary of Its Appearance in Chemical Science

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Received October 5, 2024; revised October 15, 2024; accepted October 17, 2024

Abstract—The review describes the history of the development of adamantane chemistry and shows moments that stimulated rise in the studies, as well as the main lines of research in this field and prospects thereof, on the basis of published data (up to 2024) with an emphasis on the last two decades.

Keywords: adamantane, diamondoids, synthesis, pharmacology, catalysts, polymers, nanotechnology, functional materials

DOI: 10.1134/S1070428024100014

On the table are two sealed glass ampules with adamantane crystals: one is a gift from S. Landa to B.A. Kazanskii (adamantane from petroleum ~~oil~~), and the other is a gift from B.A. Kazanskii to S. Landa (adamantane obtained from cyclopentadiene at the Chemistry Department of Lomonosov Moscow State University). 1950s–1960s.

1. INTRODUCTION

In 1933, Czechoslovak scientists S. Landa and V. Machacek isolated from petroleum and introduced into the world a new hydrocarbon with a very modest composition, amazing structure, and unusual name, adamantane $C_{10}H_{16}$ (from the ancient Greek *adamant* which means "indestructible, invincible"). A "ball-shaped" molecule consists of bonded cyclohexane rings, each having a *chair* conformation; in other words, a unit cell of a diamond. More than 20 years passed before adamantane became available, and then, less than 50 years later, a huge and intensely developing field, the chemistry of adamantane and its derivatives, appeared in organic chemistry and not only in it.

The present review is aimed at consistently reflecting the history of the development of adamantane chemistry, showing the moments that stimulated the rise in research, and highlighting the main lines of research and their possible prospects, on the basis of materials published up to 2024 with an emphasis on the last two decades.[1]

2. ADAMANTANE. APPEARANCE IN THE WORLD AND THE FIRST THIRD OF LIFE (1924–1957)

2.1. The Long and Hard Path of Adamantane to Chemical Science

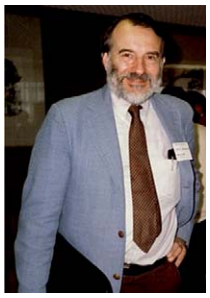
It all started in 1924. At the 88th Meeting of German Natural Scientists and Physicians in Innsbruck, the German scientist Decker expressed the idea that the hypothetical structure of $C_{10}H_{16}$, which he called decaterpene, could be self-organized into a diamond-like structure under certain conditions [1].

The idea has interested chemists, especially since an attempt to synthesize a compound with a similar structure has already been known. In 1922, the German researcher Meerwein reported the isolation of the desired hydrocarbon, which he called adamantane [2]. However, Meerwein was mistaken; he called one of the intermediate compounds, namely tetramethyl 2,6-dioxobicyclo[3.3.1]nonane-1,3,5,7-tetracarboxylate, later known as Meerwein's ester, adamantane. In 1933, Landa and Machacek isolated adamantane from oil from the Hodonin field [3]; the concentration of adamantane therein was 0.0004%. In 1941, Prelog and Seiwerth synthesized adamantane starting from Meerwein's ester in four steps with a yield of 0.16%, based on the initial tetraester [4]. The product turned out to be identical to the compound isolated by Landa and Machacek from petroleum. And finally, it was not until 1957 that P.v.R. Schleyer made adamantane accessible via isomerization of hydrogenated cyclopentadiene dimer in the presence of aluminum chloride [5] (Scheme 1).

The yield of the target product was 15–20%. Subsequently, after thorough study and optimization of

S. Landa
(Aug 30, 1898–Mar 31, 1981)

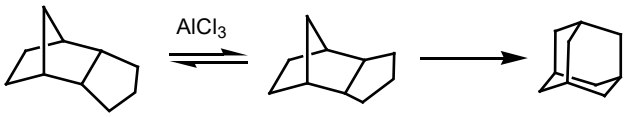
V. Prelog
(Jul 23, 1906–Jan 7, 1998)



P.v.R. Schleyer
(Feb 27, 1930–Nov 21, 2014)

[1] The chemistry of adamantane is not just huge – it is super-huge; the number of published materials constantly increases every year. This has led to the fact that the proposed review turned out to be to a large extent not just a review, but a "review of reviews" as a kind of reference book, allowing one to some extent to find answers to the questions: what?, where?, when? By indicating the countries of which the authors of the cited works are citizens, we wanted to confirm the prevalence of the conducted research across the globe.

Scheme 1.



the isomerization process, the yield of adamantane was improved to 60% [6]. In 1964, Schleyer wrote: "… for nearly 25 years, Landa had a practical, although not absolute, monopoly of the world's supply of adamantane. Convenient quantities of adamantane were obtained by the processing of enormous quantities of oil; for example, 66 kg of petroleum steam distillate yielded 200 g of adamantane. Yields of adamantane from synthesis were uniformly low; probably no other investigator had more than a few hundred milligrams at any one time." [7].

The method of synthesis of adamantane from available raw materials was very quickly implemented on an industrial scale in many countries, including the Soviet Union. The interest in adamantane, which arose back in the 1920s, has grown unusually.

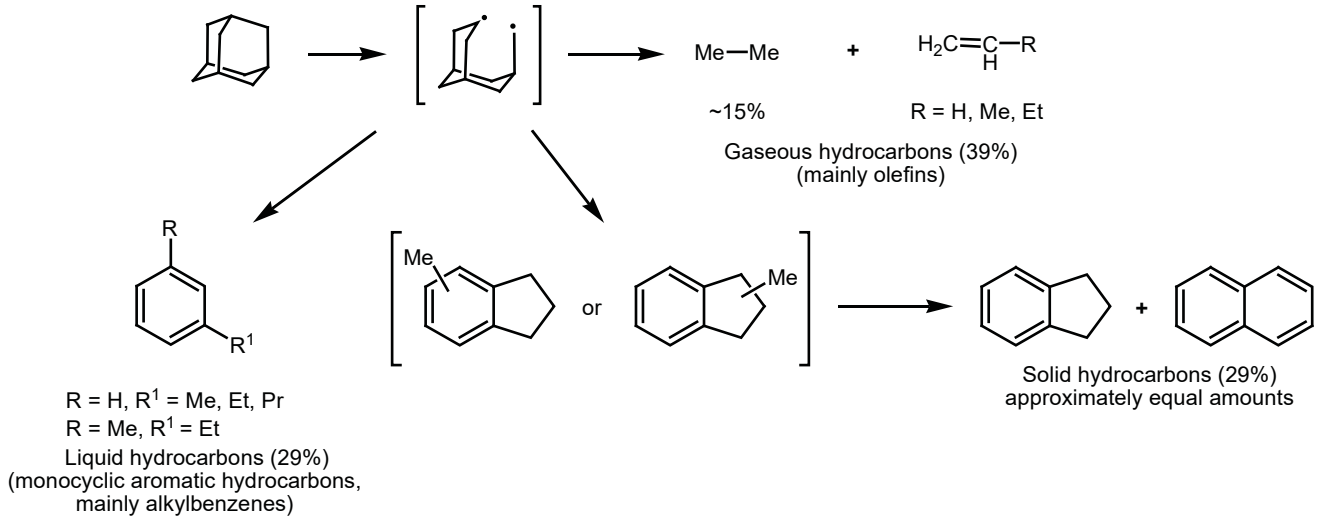
What is adamantane? What is the reason for the extraordinary interest in this fairly simple hydrocarbon of the composition $C_{10}H_{16}$?

In 1969, A.N. Nesmeyanov [8] wrote about adamantane: "… the skeleton of this compound is a structural unit of diamond. A diamond crystal is like a polymer built on the basis of an adamantane skeleton in which all C–H bonds are replaced by C–C bonds. The adamantane molecule is highly symmetrical, all cyclohexane rings are fixed in the *chair* form and are devoid of angular stress." The melting point of adamantane (269°C) is unusually high for hydrocarbons; it easily sublimes even at room temperature and crystallizes. Adamantane is characterized by high thermal and catalytic strength [9]; its pyrolysis begins at 660°C and occurs almost completely (94%) at 675°C. As a result, gaseous, liquid, and solid hydrocarbons are formed (39, 29, and 29%, respectively, based on the original adamantane), as well as coke (Scheme 2).

Adamantane molecule decomposes at 550–570°C in the presence of oxide catalysts such as industrial aluminosilicate cracking catalyst (82% SiO_2) and chromium oxide (20%) on aluminum oxide which possesses cracking and isomerizing properties. The decomposition directions are the same as in the pyrolysis with the difference that the decomposition products (especially in the presence of aluminosilicate catalyst) contain alkylnaphthalenes with a higher molecular weight than that of initial adamantane.

The stability of adamantane under catalytic conditions was studied using metal catalysts (Ni, Pt, Pd, Ir on various supports). All reactions were carried out in a stream of hydrogen. It was found that kieselguhr- or Al_2O_3-supported Ni (20 or 50%) reduce the decomposition temperature of adamantane to 500, 450, and 350°C, respectively, and that only gaseous hydrocarbons (mostly methane) are formed. The use of Ir and Pt on Al_2O_3 or industrial reforming catalyst AP-56 provide decomposition of adamantane at 500–535°C, whereas in the presence of activated carbon-supported

Scheme 2.



Pt, Pd, and Ir catalysts, adamantane decomposes at 440–540°C.

These findings unambiguously indicate the high stability of adamantane molecule and that all its transformations begin in a similar way, starting from the dissociation of any of the identical C–C bonds with the formation of bicyclo[3.3.1]nonane system. However, attempts to detect bicyclo[3.3.1]nonane among the transformation products were unsuccessful. This was not surprising, since as early as 1955 Zelinsky and Ivanov showed that bicyclo[3.3.1]nonane in the presence of Pt/C is converted into *n*-propylbenzene even at 310°C [10].

We believe that the given data may be useful for researchers engaged in problems related to the origin of oil and "forecasting" oil deposits that could contain adamantane and, probably, other uncommon structures.

2.2. Adamantane Chemistry in 1957–1981. Adamantane Isomerization and Its Mechanism. Related Polycyclic Hydrocarbons. Discovery of the Antiviral Activity of Aminoadamantane

The excellent review by Fort and Schleyer published in 1964 (Adamantane: Consequences of the Diamondoid Structure) [7] summarized the data available by that time on the chemistry of adamantane and related compounds (Fig. 1). The structure, physical and chemical properties, and their interrelations were considered in the context of the corresponding data for related polycyclic systems such as thiaadamantane, hexamethylenetetramine, homoadamantane, twistane, and bicyclo[2.2.2]octane. The results of X-ray diffraction, electron diffraction, thermochemical/thermodynamic properties, molecular diamagnetism, dipole moment, and IR, NMR, and mass spectral studies of adamantane and its derivatives were discussed. A detailed analysis of the chemical properties of adamantane, its mono-, di-, tri-, and tetrasubstituted derivatives at the bridgehead positions, and mono- and disubstituted derivatives at the bridging positions was performed. The review included special sections devoted to homoadamantane and twistane. On the whole, the number of adamantane derivatives listed only in tables exceeded 150.

Particular attention was paid by the authors to the synthesis of adamantane from hydrogenated cyclopentadiene dimer, specifically to the reaction conditions and, even to a greater extent, to the proposed mechanism of "adamantane" isomerization [7, 11] (Scheme 3).

The questionable stage was 2,6-alkyl migration **A** → **B**, which at that time had no direct analogues in the literature. Similar 2,6-hydride shifts accompanied

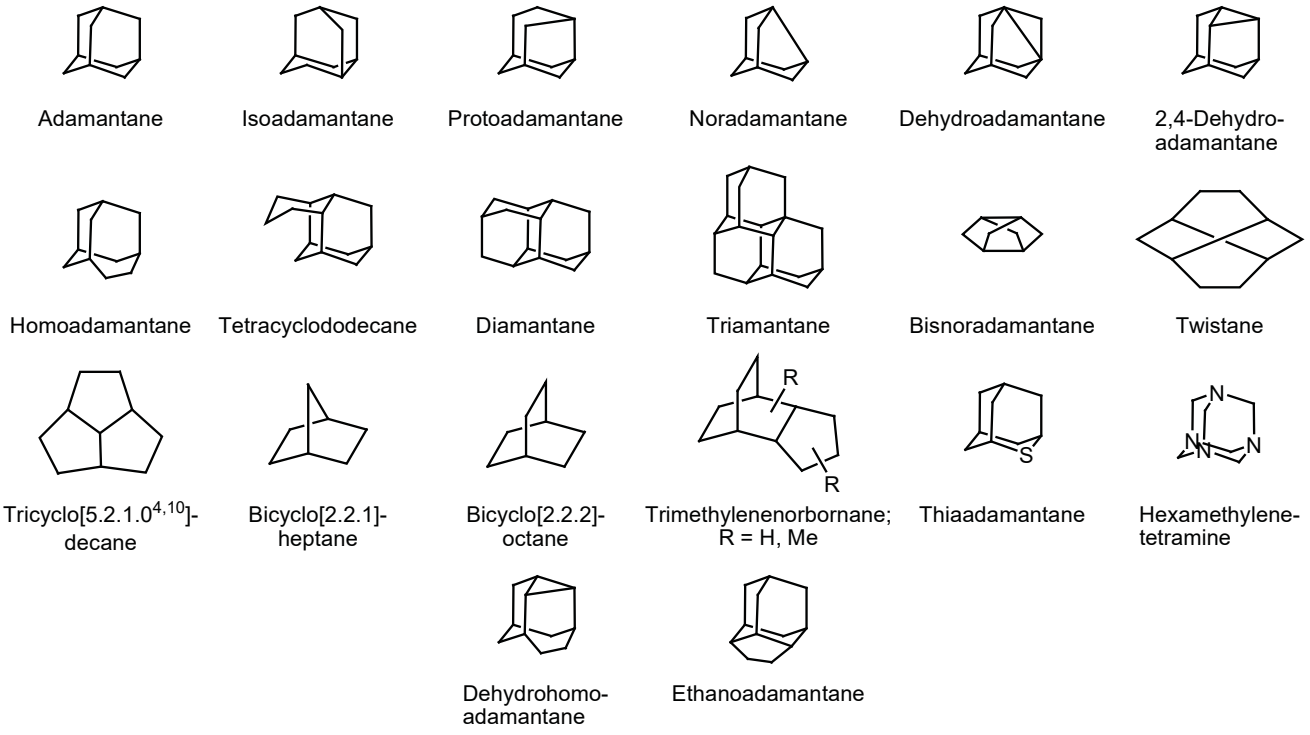
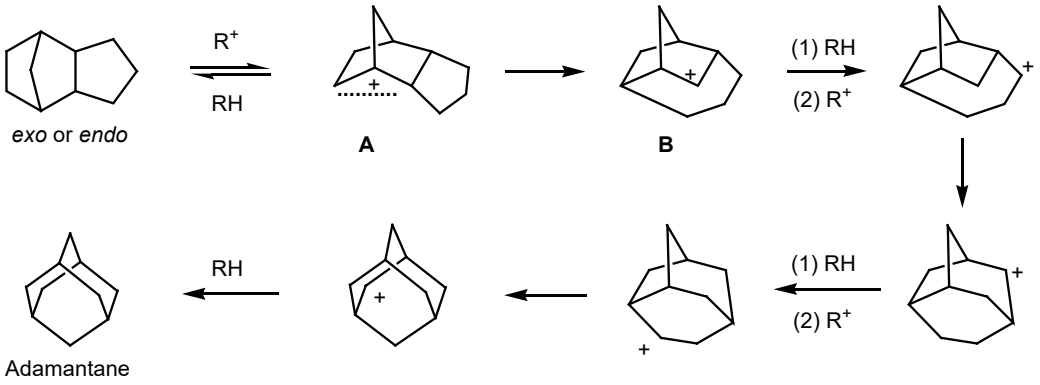


Fig. 1. Adamantane and related polycyclic hydrocarbons most frequently noted in review [7].

Scheme 3.



by a decrease in strain were well known. To confirm the proposed hypothesis (or, conversely, to reject it) the adamantane isomerization of methyl-substituted *endo*- and *exo*-trimethylenenorbornanes with different positions of the CH_3 group (a "label," as conceived by the authors [12]; Fig. 2) was studied (the review presents the results in detail).

According to the mechanism shown in Scheme 3, the use of 7-methyl-*endo*-trimethylenenorbornane as initial compound should lead to the formation of 2-methyladamantane. However, in all cases, the isomerization of any methyl derivative gave a mixture of two isomeric 1- and 2-methyladamantanes, where the fraction of the former ranged from 85 to 90%. This was explained as follows. The methyl group in 1-methyladamantane is equatorial with respect to all cyclohexane rings and is linked to the tertiary carbon atom, so that the molecule is devoid of repulsive interactions and is therefore stable. The methyl group in 2-methyladamantane is equatorial with respect to one of the fused cyclohexane rings but is axial with respect to the other, which destabilizes the molecule. This assumption is confirmed by the data given in [7] for the equilibrium between 1- and 2-methyladamantanes (Scheme 4).

The review by Bingham and Schleyer published in 1971 (Recent Developments in the Chemistry of Adamantane and Related Polycyclic Hydrocarbons) [13] was an extension of the review [7]. The authors [13] considered protoadamantanes, twistanes, tricyclo[5.2.1.$0^{4,10}$]decanes, homoadamantanes, noradamantanes, bisnoradamantanes, dehydroadamantanes, and dehydrohomoadamantanes (Fig. 1) and noted that they aimed "not only to review the recent synthetic developments but also to emphasize the many applications of diamondoid substrates for testing various theories of physical-organic chemistry." Even an analysis of the Contents of [7] and [13] makes it possible to unambiguously conclude about the development that the chemistry of adamantane and related cage hydrocarbons has achieved in a wide variety of areas in less than 15 years since adamantane has become available for study.

Almost simultaneously with review [13], two more reviews entitled "Advances in the Chemistry of Adamantane" were published by Soviet scientists

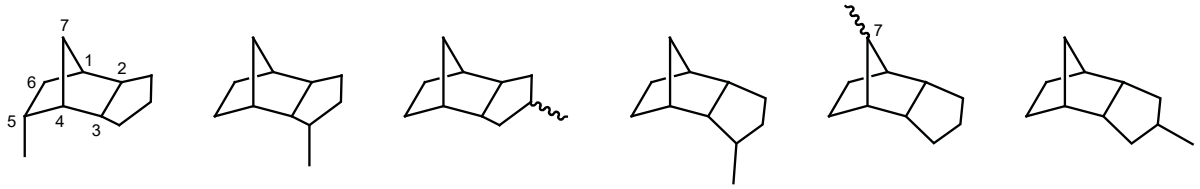
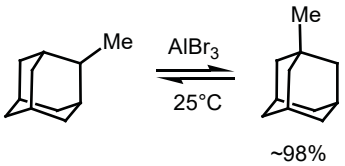


Fig. 2. Methyl-substituted *endo*- and *exo*-trimethylenenorbornanes.

Scheme 4.



ΔF°_{298} = –2.4±0.2 kcal/mol
ΔH = –2.5±0.2 kcal/mol
ΔS = –0.2±0.2 eu

~98%

Sevost'yanova, Krayushin, and Yurchenko [14] and by Czech authors Weidenhoffer and Hala [15]. Both reviews were largely synthetic in nature, and they considered the synthesis of adamantane, its derivatives, and adamantanoid hydrocarbons. The term "adamantanoids" was applied to hydrocarbons containing at least 10 carbon atoms and forming molecules similar to adamantane and structurally related hydrocarbons.

Review [14] covers the data published before July 1969 and is written according to a template reproducing review [7]. Review [15] covering the literature published in 1964–1967 (348 references), deserves special attention. Already in the Introduction, the authors very clearly defined the cornerstones that determined the rapid development of adamantane chemistry (i.e., adamantane isomerization of trimethylenenorbornane and the discovery of antiviral activity of 1-aminoadamantane), recorded the growth of scientific schools (laboratories) engaged in research in this field, and noted an exceptionally large increase in the number of patents which amounted to 20 (1964), 27 (1965), 35 (1966), and 45% (1967) of the total number of publications. One third of the literature cited in the review was represented by patents. The content of the review and data presentation therein provide clear definition of the types and classes of adamantane derivatives that attract particular attention from chemists. For the first time, a separate section concerning pharmacological activity of adamantane derivatives has been introduced, and a specific classification of pharmacological activity with respect to the type of adamantane-containing derivative has been given (Table 1).

After the discovery of antiviral activity of 1-aminoadamantane [16] and inhibitory effect of its analogue, 1-(α-aminoethyl)adamantane (rimantadine) against mycoviruses in vivo and in vitro [17] (1964–1965), a comparative study of antiviral activity of both compounds against influenza A2 viruses was performed. Rimantadine was very rapidly introduced into the healthcare practice, and a sharp increase in research aimed as searching for adamantane-containing antiviral drugs, primarily among nitrogen-containing derivatives, was observed worldwide.

Antiviral activity (mainly against influenza viruses) of four groups of compounds, namely mono- and trisubstituted adamantanes, alkyladamantylpiperazines, and some isomers and homologs of aminoadamantane (about 150 compounds) was studied at the Kirhenšteins Institute of the Academy of Sciences of Latvian SSR. In vitro inhibitory activity against influenza viruses was found for 72% of the tested compounds. In 1981, the researchers published a book [18] containing a review and analysis of their own and literature data available at that time on the mechanism of the antiviral action of adamantane derivatives. The authors stated that the mechanism of action of adamantyl-containing drugs has not been precisely established and that the literature contains much contradictory data. Nevertheless, they noted that adamantane derivatives do not have a direct virucidal effect on free viral particles. As for the area of action of chemotherapeutic drugs, it can be any stage of viral reproduction, including its transcription (interaction of viral particles with the cell membrane), penetration into the cell, and the release of viral nucleic acid (deproteinization of the viral genome). The authors considered the data on inhibition of virus-specific syntheses, such as the synthesis of virus-induced RNA-RNA polymerase and virus-specific polypeptides, by adamantane derivatives to be convincing.

Table 1. Pharmacological activity of adamantane derivatives

Adamantane derivative	Pharmacological activity
1-Aminoadamantane and its derivatives, adamantanecarboxamides	Antiviral
Derivatives of arenesulfonylureas, guanidine, and biguanidine	Antidiabetic
Adamantylarylureas	Tuberculostatic
Barbituric acid esters, *N*-alkyltrimethyladamantanecarboxamides	Sedative and hypnotic
1-Hydroxyadamantane ethers	Choleretic
Steroid esters and adamantane-1-carboxylic acid esters	Estrogens, androgens, corticosteroids
6-Aminopenicillanic acid esters	Antibiotic
Naphthoquinone derivatives	Antimalarial
Phenothiazine, benzoxazepine, and benzothiazepine derivatives	Antidepressant

In the last 50 years, up to the present time, the intensity of research has not decreased; moreover, it is being detailed and specified. The development of methods for the synthesis of adamantane derivatives, related compounds, and modification of known drugs still occupies a leading place in adamantane chemistry. At the same time, huge work is being carried out to study the effect of adamantane fragments on the properties of the obtained compounds. To the greatest extent, this applies to medicine and pharmacology; every year the number of such works increases, and the search for areas of possible use of adamantanoid drugs is expanding. These issues are the subjects of the next sections of the review.

3. CHEMISTRY OF ADAMANTANE AND DIAMONDOIDS IN THE LAST DECADES

Undoubtedly, the chemistry of adamantane is unique due to the unique properties of adamantane itself. Adamantane is unique in all respects. This follows from almost all publications related to adamantane. Compounds containing an adamantane moiety often exhibit unusual properties, and they have become the subjects of study not only by organic chemists but also specialists in a wide variety of fields of science and technology, primarily in medicine.

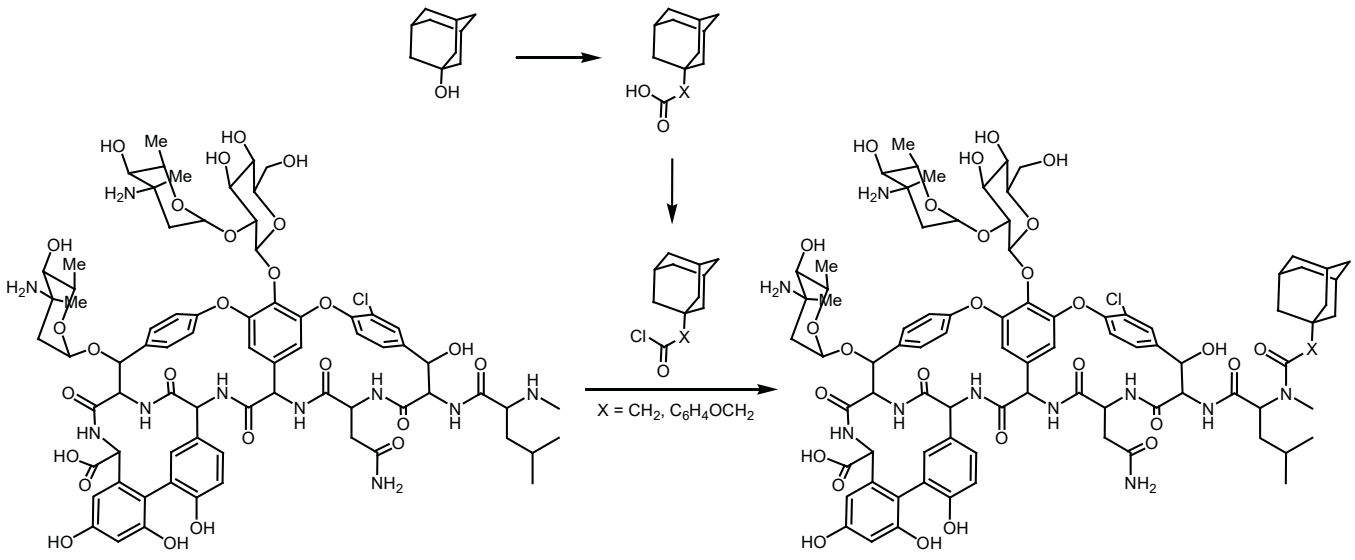
There are many examples in the literature. In particular, in 2009, Kovalev et al. [19] modified the glycopeptide antibiotic eremomycin (which was discovered in Russia [20]) by selective acylation of its N^1-terminal amino group with adamantane-1-acetic and 2-[4-(adamantan-1-yl)phenoxy]acetic acids (Scheme 5). Eremomycin is used for the treatment of diseases caused by gram-positive bacteria. The adamantane-containing conjugates obtained as a result of modification showed somewhat lower antibacterial activity but pronounced antiviral activity, and they suppressed reproduction of antigenic type herpes simplex-2 viruses with a selectivity index of ~10.

Taking into account the unpredictable uniqueness of adamantane and its derivatives, we believe that important are studies aimed at developing convenient methods for the synthesis of a wide variety of compounds based on the adamantane scaffold, modifying compounds with some certain properties via introduction of adamantyl-containing fragments, and creating novel types of adamantyl-containing organic molecules. Accordingly, the data of this section are presented with an emphasis on the general synthetic methods and particular types (classes) of adamantane derivatives. In some cases, for the sake of completeness, articles published as a rule in the most recent years were included in our "review of reviews."

3.1. Adamantane Derivatives of Various Types and Classes

In 1999 and 2022, two reviews by Russian researchers were published [21, 22]. The review by Moiseev et al. (Samara State Technical University) [21] was devoted to the synthesis of functional adamantane derivatives by reactions in electrophilic media. Three fourths of references cited in the review correspond to 1970–1999. The adamantane derivatives included mono- and polyfunctionalized halo, hydroxy,

Scheme 5.



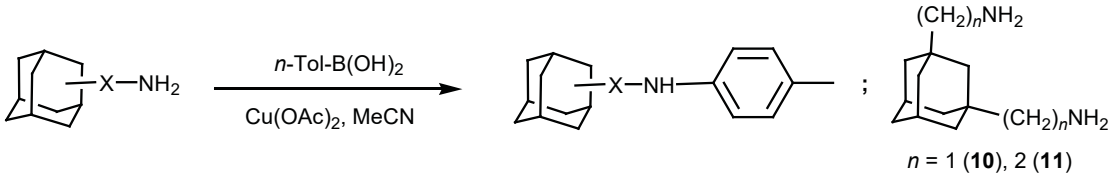
nitrooxy, carboxy, amino, and aryl adamantanes. Conditions of synthesis of a large number of various adamantane derivatives in electrophilic media were given. Study of the behavior of adamantane in electrophilic media made it possible to extend insights into the mechanism of C–H bond activation and develop preparative procedures for obtaining halo-, hydroxy-, and nitrooxyadamantanes. Among the adamantane functionalization methods, reactions in nitric acid and its mixtures with acetic acid or acetic anhydride were shown to be of particular interest.

The review by Baranov et al. (Peoples' Friendship University of Russia, Institute of Petrochemical Synthesis of the Russian Academy of Sciences) [22] entitled "Advances in the Chemistry of Unsaturated Adamantane Derivatives" covered studies performed in 2000–2020, which constituted 90% of the review. The unsaturated derivatives under consideration were divided into three groups: dehydroadamantanes, compounds with an exocyclic double bond, and those with a multiple bond in the side chain. About 2/3 of the review was devoted to the methods of their synthesis (the conditions and yields of 46 reactions were given. The minor part included data on the "polymerization and oligomerization of unsaturated derivatives" (see Section 5 of the present review).

In 2023, Kuliukhina et al. [23, 24] studied copper-catalyzed arylation of mono- and diaminoadamantanes with *p*-tolylboronic acid (Chan–Lam coupling; Scheme 6). Under the optimized conditions, the yields were 56–74% (amines **1**, **2**, **8**, and **9**) and 19–49% (**3**, **5**, **6**). Diamines **10** and **11** reacted at both amino groups with 56 and 42% yields, respectively. High yields (up to 93%) were obtained using 2-iodonaphthalene and 6-iodoquinoline as arylating agents. This is the first example of successful arylation of adamantyl-containing amines under modified Chan–Lam coupling conditions. The importance of studies in this field was reliably confirmed by the well designed review [25] on Cu-catalyzed arylation of adamantane-containing amines.

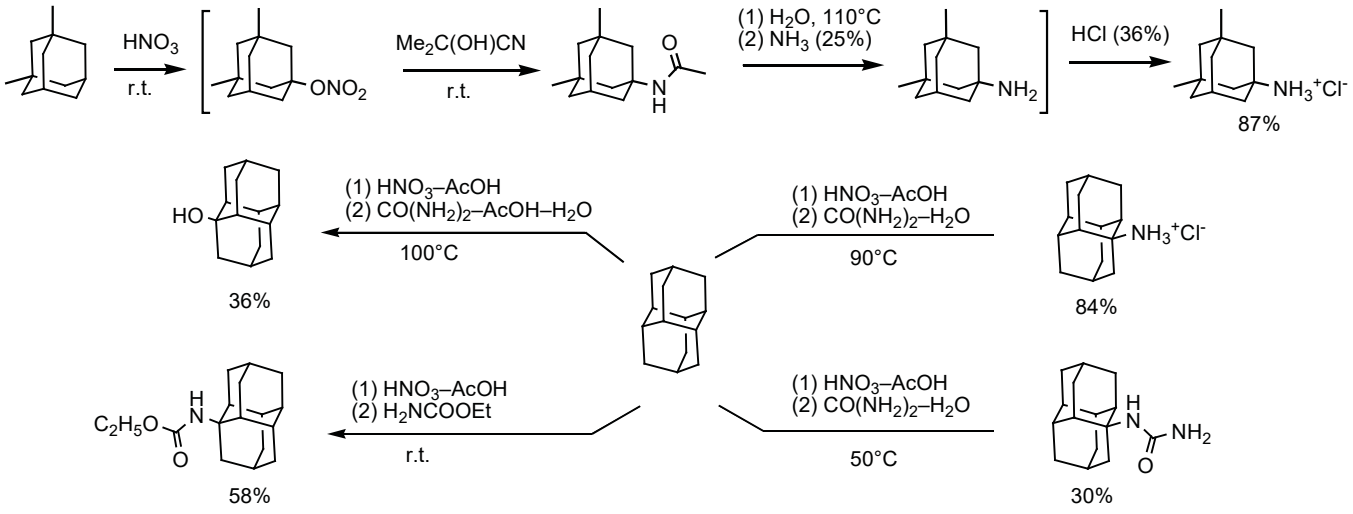
The known method of nitroxylation of adamantane and its derivatives with fuming nitric acid [21] was recently utilized in the development of a new one-pot synthesis of the anti-Alzheimer drug memantine [26], as well as for the selective functionalization of diamantane at the medial position [27] (Scheme 7).

Scheme 6.



1–X–NH_2: X = $(CH_2)_2$ (**1**); CH_2 (**2**); CH(Me) (**3**); $CH_2CH(Me)$ (**4**); CH(Ph) (**5**)
2–X–NH_2: X = $(CH_2)_n$, *n* = 0 (**6**), 2 (**7**); X = $CH(Me)CH_2$ (**8**), CH(Et) (**9**).

Scheme 7.



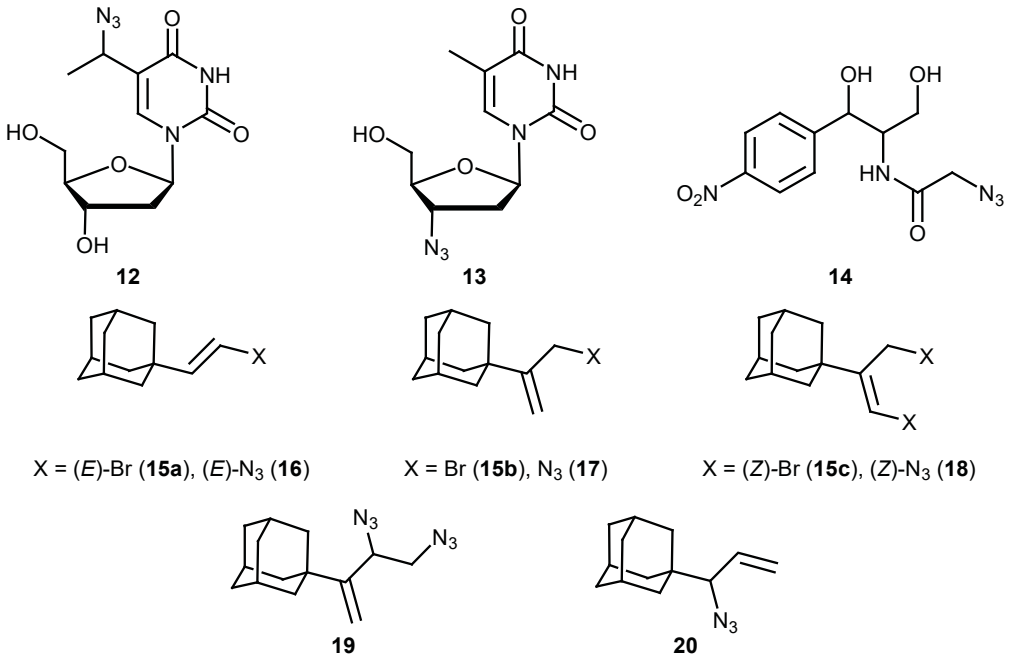


Fig. 3. Structures of 5-(1-azidoethyl)-2′-deoxyuridine (**12**), azidothymidine (**13**), azidamfenicol (**14**), and new azido derivatives **16**–**20**.

The presence of an azido group in the molecules of a number of drugs, such as 5-(1-azidoethyl)-2′-deoxyuridine (**12**, antiviral), azidothymidine (**13**, anti-HIV), and azidamfenicol (**14**, antibiotic), stimulated the authors of [28] to study the synthesis and some properties of adamantane derivatives containing azido groups (Fig. 3). Allyl azides **16**–**20** shown in Fig. 3 were synthesized from the corresponding bromides **15** and sodium azide, and epoxidation of some of them was studied.

In 2011, we published a review [29] of literature data on the synthesis and transformations of adamantane-containing keto esters and keto acids that are highly reactive polyfunctionalized compounds playing an important role in the chemistry of adamantane. The data were systemized on the basis of the compound structure: keto esters and keto acids in which (**a**) the ketone carbonyl carbon atom is a part of the adamantane skeleton linked to an ester or carboxy group and (**b**) both ketone and ester (acid) functionalities are

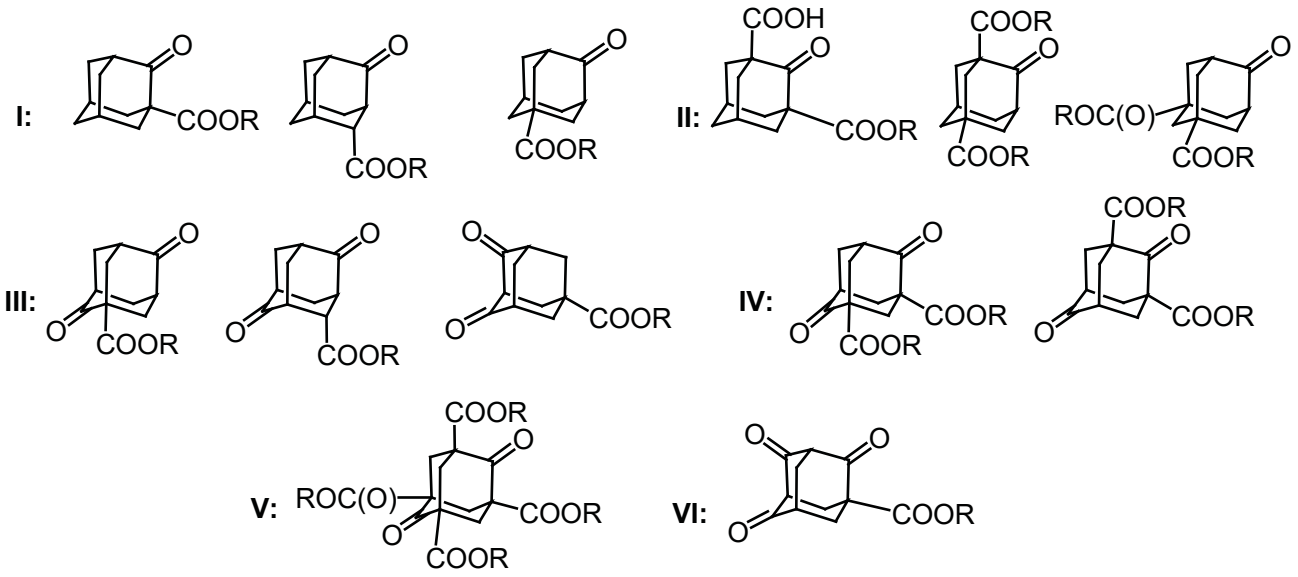


Fig. 4. Main types of carbonyl-containing adamantane derivatives.

incorporated in a side chain were considered separately. Depending on the number and mutual position of the ketone and ester (acid) groups, group (**a**) included six types of structures (**I**–**VI**; Fig. 4).

The synthetic methods considered in the review were grouped according to the nature of the initial compounds: Meerwein ester and cyclohexanone and adamantane derivatives for group (**a**) compounds; diethyl malonate and its homologs and analogues, ethyl acetate, ethyl acetoacetate and ethyl cyanoacetate, triphenylphosphoranes, adamantyl-containing keto esters and keto esters containing carbo- and heterocyclic fragments, etc., for group (**b**) derivatives.

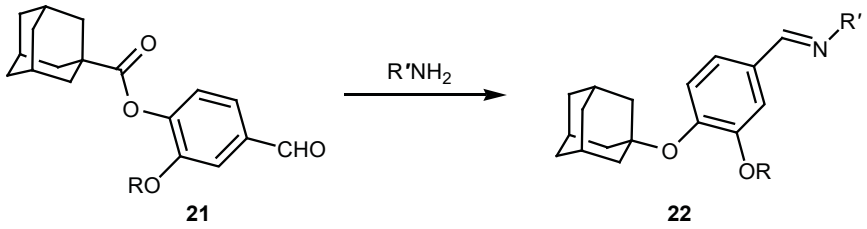
The second part of the review focused on the prospects of using keto esters and keto acids of the adamantane series in the synthesis of a wide variety of adamantane derivatives, including carbo- and heterocyclic ones. The data on biological activity of some compounds obtained from adamantyl-containing keto acids (esters) are included in Section 4 of the present review.

The review ends with examination of a new original method of obtaining adamantyl-containing keto esters and keto acids via self-acylation of adamantane-1-acetic acid in the system $CF_3CO_3H/(CF_3CO)_2O$. The given self-acylation process has a general character and is, in fact, a method rather than a technique; therefore, it is considered separately in Section 3.2.1 of the present review.

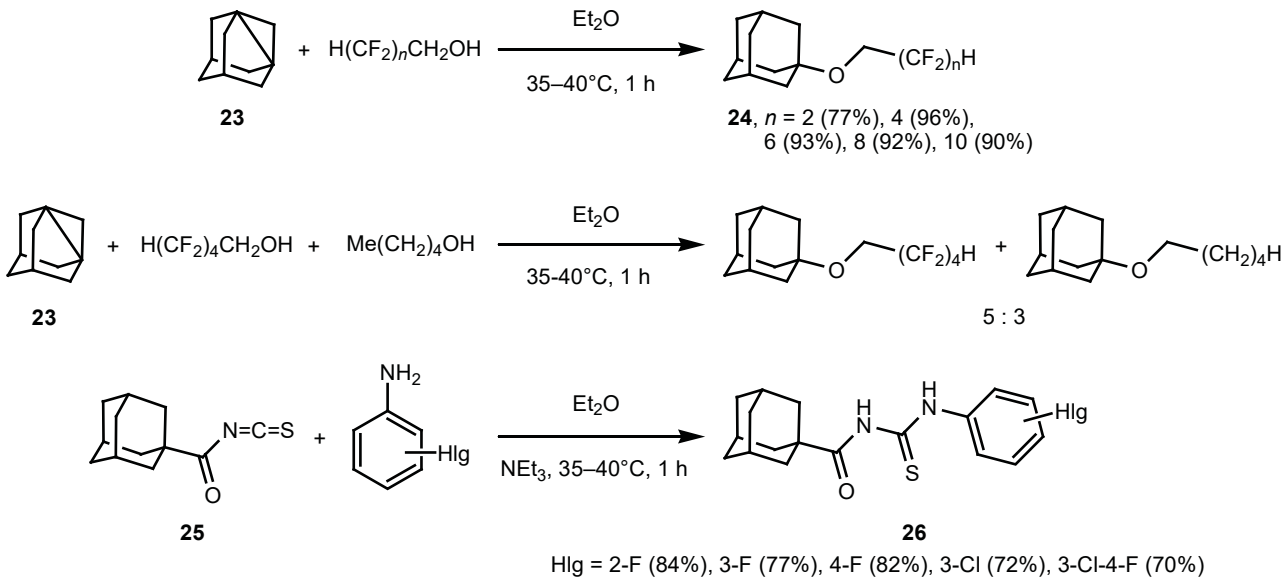
Dikusar et al. (Belarus) [30, 31] studied derivatives of adamantane-1-carboxylic acid and obtained new esters, amides, and thioesters, including those containing a peroxy group. The synthesized compounds featured a great diversity of pharmacophoric fragments. About ~40 Schiff bases **22** containing one or two adamantyl fragments were synthesized only by the condensation of aliphatic, cycloaliphatic, and aromatic amines with esters **21** derived from adamantane-1-carboxylic acid and vanillin (Scheme 8).

In 2023, Butov et al. (Volgograd, Russia) synthesized in one pot adamantan-1-yl polyfluoroalkyl ethers **24** [32] and *N*-(adamantane-1-carbonyl)-*N*′-(halophenyl)thioureas **26** [33]. In the synthesis of **24**, the adamantane-containing component was 1,3-dehydroadamantane **23** [34], and in the synthesis of **26**, adamantane-1-carbonyl isothiocyanate **25**. When equi-

Scheme 8.



Scheme 9.



molar amounts of two alcohols (in the first case) or two haloanilines (in the second case) were used, mixtures of the corresponding products were formed (Scheme 9). The effect of the carbonyl group in thioureas **26** on their solubility in water was studied, and in silico analysis of their biological properties predicted possible antiviral and nootropic activities.

In recent years, there has been growing interest in polysubstituted adamantane derivatives with various functional groups at the bridgehead positions. This is related mainly to the search for new biologically active compounds and design of functional hybrid materials. Two reviews were published shortly after each other. The first one is our review published in 2012 [35], and the second was published in 2014 by Grillaud and Bianco [36].

The review [35] summarized and analyzed the data of two approaches to the synthesis of such compounds. Approach **A** is based on selective functionalization of tertiary C–H bonds in mono- and polysubstituted adamantanes, and approach **B** involves partial desymmetrization of polyfunctionalized adamantane derivatives with similar substituents.

Approach **A** includes functionalization of the adamantane core in electrophilic media, reactions with electrophilic reagents and transition metal salts and complexes, and radical, radical cation, and electrochemical reactions. The mechanism of C–H bond activation with various electron-deficient species involves the formation of close cationic or radical cationic transition states **TS1**–**TS3**, and it can be described by the H-bonding electron transfer model through the formation of transition state $[C\cdots H\cdots E]^{+}$ similar to the single-electron transfer (SET) transition state (oxidative pathway; Fig. 5) [37].

Other interpretations of the mechanism of C–H bond activation were also proposed in the literature, in particular electrophile (E^{+}) insertion into the σ-C–H bond through a three-centered two-electron transition state and direct attack of an electrophile on the σ-bonded carbon atom.

Approach **B** is nothing more than the synthesis of ligands with a molecular tripod structure. These include rigid 1,3,5,7-tetrasubstituted adamantanes with three similar substituents at positions *1*, *3*, and *5* containing COOR, CN, or sulfur or nitrogen anchoring functional groups. In all cases, the key stage in the synthesis of such compounds was selective substitution of one iodine atom in 1,3,5,7-tetrakis(4-iodophenyl)-adamantane (obtained in two steps from 1-bromoadamantane in 50% yield). Two synthetic routes to such tripods are known, which are based on Sonogashira (**S1**) [38] and Suzuki (**S2**) [39, 40] cross-couplings and carboxylation [41] (Scheme 10).

In both cases, the key stage is that in which the tetrahedral precursor is converted into the triiodide (first stage in path *a*) or tricarboxy derivative (second stage in path *b*). However, the selectivity of these processes is very low, the yields are poor, and the product isolation procedure is laborious.

The data presented in review [35] covered a very large number of polyfunctional adamantane derivatives with an emphasis on the conditions of synthesis and advantages and disadvantages of synthetic procedures. Particular attention was given to the properties and possible application of the unique compounds, ada-

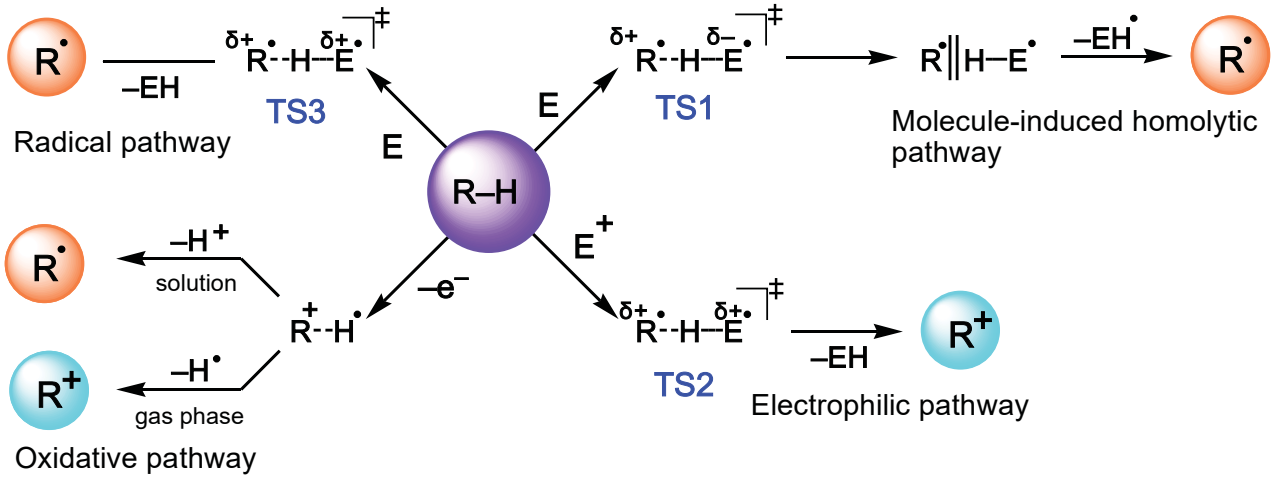
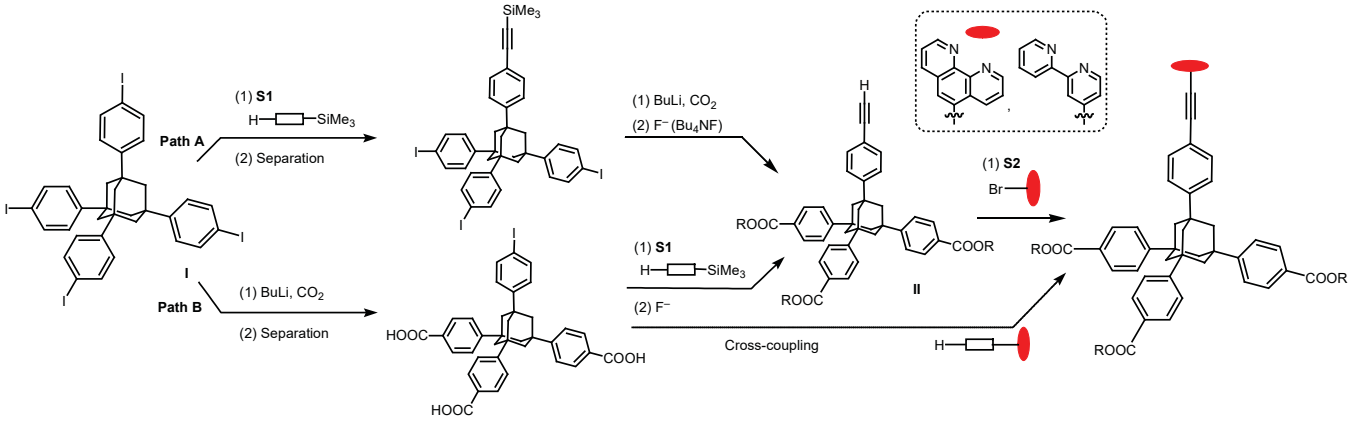


Fig. 5. Activation of C–H bond in alkanes by neutral (E) and charged (E^{+}) electrophiles, radicals ($E^{\cdot}$), and electron acceptors ($-e^{-}$) (modified from [37]).

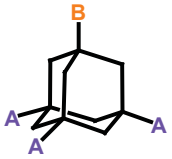
Scheme 10.



Sonogashira reaction (**S1**): $Pd(dba)_2PPh_3$ or $Pd(PPh_3)_2Cl_2$, CuBr or CuI, *i*-PrNH or $(i\text{-Pr})_2NEt$; Suzuki reaction (**S2**): B-MeO-9-BBN (9-methoxy-9-borabicyclo[3.3.1]nonane), $Pd(PPh_3)_4$; carboxylation: BuLi, CO_2.

mantane-based molecular tripods (see Section 5 of the present review).

The review by Grillaud and Bianco [36] considered in detail various methods of synthesis of [3+1]-building blocks based on polyfunctional tetrasubstituted adamantanes, and presented data on the possible use of their conjugates with peptides as multivalent ligands for biomedical studies (Table 2).



Adamantane-based
3+1 building blocks

Methods for the modification of cage structures were the subject of the review by Grover and Senge (The University of Dublin, Ireland) entitled "Synthetic Advances in the C–H Activation of Rigid Scaffold Molecules," which was published in 2020 [42]. The review considered functionalization of cubane, bicyclo[1.1.1]pentane, and adamantane via both carbocationic and radical processes (Fig. 6). As concerns adamantane itself, the data summarized in [42] provide a good supplement to those reviewed in [35, 36].

In 2019, Hrdina (Giessen, Germany) [43] published the review "Directed C–H Functionalization of the Adamantane Framework" which summarized literature data related to the synthesis of 1,2-disubstituted derivatives; 80% of references cited therein correspond to 2000–2018. The discussed processes included the formation of some non-isolable intermediate which is converted to the desired product as a result of intramolecular transformation. Various substituted adamantanes (R is a functional substituent) were considered as starting materials in the synthesis of 1,2-disubstituted adamantanes (Fig. 7).

The nature of intermediates is different. They can be carbenoids, nitrenoids, vinylcarbenoids, nitrogen- and oxygen-containing radicals, metal–organic complexes, etc., depending on the nature of the activating agent. The reactions could lead to the formation of two types of 1,2-disubstituted adamantanes, namely derivatives with two different functional substituents and fused derivatives at the C^1–C^2 bond. The latter originate from intramolecular cyclizations accompanying the process and serve as polyfunctional carbo-

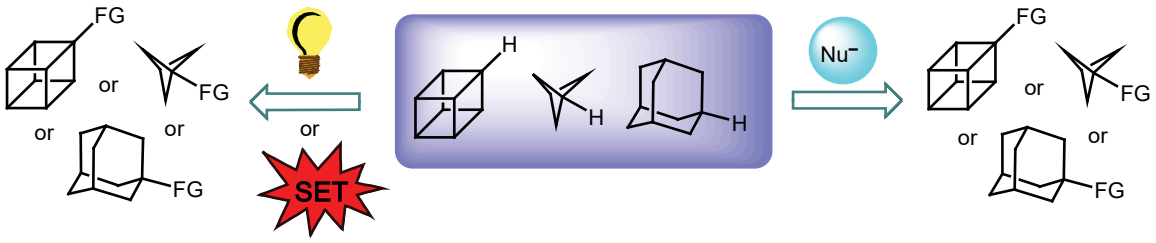
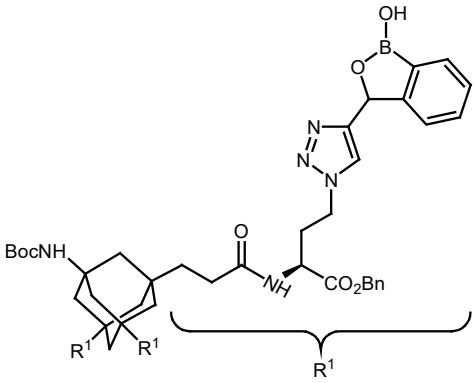
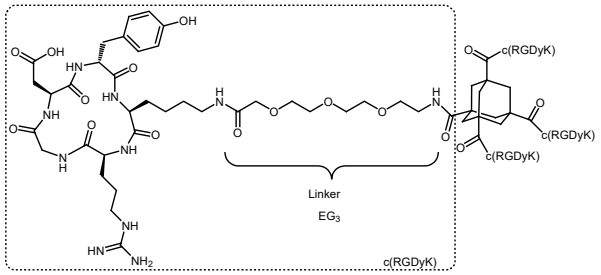
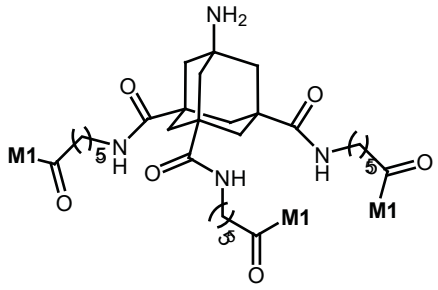
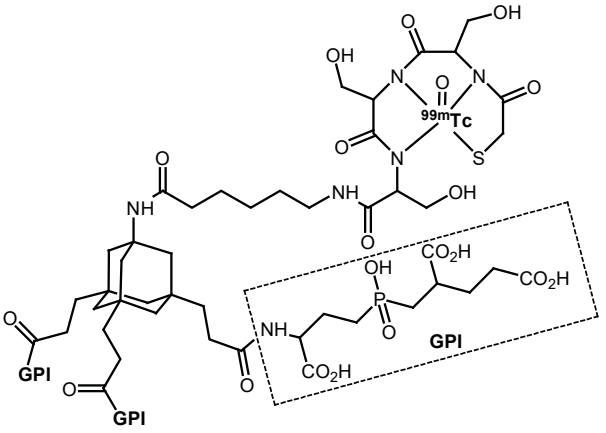
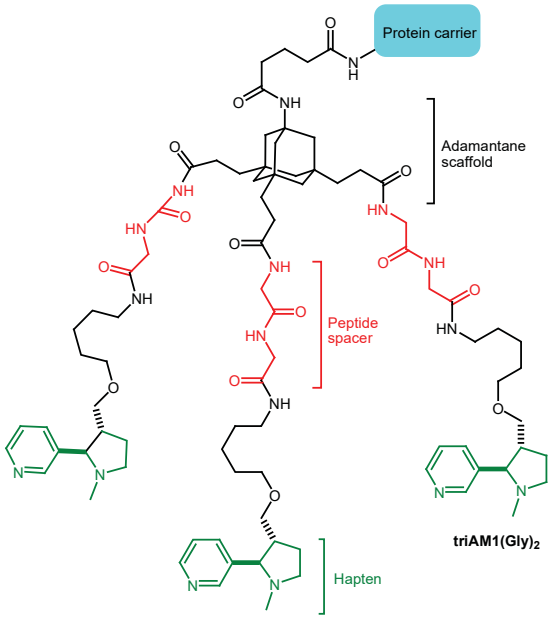
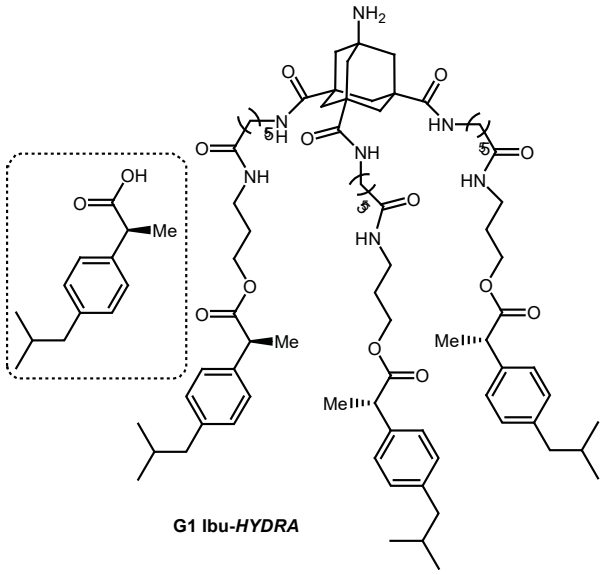


Fig. 6. C–H bond activation in rigid cage structures. Modified from [42].

Table 2. Multivalent peptide ligands based on the adamantane scaffold

Entry no.	Structure	Entry no.	Structure
1	 Lectin mimetics	2	 Integrin ligands
3	 **M1** = Ac-WDCLDNRIGRRQCVKL-NH_2 Monomer Apoptosis-inducing TR2 ligands	4	 Radiotracers for prostate tumor imaging
5	 Haptens for eliciting anti-nicotine antibodies	6	 Multifunctional adamantane-based dendrons for drug delivery

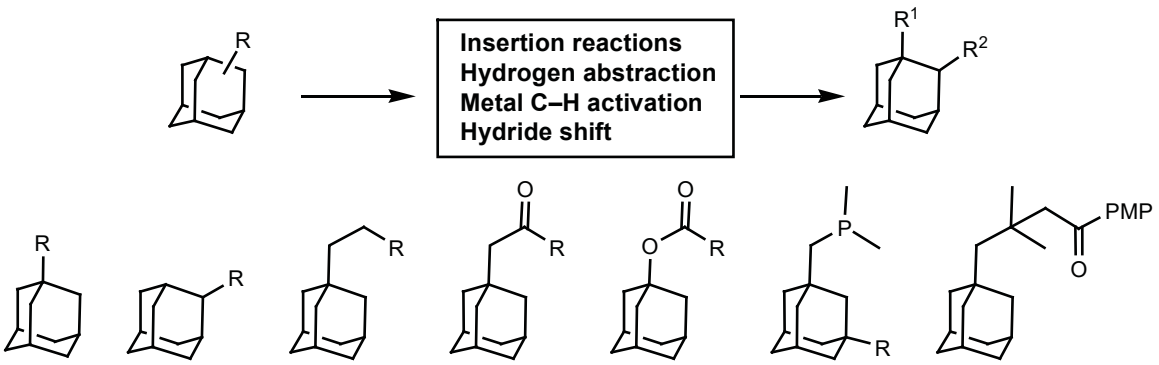


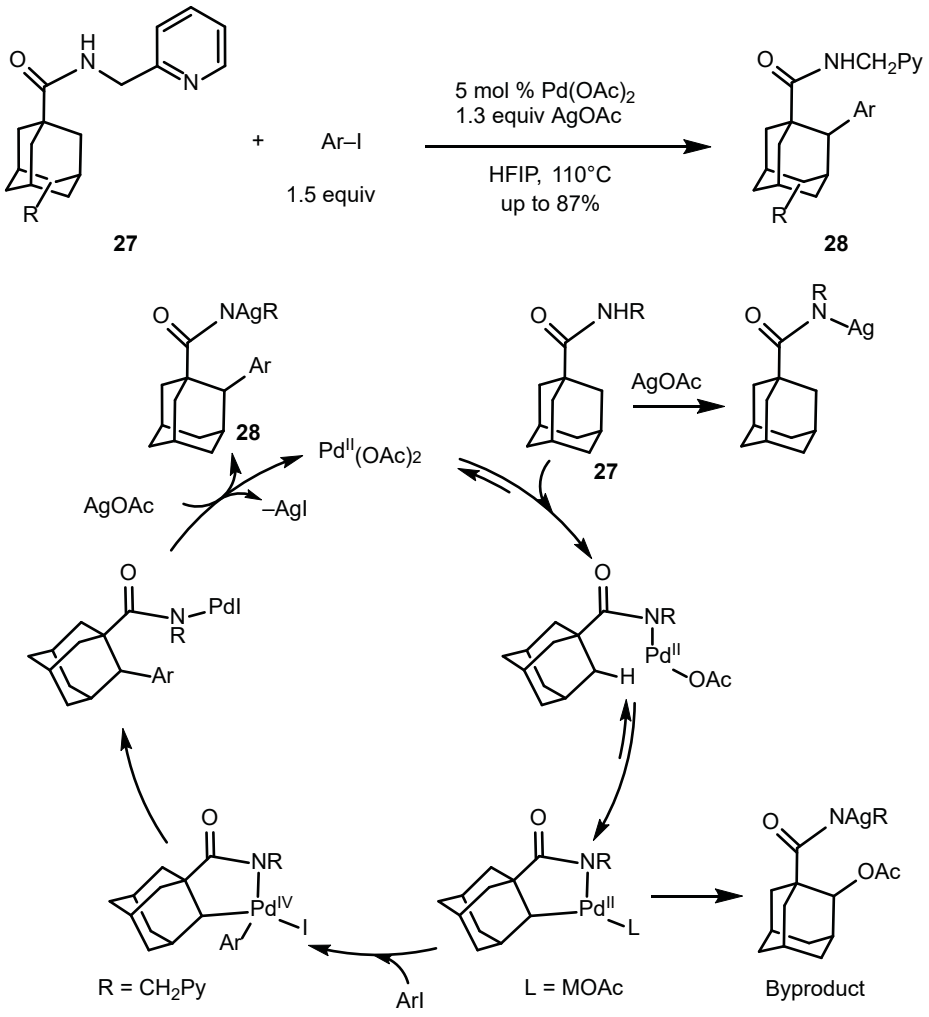
Fig. 7. Adamantane derivatives used in the synthesis of 1,2-disubstituted adamantanes.

and heterocyclic adamantane-containing scaffolds. The review described in detail ~50 reactions, their conditions, possible mechanisms, and products.

As examples, two schemes of synthesis of two types of 1,2-disubstituted adamantane derivatives from review [43] are given below. Scheme 11 illustrates catalytic arylation of adamantanecarboxamide **27** through five-membered palladium-containing intermediate with the formation of compound **28** [44].

The second scheme (Scheme 12) shows carbonylation of 1-(1-aminoethyl)adamantane derivative **29** to produce γ-lactam **30** [45]. In this reaction, the source

Scheme 11.



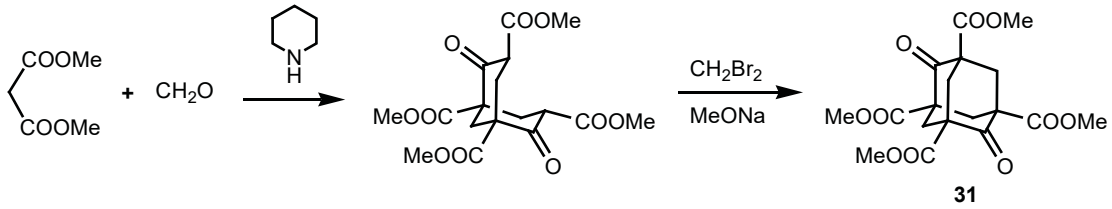
Scheme 12.

29 **30**, 33%

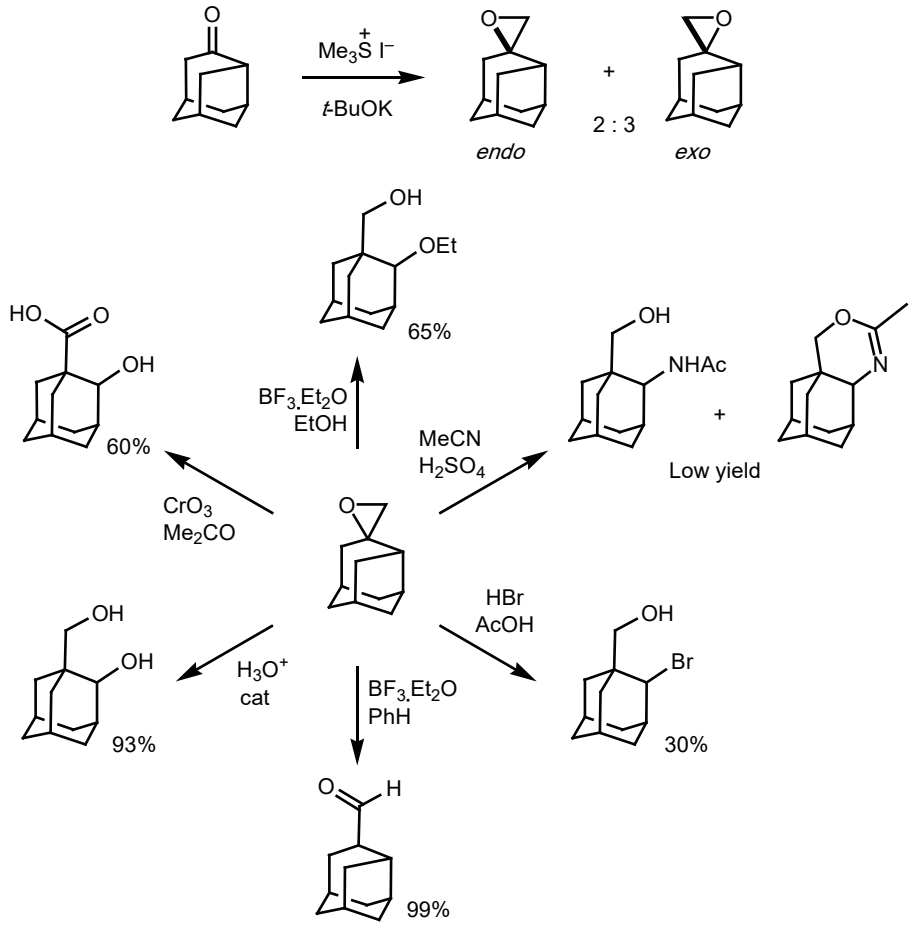
of CO was $Mo(CO)_6$, and the process was catalyzed by 20 mol % $Pd(OAc)_2$. The *N*-(pyridine-2-sulfonyl) substituent in **29** acts as a directing group. Lactam **30** was formed as a mixture of diastereoisomers.

The review by Todd and Hrdina was published in 2023 [46] and was a valuable logical extension of review [43]. Like the preceding review, it was devoted to the synthesis of 1,2-disubstituted adamantanes,

Scheme 13.



Scheme 14.



specifically to synthetic approaches in which the adamantane framework is constructed during the synthesis. According to the authors, tetramethyl 2,4-dioxoadamantane-1,3,5,7-tetracarboxylate (**31**) [4] was the first derivative obtained in this way (Scheme 13).

The data representation in review [46] was organized in accordance with the structure of initial compounds used for the synthesis of 1,2-disubstituted adamantanes. They included acyclic, monocyclic, and bicyclic derivatives. The major part of the latter were bicyclo[3.3.1]nonane derivatives (diolefins, keto olefins), protoadamantanes, and noradamantanes. The review contains 56 reaction schemes, most of which illustrate as a rule the synthesis of a large series of compounds rather than a single 1,2-disubstituted adamantane derivative. An example is Scheme 14.

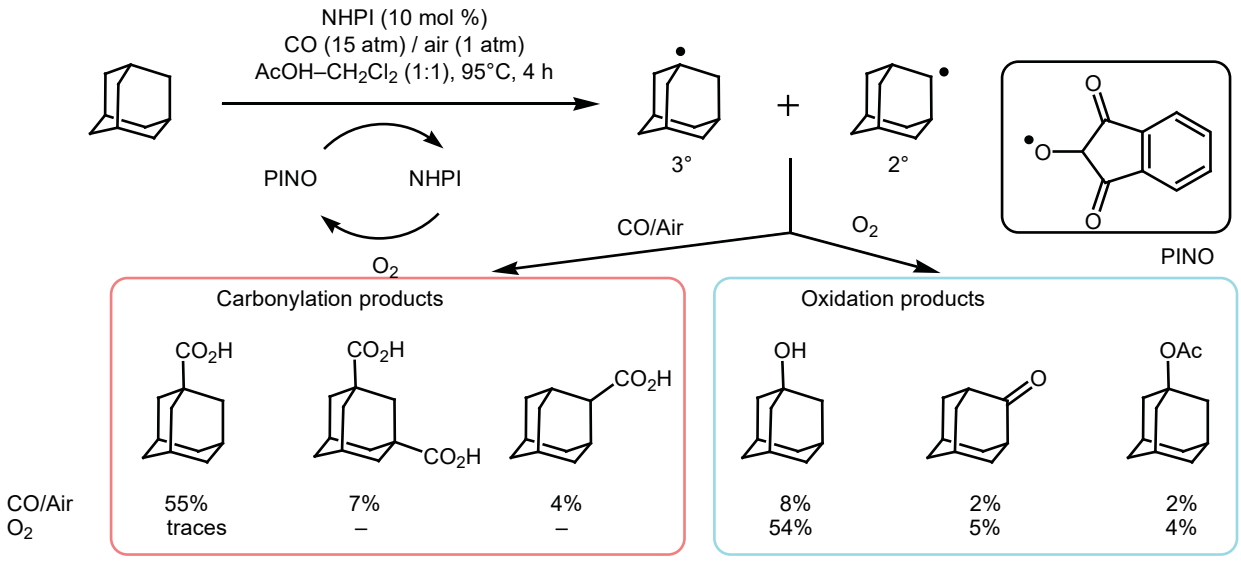
The review by Weigel et al. (University of Iowa, University of California; 2022) [47] discussed radical reactions providing functionalization of adamantane and diamondoids via transformation of C–H bonds to C–C bonds. The review covered literature data reported over the last 50 years, primarily the results of studies directly related to adamantane. As concerns radical reactions of diamondoids, the relevant information is given in Section 3.3 of the present review.

The authors [47] have done a large, painstaking, and very useful work for researchers in this field. Having presented the process of radical functionalization in the general form and paying special attention to the reaction selectivity, the authors concluded that the "key" factor responsible for the selectivity of radical processes is the nature of H-atom abstracting species. Accordingly, the available literature data were classified by the reaction type (the number of relevant subsections of the review is given in parentheses): acylation (4), carbonylation with carbon monoxide (4), alkylation through intermediate alkenylation (5), addition–fragmentation processes in reactions with alkenes and alkynes (5), arylation (4), and introduction of nitrogen-containing groups (2).

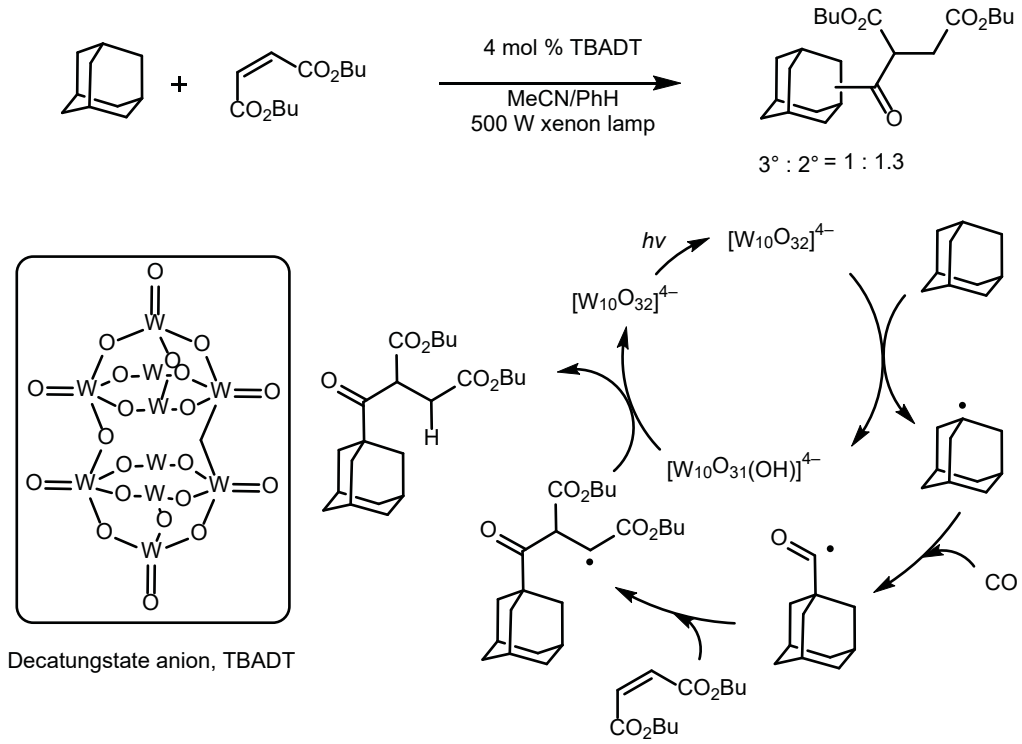
In all cases, different types of radical processes were discussed, namely conventional, catalytic, photochemical, and photocatalytic. Particular attention was given to the H-atom abstractors used. In all cases, adamantane was the initial compound. A scheme was provided for each particular case, which contained all data necessary to reproduce the process in a laboratory even in the absence of the original article. There are 49 such schemes in the review, which encompass more than 160 adamantane derivatives. Two schemes from the review are shown below as examples. Scheme 15 [48] illustrates the process favorable for the substitution at the tertiary carbon atom (intermediate **3°**), whereas Scheme 16 [49] depicts the formation of a product mixture where structure **2°** (substitution at the secondary carbon atom) predominates (the notations **3°** and **2°** were taken from [47]). Based on the performed analysis, the authors [47] compared the most often used H-atom abstractors (Fig. 8), which undoubtedly deserves due attention when planning and conducting further studies in this field.

In 1990, the first stable diradical of the adamantane series, 4,4′-[adamantane-1,3-dicarbonylbis(oxy)]bis-(2,2,6,6-tetramethylpiperidine 1-oxyl), was synthesized

Scheme 15.



Scheme 16.



from adamantane-1,3-dicarbonyl chloride and 2,2,6,6-teramethyl-4-hydroxypiperidin-1-oxyl in pyridine at room temperature [51] (Scheme 17). It was isolated as an orange–yellow crystalline powder, and it formed well shaped transparent deep ruby red crystals on slow crystallization. The temperature dependence of its ESR spectrum suggested the possibility of conformational transitions.

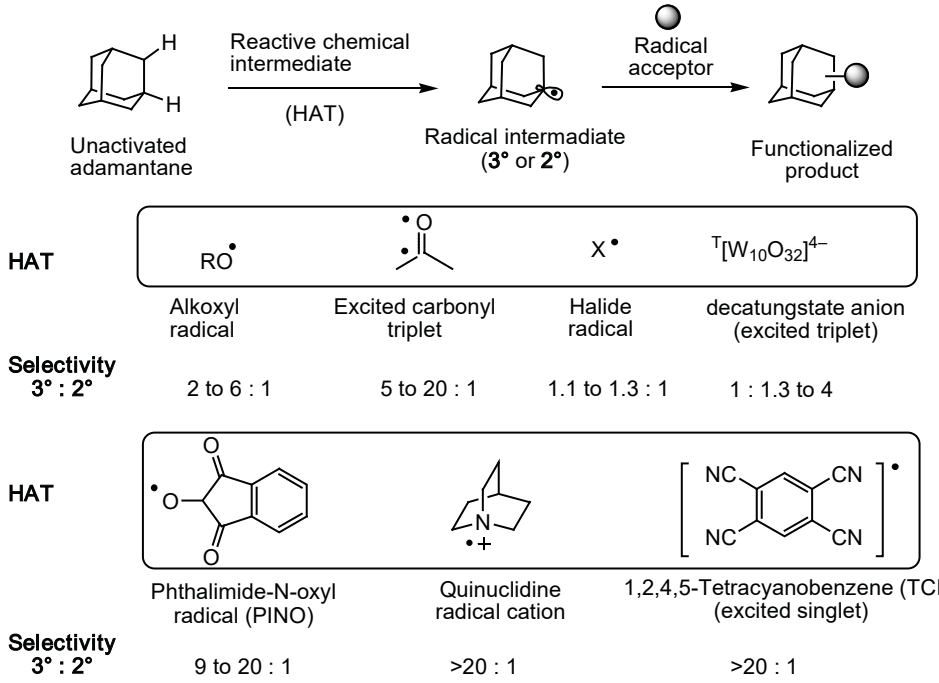
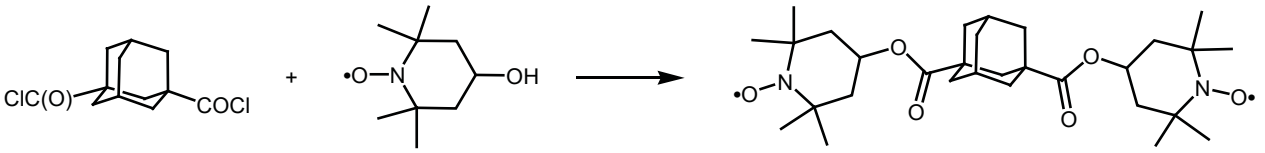


Fig. 8. Selectivity profiles for the most frequently used hydrogen atom acceptors. Dissociation energies of C–H bonds in adamantane: C_{tert}–H 99 kcal/mol, C_{sec}–H 96 kcal/mol [50].

Scheme 17.



The articles published in 2013 [52] and 2016 [53] were two parts of one review. The first part [52] summarized, systemized, and analyzed literature data on the synthesis and chemical properties of adamantyl-containing nucleobases and related compounds over a period of 1999–2011. The continuing interest in these compounds is determined primarily by the desire to create new highly efficient and selective drugs. Almost every work cited in the review consists of two parts, chemical and biological. The results of biological testing of adamantyl-containing mono- and polycyclic pyrimidine derivatives were given in [53] (see Section 4 of the present review).

The methods of synthesis of the compounds considered in [52] were systemized as follows. The compounds were synthesized (a) by cyclocondensation of adamantyl-containing carbonyl compounds (aldehydes, ketones, carboxylic acids, ketocarboxylic acids) with nitrogen-containing components (urea, thiourea, guanidine, acetanilide) or (b) by direct adamantylation of cyclic nucleobases. In the latter case, the C–C bond can be formed between the initial heterocycle and adamantane core or the adamantane core can be linked to a heteroatom through various bridges.

Detailed description was given in the review for the syntheses and chemical properties of a large number of adamantyl derivatives of a wide variety of heterocyclic compounds, such as monocyclic pyrimidines (pyrimidinones, uracil, cytosine, uridines, etc.), fused bi- and polycyclic compounds (pyrazolopyrimidines, triazolopurine, xanthene, etc.), and adenosines with a wide variety of substitution patterns and substituent natures.

Belarusian and Russian scientists reported [54] the synthesis of adamantyl-containing five-membered heterocycles **32**–**37** (Fig. 9): adamantylpyrazole **32**, adamantylisoxazoles **33**, **34**, and **36**, and adamantylthiazoles **35** and **37**; the synthesized compounds were evaluated for their antiviral activity against FPV/Rostock influenza virus (**32**, **34**, **36**, **37**) and herpes simplex-1 virus (**32**, **33**).

In 2022, Ivleva et al. [55] proposed a new method for the synthesis of previously unknown 2-oxaadamantane derivatives by reaction of 1,3-dichloroadamantanes with fuming nitric acid. The reaction involved intermediate formation of nitrooxy derivatives which underwent skeletal rearrangements such as Grob fragmentation and transannular cyclization (Scheme 18). Scheme 19 illustrates the mechanism of formation of the major product, compound **38**. The synthesized 2-oxaadamantane derivatives can be used as starting materials for obtaining biologically active compounds with a broad spectrum of action.

Adamantane derivatives are used to catalyze organic reactions. In 2016, Agnew-Francis and Williams (Australia) [56] reviewed the data on a wide variety of organocatalysts and organometallic catalysts based on adamantyl-containing molecular scaffolds. The review contained information on more than 60 catalysts and almost unlimited potential of their use. Such a generalization was made for the first time. The authors considered 8 types of reactions occurring in the presence of adamantyl-containing organometallic catalysts (arylpalladium addition, C–H activation, metathesis, Diels–Alder reaction, cyclopropanation,

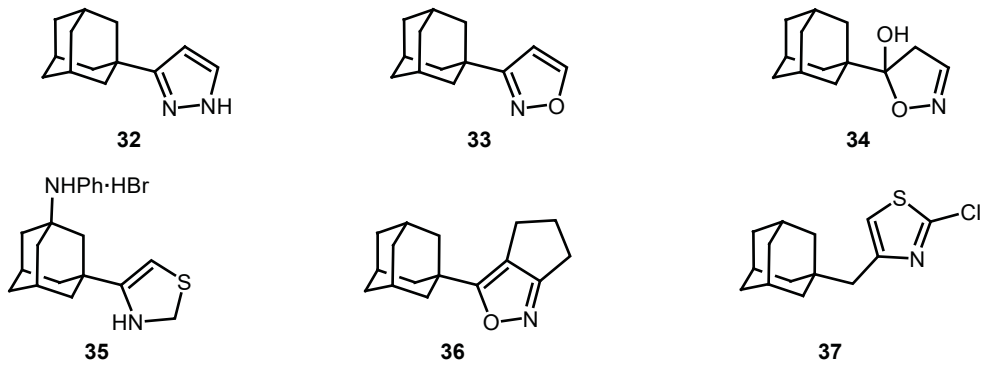
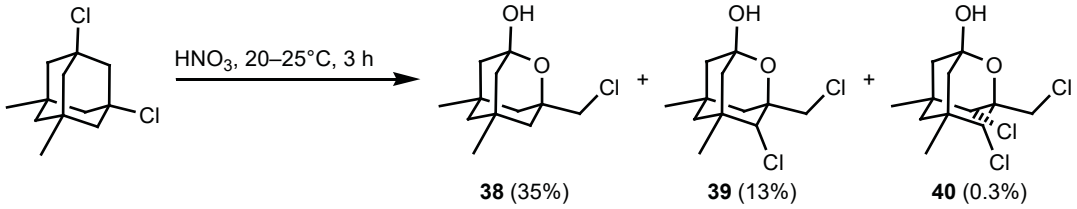
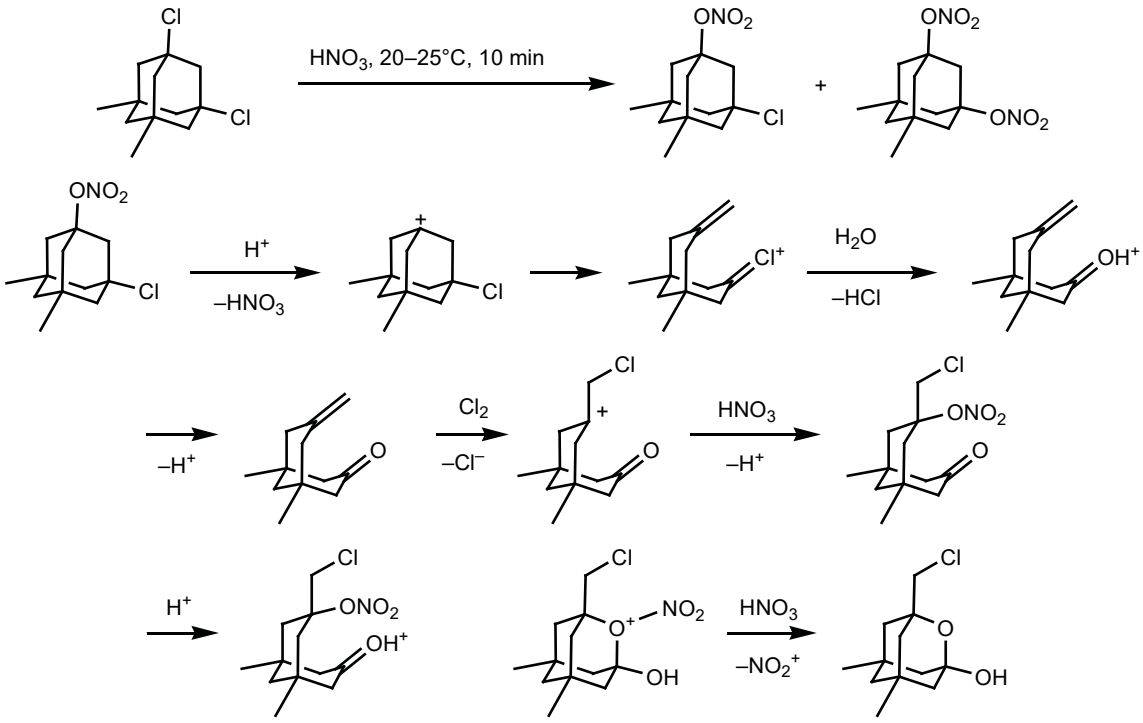


Fig. 9. Adamantyl-containing five-membered heterocycles.

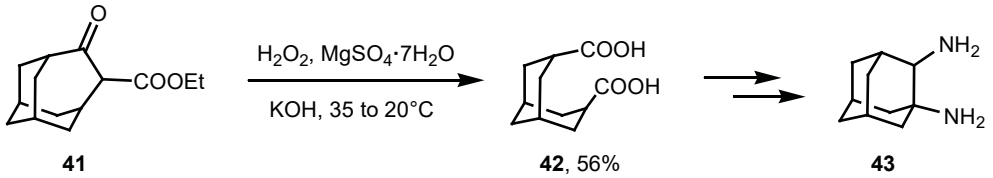
Scheme 18.



Scheme 19.



Scheme 20.



alkynylation, hydrogenation, catalysis by dendrimers) and 6 types of reactions catalyzed by adamantane-based organocatalysts (oxidation of alcohols, Michael addition, reactions of 1,3-dicarbonyl compounds, Strecker reaction, catalysis by *N*-heterocyclic carbenes).

Adamantyl-containing ligands are fantastically diverse in structure. They differ in literally everything: the number of adamantyl substituents, the number and chemical nature of the substituents, the variety of metals in organometallic catalysts, etc. The presented material features excellent systematization, careful selection, and communication of experimental data to the reader.

In 2023, Man'kova et al. (Russia) [57] reported a seven-step synthesis of racemic 1,2-diaminoadamantane **43** starting from ethyl 5-homoadamantane-5-carboxylate **41**. The first step of the process was the synthesis of *endo*,*endo*-bicyclo[3.3.1]nonane-3,7-dicarboxylic acid **42** (Scheme 20).

Racemic diamine **43** was separated into individual enantiomers using L-tartaric acid, and the pure (*S*)-enantiomer (yield 96%) was used to obtain a number of N-donor ligands and their complexes with

Cu(II), Mn(III), and Ni(II). The catalytic activity of the latter was studied in Henry and Michael reactions and epoxidation.

3.2. Acidic Fluorine-Containing Reagents in the Chemistry of Adamantane

This section of the review is devoted to a new line of research in the adamantane chemistry, which involves the use of acidic fluorine-containing reagents, such as trifluoroacetic acid (TFA) and its anhydride (TFAA), trifluoromethanesulfonic acid (CF_3SO_3H, TfOH), and boron trifluoride complexes ($BF_3·H_3PO_4$, $BF_3·2AcOH$, $BF_3·Et_2O$), in electrophilic reactions accompanied by the formation of 1- and 2-adamantyl cations.

The dissociation constant of TFA (pK_a = 0.23 at 20°C) is close to those of strong mineral acids. The acid itself and its anhydrides are good acylating agents [8]. The complex of BF_3 with orthophosphoric acid retains strong acidic properties but at the same time does not promote undesirable side processes, such as profound decomposition, oxidation, etc. The complex of BF_3 with acetic acid is comparable to sulfuric acid in acidity. Boron trifluoride–diethyl ether complex is a coordination compound acting as a donor of BF_3 (Lewis acid) in various reactions [58].

Trifluoroacetic acid and BF_3 complexes were introduced into the chemistry of adamantane in the early 1970s while studying the possibility of using adamantane as a source of hydride ions in ionic hydrogenations and the behavior of isomeric 1- and 2-hydroxyadamantanes (which are widely used in the synthesis of adamantane derivatives) in the presence of these reagents [59].

1-Hydroxyadamantane is stable in pure TFA. It undergoes insignificant disproportionation only on heating in TFA (1-AdOH:TFA = 1:10) at 71°C to give 2% of adamantane. 2-Hydroxyadamantane in TFA (1:10) is converted to a mixture of adamantan-2-yl trifluoroacetate and a fairly large amount (15%) of adamantan-1-yl trifluoroacetate. In all cases, the transformations of isomeric 1- and 2-hydroxyadamantanes in the presence of BF_3 complexes led to the formation of three main products: adamantane, adamantan-2-one, and 1-fluoroadamantane, whose ratio depended on the initial alcohol and reaction conditions (solvent, temperature, reactant ratio).

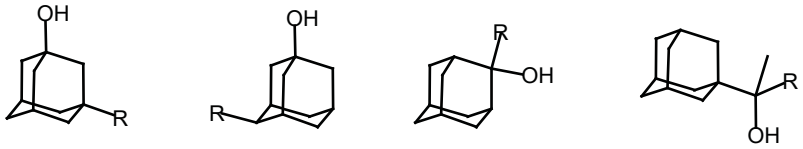
In the presence of TFA, adamantane can be used as a source of hydride ions in the reduction of 1-methylcyclohex-1-ene and triphenylmethanol to the corresponding hydrocarbons. In these reactions, adamantane is converted into a mixture of 1-hydroxyadamantane and its ester with TFA. Ketones such as cyclohexanone and adamantanone are not reduced under the given conditions. Conventional ionic hydrogenation of adamantanone with the use of TFA and triethylsilane gives 2-hydroxyadamantane. These data confirmed prospects of using the above-listed fluorine-containing reagents in the chemistry of adamantane.

3.2.1. Reactions of adamantane derivatives in trifluoroacetic acid and its anhydride. This section deals with reactions of adamantane derivatives in TFA and TFAA. All these reactions readily occur at a high rate at temperatures not exceeding 90°C, and the products are formed in high yields and can be easily isolated from the reaction mixtures.

Adamantylation of organic compounds. A new method has been developed for the synthesis of a wide variety of adamantane derivatives using hydroxyadamantanes (Fig. 10) as adamantylating agents.

Schemes 21–23 show adamantylations of unsaturated [60, 61], aromatic, and heteroaromatic [52, 62, 63] compounds and nitrogen [64] and phosphorus [65] nucleophiles in trifluoroacetic acid. The reactions of hydroxy adamantanes with P-nucleophiles selectively afforded the corresponding dichlorophosphoryl derivatives and in some cases were accompanied by skeletal adamantane–homoadamantane rearrangement.

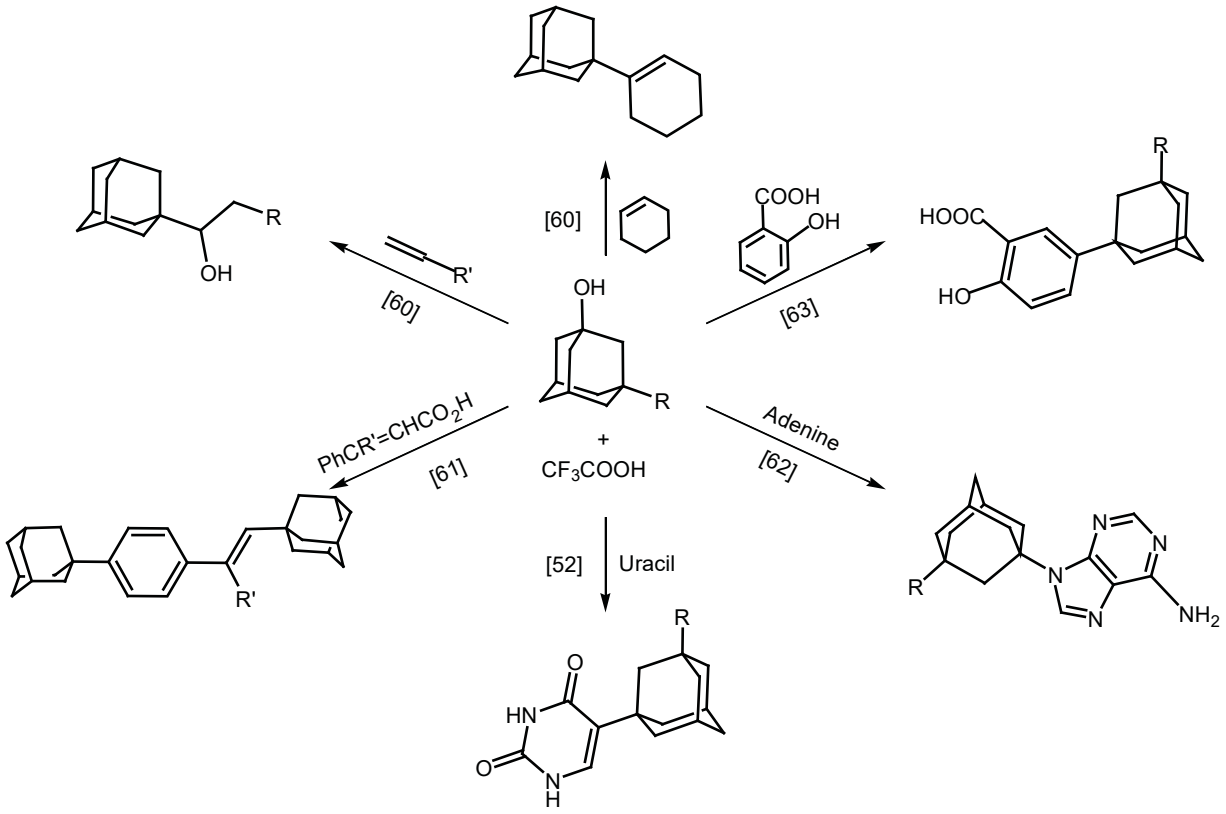
Electrophilic rearrangements. When studying the behavior of adamantane derivatives in TFA, unusual regio- and stereoselective rearrangements were discovered: (a) selective skeletal rearrangement of 1-adamantyl carbinols to homoadamantane sultones [66], (b) stereoselective rearrangement of 2-aryl-2-hydroxyadamantanes to (*Z*)-5-aryl-2-hydroxyadamantanes



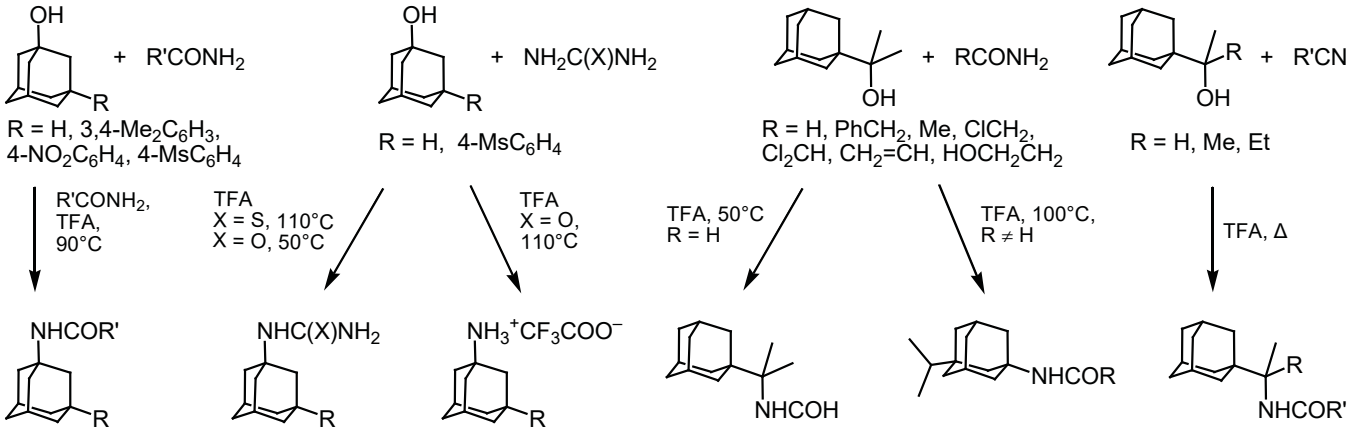
R = H, Alk, Ar

Fig. 10. Adamantylating agents.

Scheme 21.



Scheme 22.

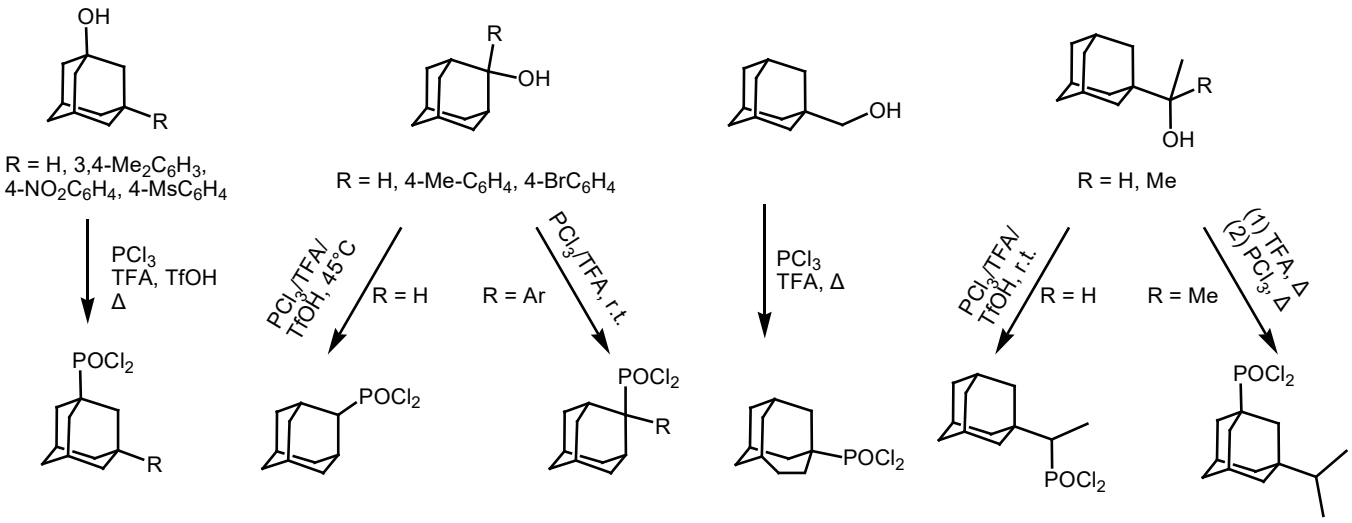


[67], and (c) regioselective rearrangement of (3-isopropyladamantan-1-yl)dimethylcarbinol to 3,5-diisopropyl-1-hydroxyadamantane [68] (Scheme 24).

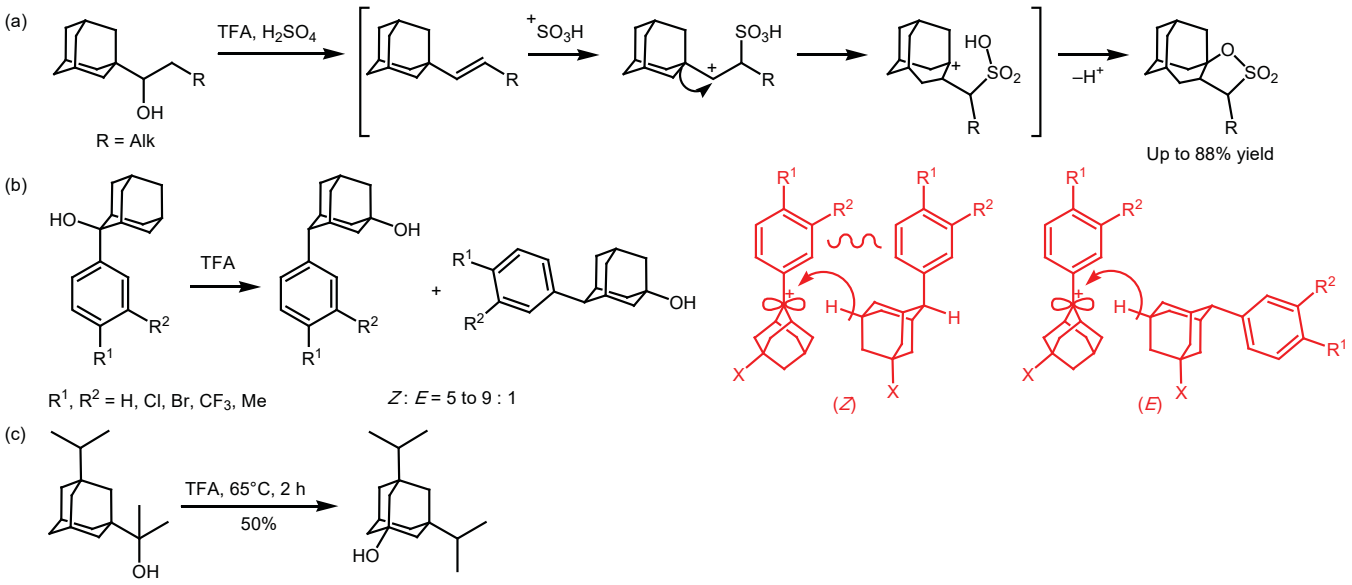
Hydroxylation of the adamantane core. Efficient methods were proposed for the hydroxylation of adamantane and its derivatives using the oxidation systems *tert*-BuOH–TFA [69] and H_2SO_4–TFAA [70], where the hydride ion acceptors were *tert*-butyl cation and mixed sulfuric–trifluoroacetic anhydride, respectively (Scheme 25).

2,6-Diformyl-4-(1-adamantyl)phenol obtained from 4-(1-adamantyl)phenol and hexamethylenetetramine was used to synthesize previously unknown polycyclic nitrogen-containing adamantanaphane derivatives **44** and **45** {via selective [1+1]-cyclization with 1,3-bis(aminoalkyl)adamantanes) and adamantylcalixsalenes **46** and **47** (selective [3+3]-cyclization with 1,2-diaminocyclohexane and [2+2]-cyclization with diethylenetriamine) [71] (Scheme 26). The reactions were carried out under high dilution conditions (MeOH–

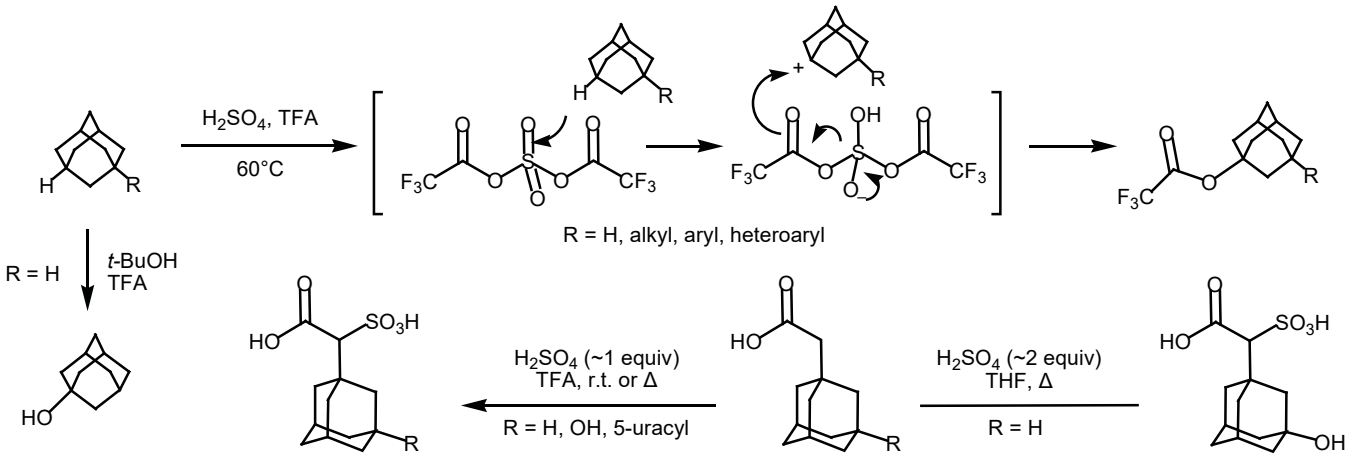
Scheme 23.



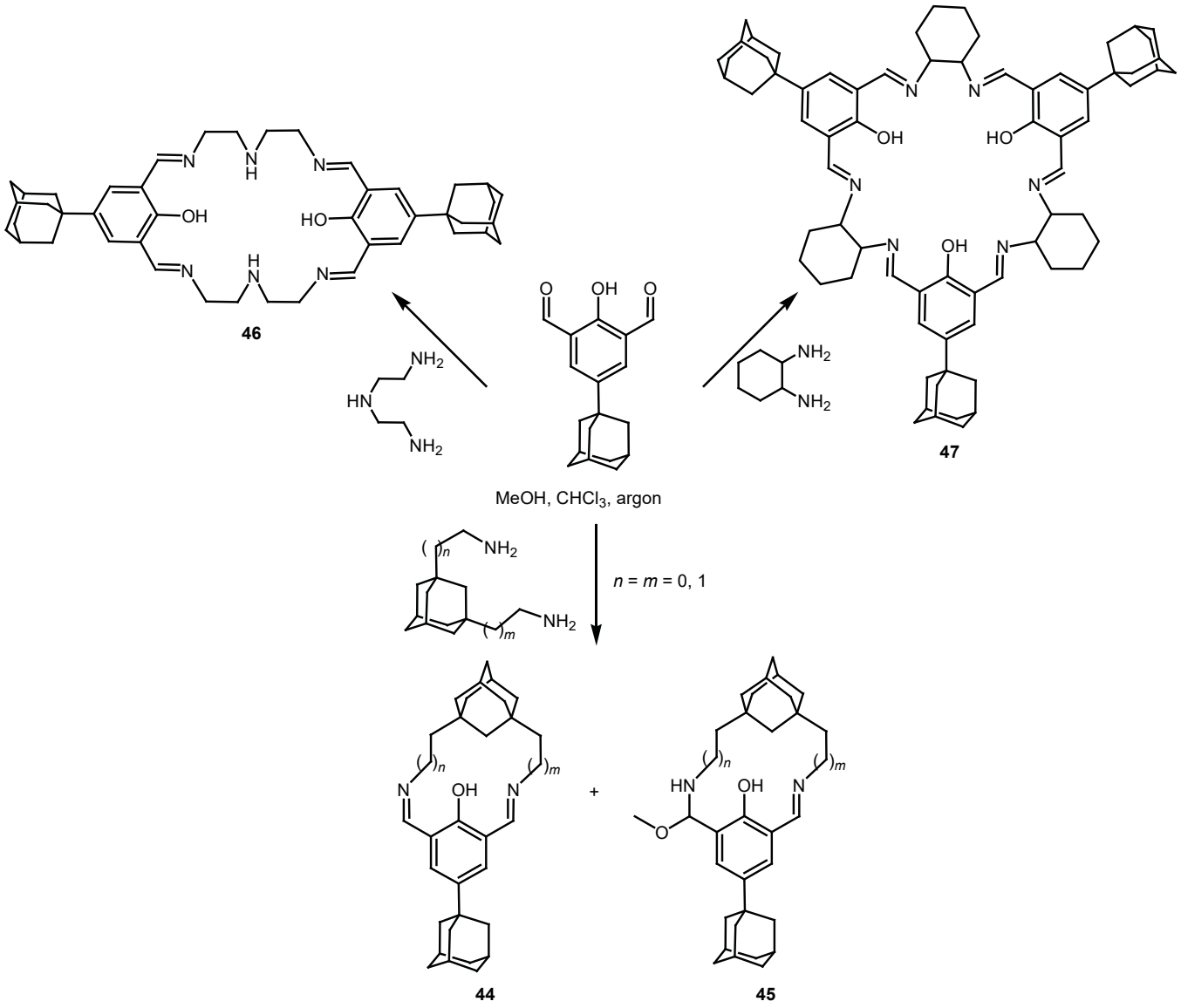
Scheme 24.



Scheme 25.



Scheme 26.



$CHCl_3$, argon) and via ion-template synthesis in the presence of H_3BO_3. The [1+1]-cyclization process afforded macrocyclic Schiff bases **44** together with products of methanol addition to one of the double bonds of **44** (compounds **45**). Variation of the reaction conditions (time and temperature) made it possible to perform the reaction in a selective manner and obtain the desired products in 80–100% yield [72].

The design of new molecular receptors is one of the most important problems of supramolecular chemistry. For this purpose, exceptionally useful compounds are calix[*n*]arenes (*n* = 4, 6, 8), the chemistry of which has been extensively explored over the last decades [72, 73]. The prospects of calixarenes are determined by the presence in their molecules of a hydrophobic aromatic cavity and by the possibility of modifying them at the upper and lower rims through introduction of functional groups. This offers great potential for using the resulting compounds to simulate biochemical processes, molecular recognition, membrane transfer, and enzymatic catalysis. Modification of the upper rim of calix[*n*]arenes with adamantyl fragments, due to the specific shape, size, lipophilicity, and possibility of functionalization of the latter, opens new ways of fine tuning of the receptor properties of such macrocycles.

The first adamantane-containing calixarene, *p*-(1-adamantyl)calix[8]arene (**I**), was synthesized in 1993 [74] by the classical method, condensation of 4-(1-adamantyl)phenol with paraformaldehyde in diphenyl ether in the presence of potassium hydroxide

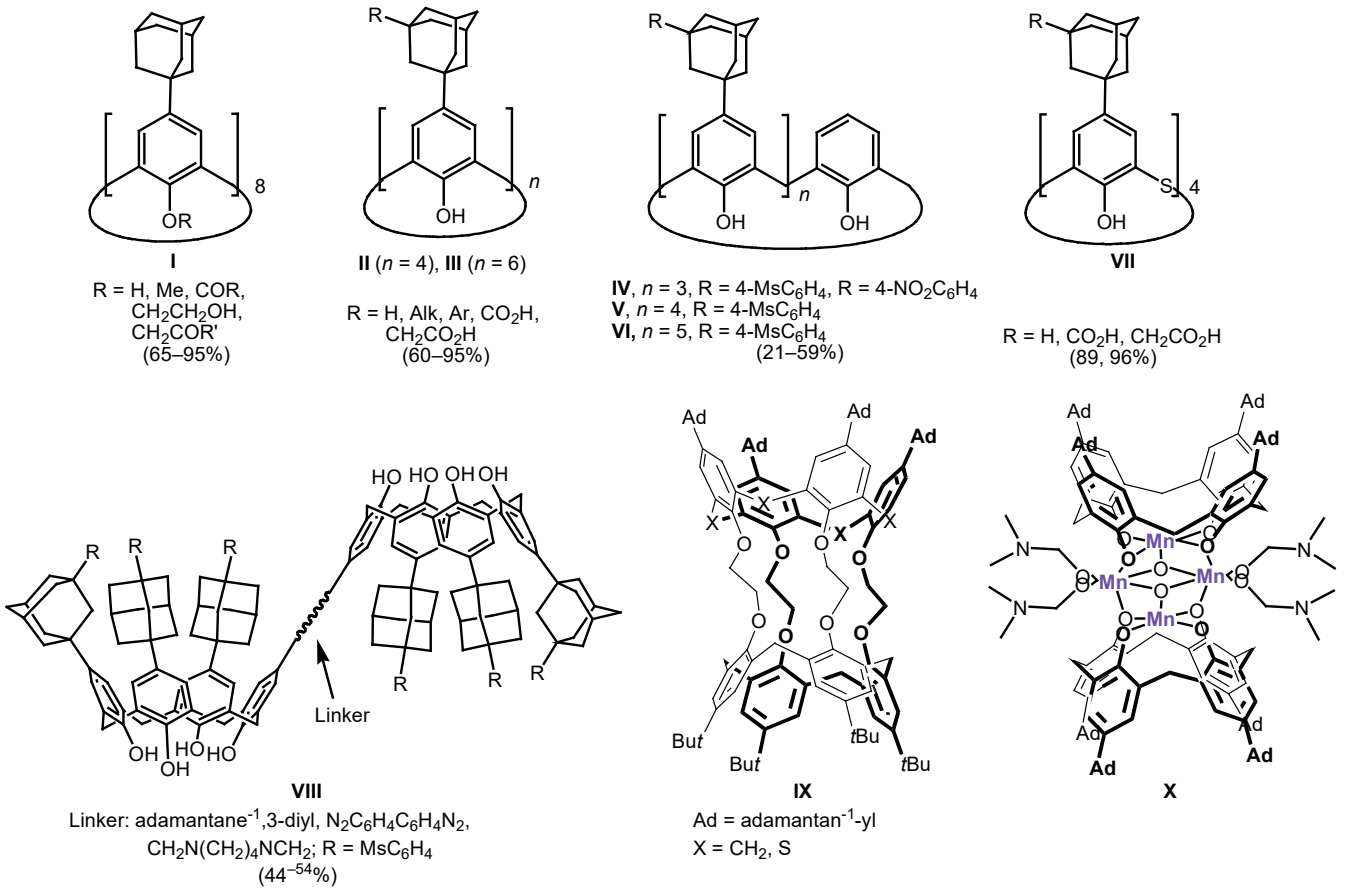


Fig. 11. Adamantylcalix[*n*]arenes.

(Fig. 11). Compound **I** was subjected to functionalization at the lower rim, and the obtained derivatives were used as active components of ion-selective electrodes [75].

In 1994, we synthesized adamantylcalix[4]arenes **II**, which initiated the development of the chemistry of such molecular receptors [76]. As a result, a general method was proposed for the synthesis of adamantyl-containing calix[4–6]arenes by reacting unsubstituted calix[4–6]arenes with hydroxyadamantanes in trifluoroacetic acid [77–79]. Adamantylcalix[6]arenes **III** containing carboxy groups linked to the adamantane core were found to exhibit a unique reduction in the conformational mobility of the macrocycle due to intramolecular interactions between the functional groups. When the initial adamantan-1-ols contained an electron-withdrawing group (R = 4-MsC_6H_4, 4-$NO_2C_6H_4$) at the 3-position, adamantylated calix[*n*]-arenes (*n* = 4–6, compounds **IV**–**VI**) were selectively obtained in satisfactory yields. Calix[4]arenes with one or two acyl groups on the lower rim were selectively adamantylated at the upper rim with 3-R-adamantan-1-ols (R = H, *i*-Pr, 4-MeC_6H_4) [80].

In 2000, Konig and Fonseca [80] were the first to report a new family of calixarenes, thiacalix[4]arenes, in which the methylene bridges connecting the aromatic fragments were replaced by sulfur. The C–S bond (1.77 Å) is longer than C–C (1.54 Å), so that the calixarene cavity increases, whereas the sulfide bridges are not only additional coordination centers but also sites for further functionalization. Undoubtedly, all these factors significantly affect the receptor properties of thiacalixarenes. The chemistry of thiacalixarenes was reviewed by Russian [81] and Japanese scientists [82]. In 2002, we synthesized the first representatives of a new type of thiacalixarenes – *p*-(3-R-adamantan-1-yl)thiacalix[4]arenes, compounds **VII** (R = H, COOH, COOMe) [83], which were then used to obtain various polymacrocycles, such as bis-calix[4]arenes **VIII** [84], adamantylated calixarene tubes **IX** [85], and molecular magnetics **X** [86].

3.2.2. The system RCOOH/CF_3SO_3H/$(CF_3CO)_2O$ as the basis of a new method for the acylation of ketones. In 2010, we showed [87] that trifluoromethanesulfonic acid-catalyzed self-acylation of 2-(adamantan-1-yl)acetic acid in trifluoroacetic an-

hydride led to the formation of previously unknown 2,4-di(adamantan-1-yl)acetoacetic acid (Scheme 27). Trifluoroacetic anhydride used as an activating agent readily reacts with carboxylic acids to give the corresponding mixed anhydrides, whereas the superacid CF_3SO_3H facilitates enolization of carbonyl compounds and enhances the acylating power of acyl trifluoroacetates. The discovered reaction is the first example of synthesis of β-keto acids directly from carboxylic acids without their preliminary activation. No reaction occurred in the absence of CF_3SO_3H.

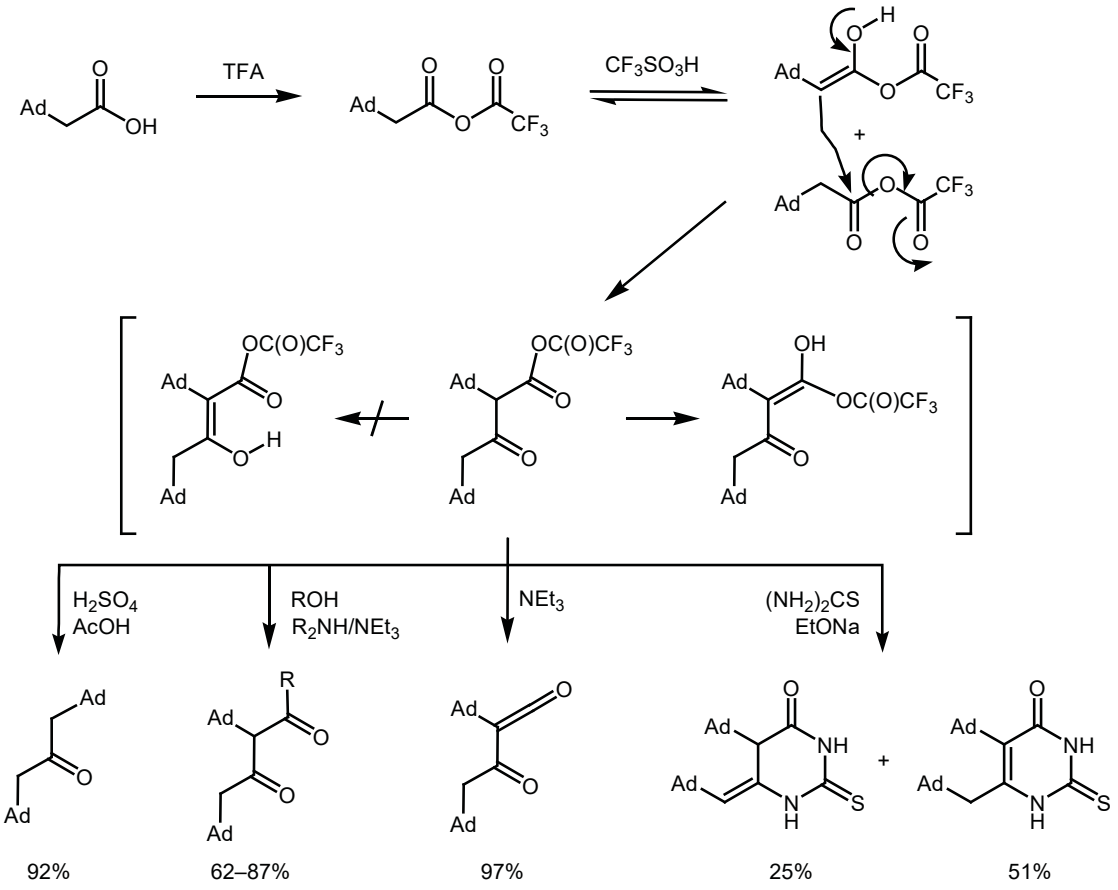
Further studies unambiguously confirmed the general character of the developed method. The proposed system $RCOOH/CF_3SO_3H/(CF_3CO)_2O$ provides highly efficient C-acylation of a wide variety of carbonyl compounds. The method is advantageous due to high selectivity, simple experimental procedure, diversity and availability of initial compounds, high yields, and easy isolation of the products. Furthermore, wide possibilities of carrying out one-pot multistep syntheses starting from the primary C-acylation products without isolating them from the reaction mixture were demonstrated. Given below are the results of some studies directly related to adamantane derivatives and reflecting the novelty and promises of the proposed method.

We were the first to synthesize β-diketones, including polyfunctional adamantyl-containing ones, from carboxylic acids (aliphatic, alkylaromatic) and alkyl, cycloalkyl, aryl, and heteroaryl ketones by a direct, simple, and efficient method [88]. A number of previously unknown adamantyl-containing β-dicarbonyl compounds were synthesized; the structures of some derivatives are shown in Scheme 28.

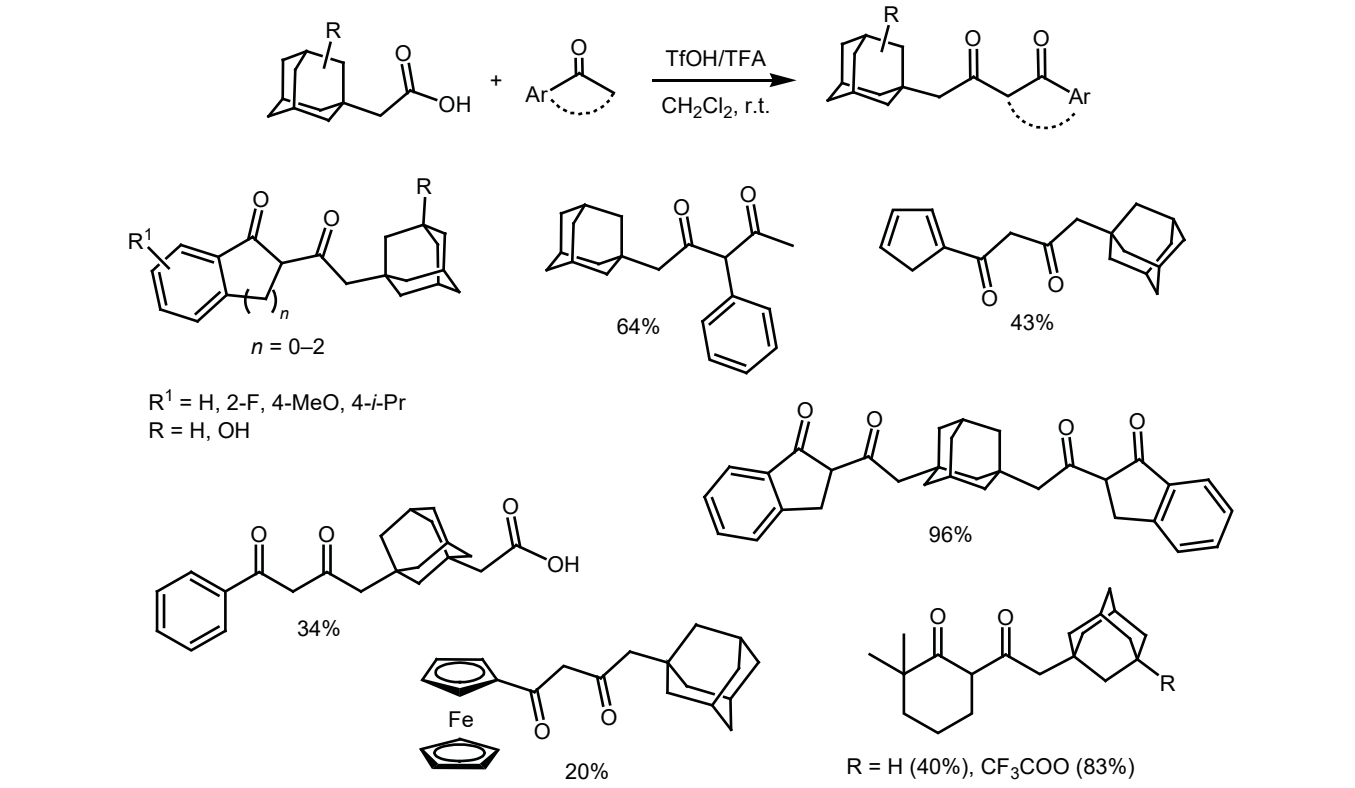
We also reported for the first time cascade intra- and intermolecular self-acylation of ω-phenylalkanoic acids in $CF_3SO_3H/(CF_3CO)_2O$, which afforded β-diketones [89]. In particular, a mixture and mono- and diketones was obtained from 3-[4-(adamantan-1-yl)-phenyl]propionic acid (Scheme 29).

The acylating system [1-(3-H,OH)-Ad]CH_2COOH/$CF_3SO_3H/(CF_3CO)_2O$ enabled us not only to perform two- and three-step one-pot syntheses of adamantyl-containing diketones from (hetero)arenes but also to use the products (without isolation) as starting mate-

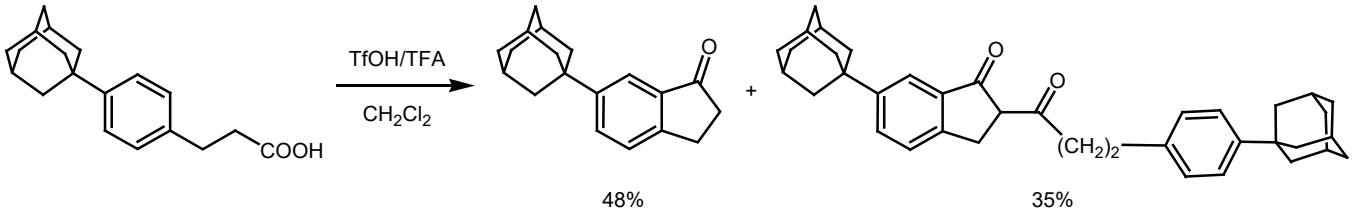
Scheme 27.



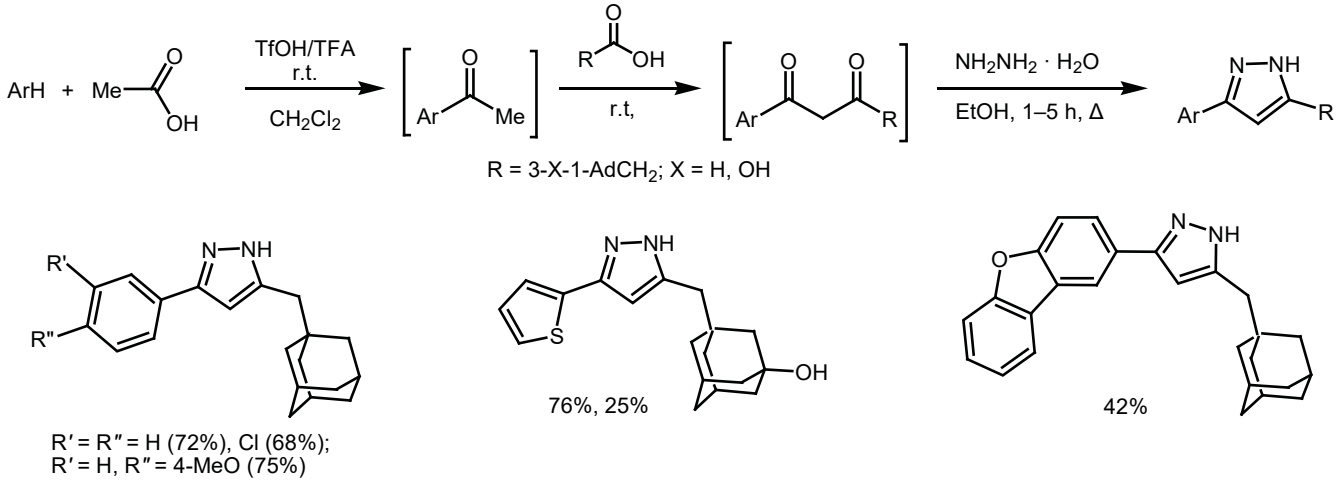
Scheme 28.



Scheme 29.



Scheme 30.

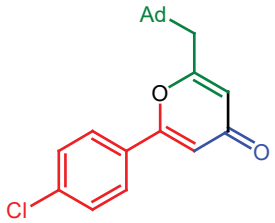


rials in further alkylation and heterocyclization processes. As a result, preparative multistep one-pot syntheses of disubstituted adamantyl-containing pyrazoles were carried out [89] (Scheme 30).

Fused polysubstituted pyrazoles were synthesized in three steps in one pot starting from β-phenylpropionic and γ-phenylbutyric acids **48a** and **48b**. The first step was selective intramolecular cyclization with the formation of indan-1-one and α-tetralone, respectively, which then reacted with adamantyl-containing acids to give diketones that were precursors to pyrazoles **49a**–**49e** [89] (Scheme 31).

The high sensitivity and selectivity of the carbonylation process with the use of $CF_3SO_3H/(CF_3CO)_2O$ was demonstrated by the reaction of *p*-chloroacetophenone **50** with isovaleric acid **51** [90]. The formation of diketone **52** was accompanied by its transformation into trisubstituted γ-pyrone **53** (Scheme 32). At a **50**:**51**:CF_3SO_3H molar ratio of 1:2:1, a mixture of diketone (39%) and γ-pyrone (58%) was obtained, whereas the latter was formed as the only product (92%) when the above ratio was 1:4:2.

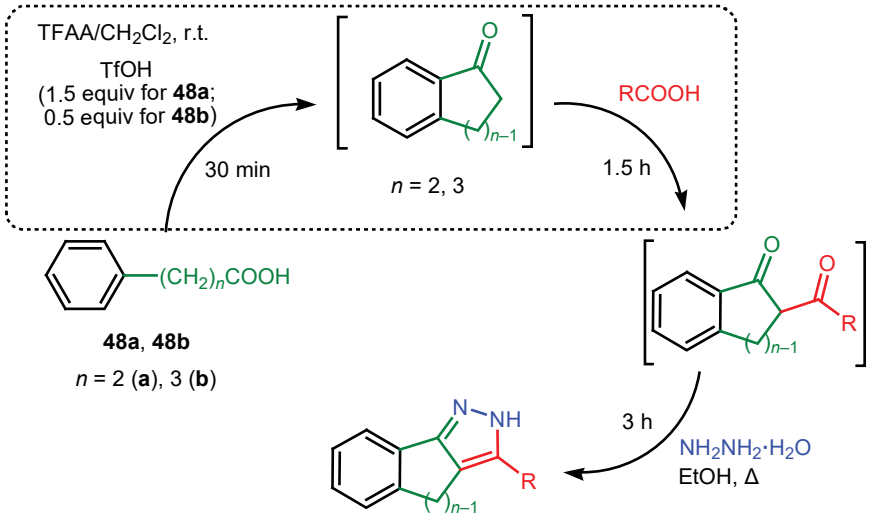
Several tens of various di- and trisubstituted γ-pyrones were synthesized in one pot via "controlled" carbonylation. For example, the yield of adamantyl-containing γ-pyrone **54** in the reaction of chloroacetophenone with adamantylacetic acid was 90%. The proposed reaction mechanism involving intermediates **A**–**L** (Scheme 33) was confirmed by DFT calculations.



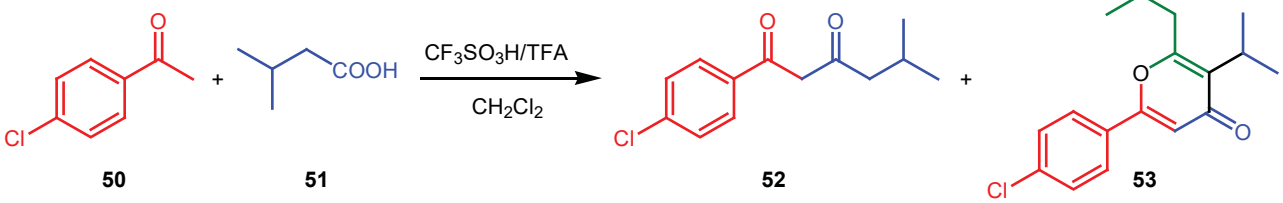
54

Previously unknown symmetrical functionally substituted 1,3-bis(3-X-adamantan-1-yl)propan-2-ones [X = OH, Ar, hetaryl, NHCOR′, $NHC(S)NH_2$] were

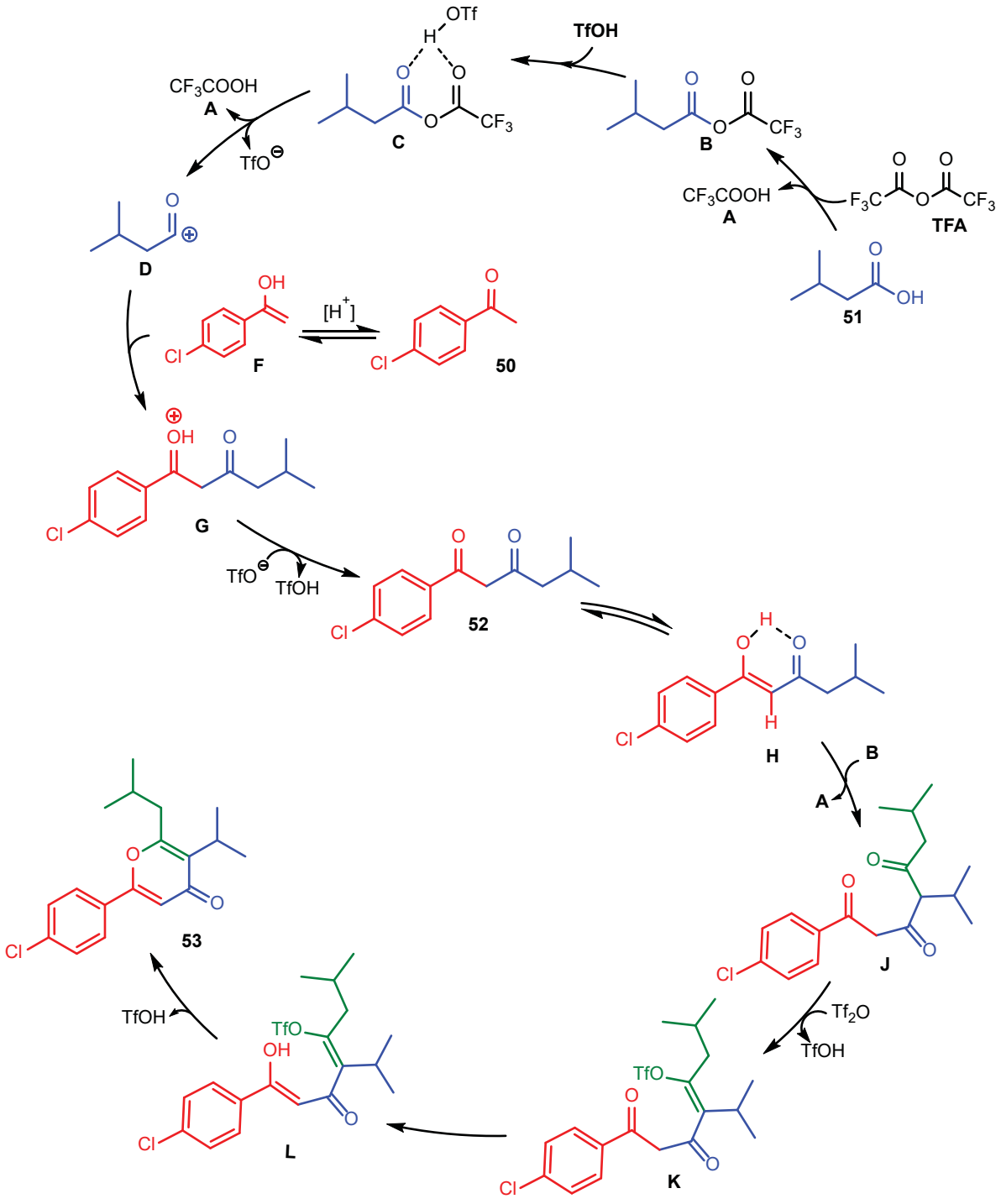
Scheme 31.



Scheme 32.



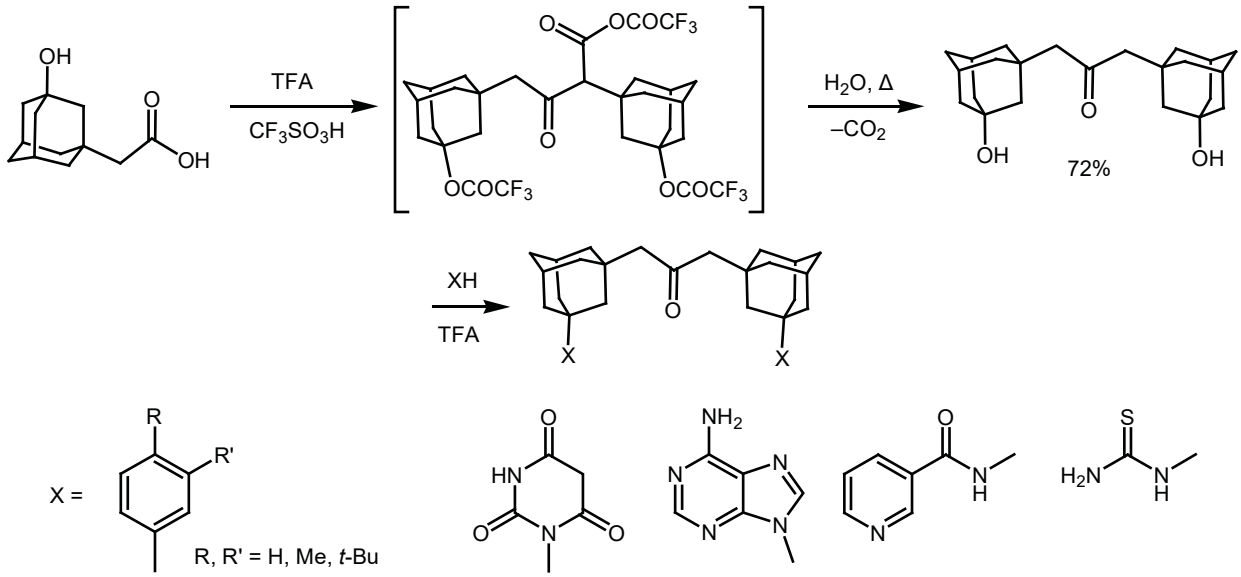
Scheme 33.



synthesized by $CF_3SO_3H/(CF_3CO)_2$-catalyzed self-acylation of 2-(3-hydroxyadamantan-1-yl)acetic acid [91] (Scheme 34).

To conclude this section, it should be noted that in 2020 we reported [92] on the use of other, more available and cheaper catalysts, such as methanesulfonic acid, *p*-toluenesulfonic acid monohydrate, and boron trifluoride–diethyl ether complex, as activating agents instead of trifluoromethanesulfonic acid in the synthesis of β-diketones. In these experiments, acetophenone and heterocyclic 2-acetylthiophene were taken as initial aromatic ketones, and the acylating

Scheme 34.



agents were 3,3-dimethylbutanoic and 2-(adamantan-1-yl)acetic acids. In the reactions catalyzed by $BF_3 \cdot Et_2O$, the resulting β-dicarbonyl compounds were isolated as BF_2 chelates.

3.3. Diamondoids

The beginning of the 21st century was marked by a sharp rise in research on cage hydrocarbons with a diamond-like structure of adamantane homologs, diamondoids, that are direct "relatives" of adamantane (structures **55**–**60** in Fig. 12). Interest in these compounds is determined primarily by their amazing structure which is expected to give rise to the truly unique properties, such as exceptional hardness, high thermal stability, chemical resistance, unusual optical properties, etc. The chemistry of diamondoids is actually becoming a large independent field of organic chemistry, which can be considered a natural extension of the adamantane chemistry. This section presents in a very concise form some fundamental data on the results of research on diamondoids in the last two decades.

A whole chapter was devoted to strategies for the synthesis of functionalized diamondoids in the collection "Strategies and Tactics in Organic Synthesis" [95]. As noted by the authors, the methods for obtaining diamondoids (di-, tri-, and isomeric tetra-, penta-, and cyclohexamantanes) from oil developed by that time make them promising unique building blocks for creating materials of great practical significance, and

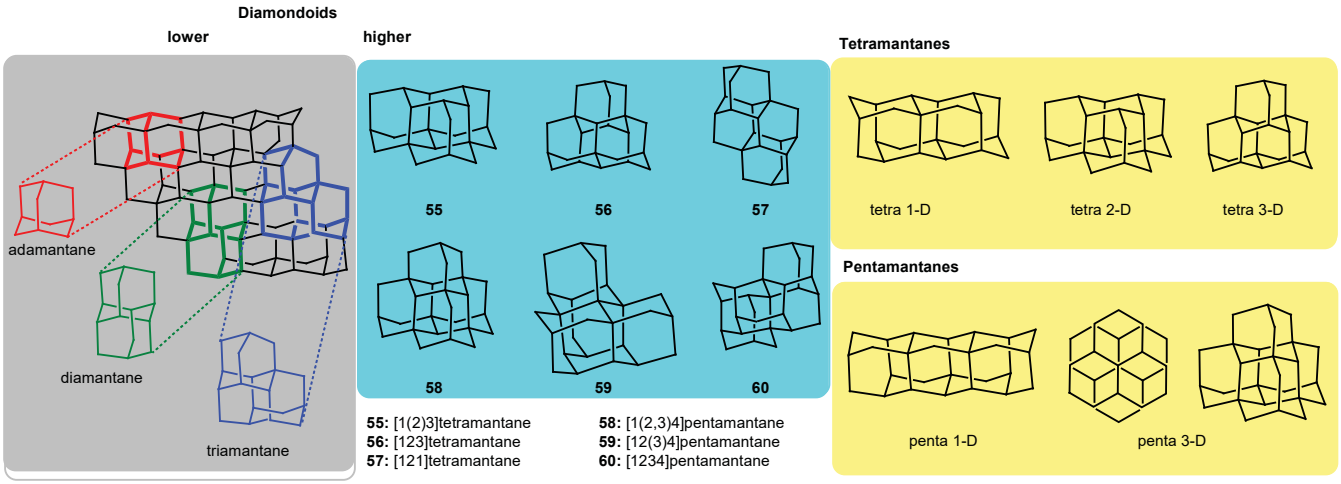
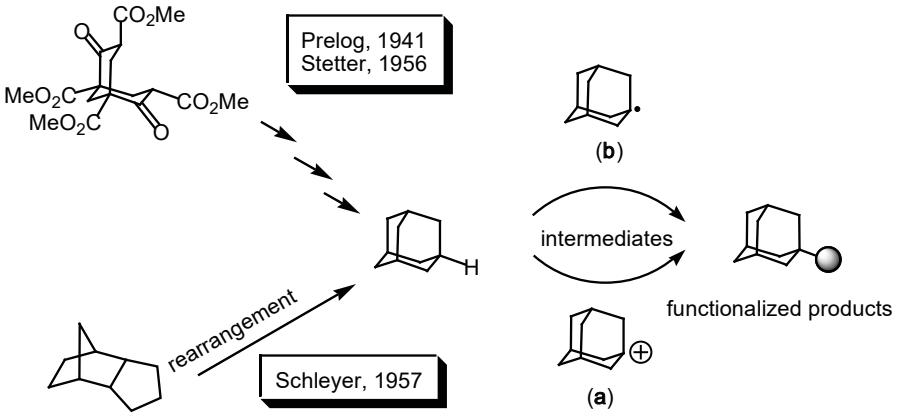


Fig. 12. Structures of adamantane and simplest diamondoids (polymantanes). Modified from [93, 94].

Scheme 35.



the fundamental requirement for achieving this goal is the development of processes for their highly efficient functionalization.

The available literature data on this topic were reviewed in [93, 94]. Both reviews were written according to similar plans under almost verbatim titles; nevertheless, they complement each other well. In both reviews, the starting point in studying the properties and potentials of diamondoids is adamantane itself and its properties. This applies to the sources of these hydrocarbons, their synthesis, functionalization, and possible application.

The subject of [94] was almost exclusively the lower diamondoid, diamantane, whereas similar data for higher diamodoids, tri-, tetra-, and pentamantanes, were presented in [93]. Halogenation, hydroxylation, metalation, carboxylation, amination, amidation, nitration, phosphorylation, phosphinylation, alkylation, and alkenylation processes were considered, and a large number of derivatives containing one or two functional groups were described.

Radical processes for the functionalization of diamondoids, such as bromination, photoacetylation, photoarylation, and cyanation, were reviewed in 2022 [47]. While discussing the mechanisms of adamantane functionalization (Scheme 35), the authors [47] considered that the adamantane molecule contains only two types of C–H bonds and that the number of C–H bond types in diamondoids is larger (three types of C–H bonds in diamantane). Tertiary carbocation **a** is very stable due to hyperconjugation of bonding orbitals inside the rigid cage structure, whereas radical **b** is destabilized since relaxation to the more stable pyramidal conformation is impossible.

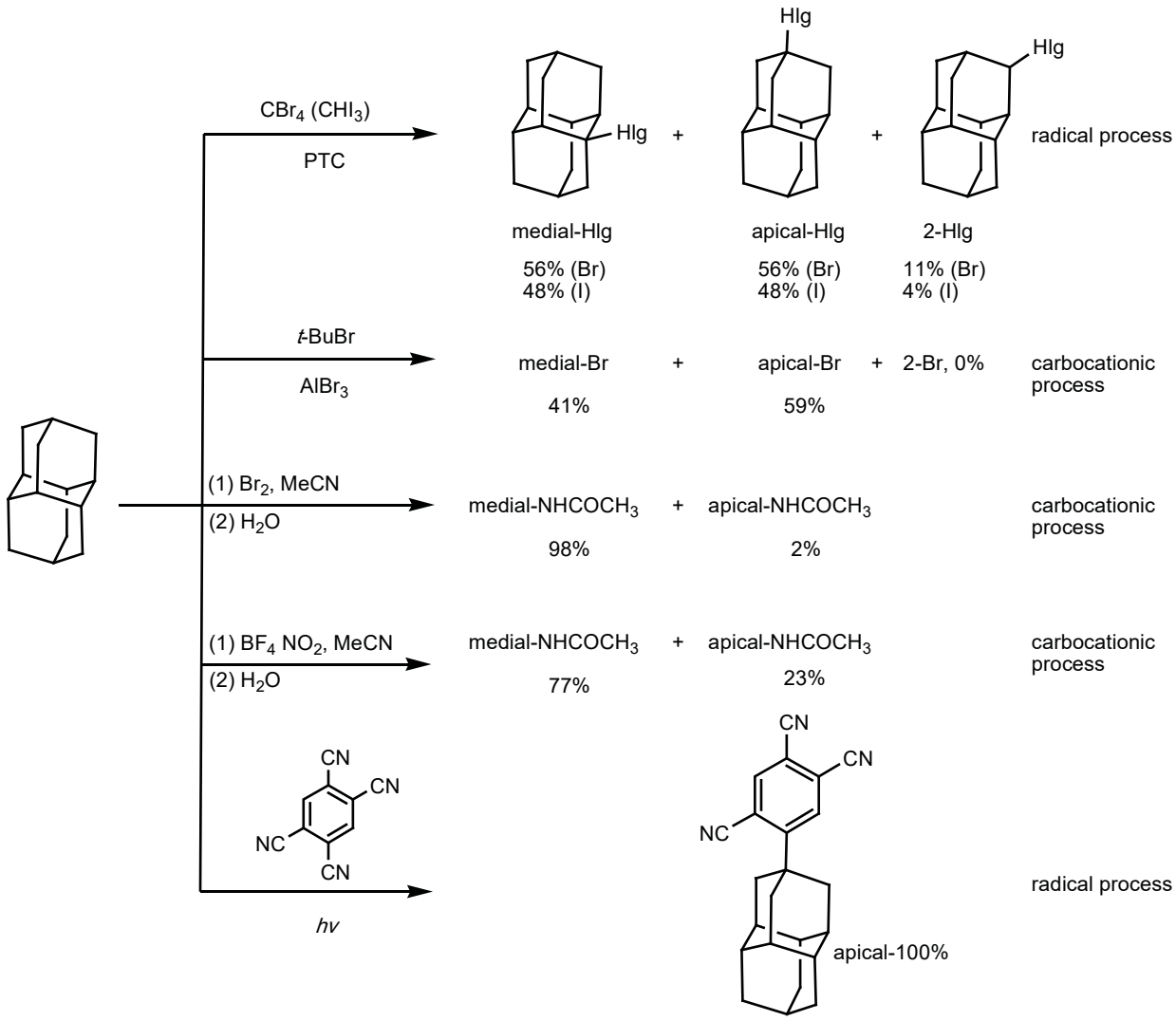
Therefore, the role of reaction conditions (primarily the nature of electrophile and hydrogen atom acceptor or H^+ intermediate) in the functionalization process is very important. This is clearly seen in the bromination of diamantane and its reactions with nitrogen-containing compounds (Scheme 36).

As concerns higher polymantanes, the bromination (including subsequent hydrolysis of the resulting bromo derivatives), acetylation, and arylation with 1,2,4,5-tetracyanobenzene of di-, tri-, tetra-, and pentamantanes were studied [47, 96, 97]. The bromination of triamantane (Br_2, $CHCl_3$, 0°C), followed by hydroxylation (HNO_3, H_2O), afforded mixtures of all possible tertiary isomers. Pentamantane exhibited higher activity and selectivity than tri- and tetramantanes not only in the bromination (Scheme 37) but also in the oxidation with nitric acid, which followed a SET mechanism [97]. A high *api* selectivity was noted in the photoacetylation and arylation with 1,2,4,5-tetracyanobenzene (Fig. 13).

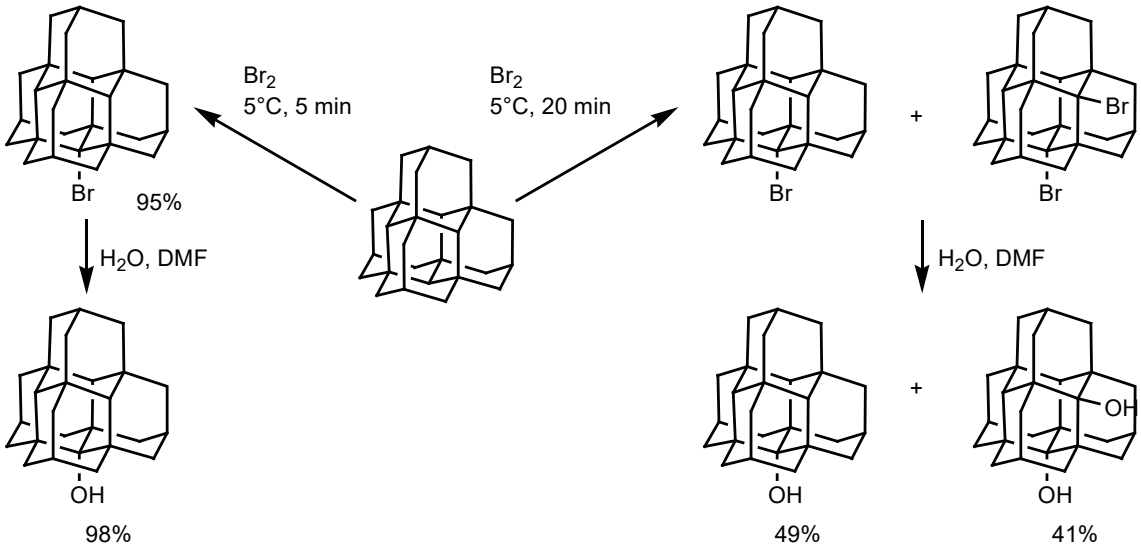
The second parts of reviews [93, 94] provided a detailed analysis of possible applications of adamantane and diamondoids in a wide variety of human activities, including fine organic synthesis, pharmacology, design of polymers with unique properties and optical materials, and photoluminescence. Prospects of research in these areas were demonstrated, and the relation between the unique properties of the adamantane fragment and unique properties of materials based thereon was discussed. The use of diamondoids in the design of nanostructured systems was considered in review [98].

A good reference for researchers may be the book by Fokin, Šekutor, and Schreiner [99] on the chemistry of diamondoids, which was published in 2024. The book considers nomenclature of diamondoids, their natural origin, synthesis and functionalization, and possible uses in medicinal chemistry and as molecular

Scheme 36.



Scheme 37.



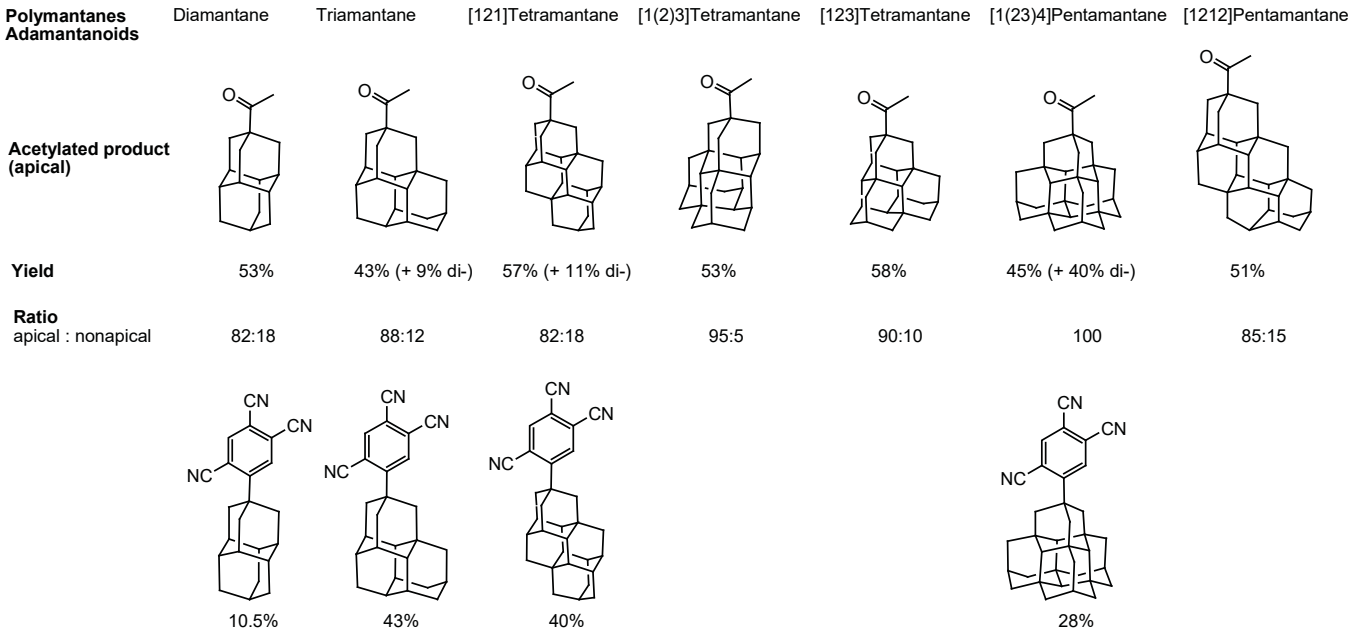


Fig. 13. Apical products of photoacetylation and arylation of diamondoids [47, 96].

building blocks ("supramolecular architecture," oligomers, and polymers, self-assembled monolayer nanomaterials, etc.); also, the authors' point of view on the prospects of further development of this area of adamantane chemistry is given.

4. ADAMANTANE AND MEDICINE

4.1. Adamantane-Containing Compounds and Pharmacology

In the early 2010s, there has been continuously increasing interest in adamantane and its derivatives from not only chemists but also biologists, physicians, and pharmacologists. Relevant reviews were published one after another: 2010 (Costa Rica) [100], 2011 (Australia) [101], 2013 (Europe, USA) [102]. The review by Lamoureux and Artavia (Escuela de Química en Centro de Investigaciones en Productos Naturales, Universidad de Costa Rica) [99] entitled "Use of the Adamantane Structure in Medicinal Chemistry" presented a patent-based list of 47 pharmaceuticals containing an adamantane moiety (83% of US patents), which were registered in 1967–2006; some of them were commercial drugs, and some were under clinical trials (Table 3).

To estimate the effect of adamantane-containing fragments in the drug molecules on their biological activity, the authors considered the following parameters: (**A**) the structure and physicochemical characteristics of adamantane itself and (**B**) change of some molecular characteristics upon introduction of adamantane-containing substituents. Group **A** included data on the three-dimensional structure of adamantane, its topology, polarization activity, insolubility in water, crystallinity, and oxidative stability. Group **B** included (a) change of the ADME properties (absorption, distribution, metabolism, excretion), (b) effect on binding to enzyme hydrophobic site and inhibitory activity, (c) effect on ion channels as a result of disrupting transmembrane flow, and (d) the ability to provide a rigid scaffold to ensure optimal realization of (a) and (b). The known data for a wide variety of adamantane derivatives were generalized in accordance with the selected parameters. The results are presented in Table 4.

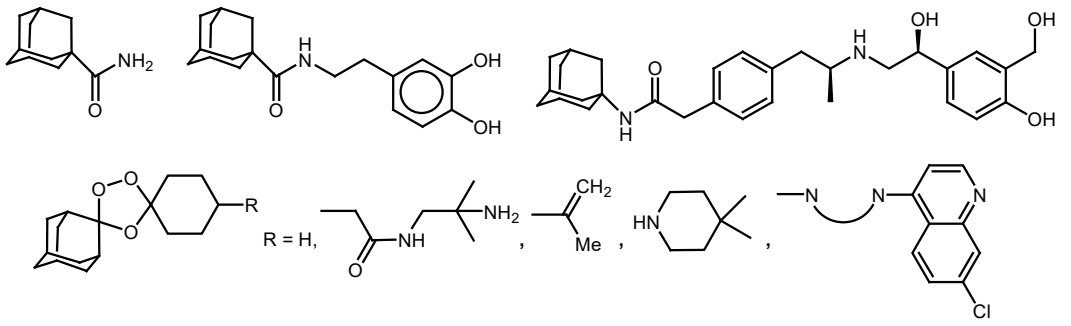
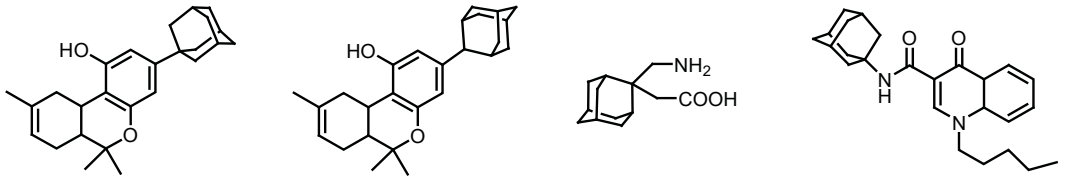
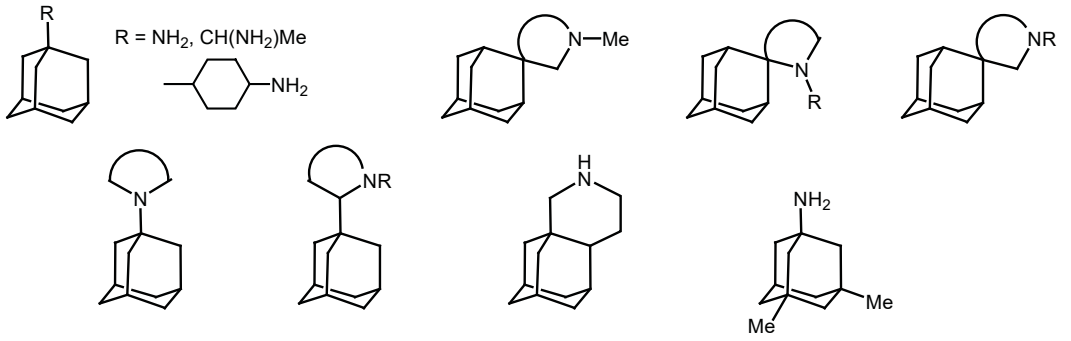
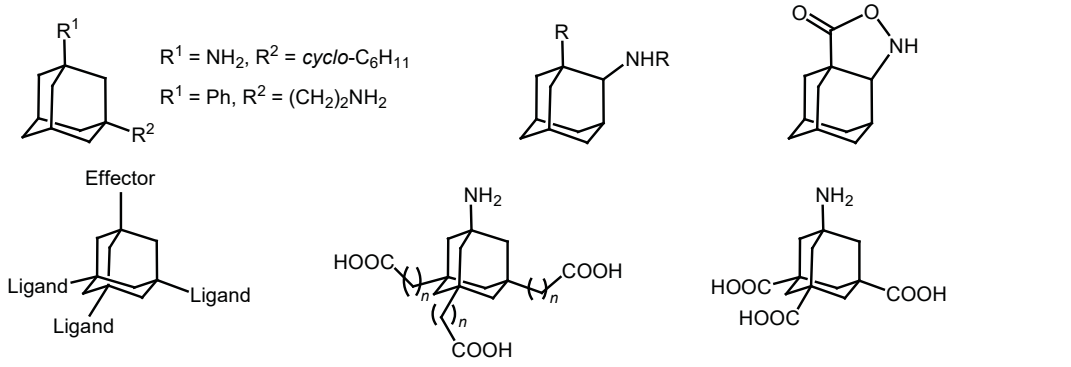
The authors concluded [100] that the relation between the structure of adamantane-containing drugs and their biological activity is complicated and unclear, and it requires further study. They ruled out the exceptional role of ion channel perturbation and believed that the reason is possible interaction of all factors considered. Furthermore, the authors noted that introduction of an adamantane-containing moiety does not always enhance biological activity, e.g., in the modification of known drugs.

The review by Liu et al. [101] entitled "The Many Faces of the Adamantyl Group in Drug Design" focused on adamantane derivatives as potential therapeutics for the treatment of blood diseases, neurological conditions, malaria, type 2 diabetes, tuber-

Table 3. Adamantane-containing pharmaceuticals in patent literature [100] (Ad = adamantyl)

Patent no.	Year	Description	Use
US 3328251	1967	Amino 2-Ad	Antiviral
US 3352912	1967	Rimantadine	Influenza, viral infections
US 3374244	1968	Ad-carboxamides	Anti-inflammatory, antimicrobial
US 3391142	1968	2° amino-1-Ad	Antiviral
US 3439036	1969	Diphenylacetamido-Ad	Analgesic
US 3.464998	1969	Ad-Pyridinecarboxylate	Antiulcer, antibiotic
US 3471491	1969	Ad-Triazines	Antimicrobial, hypoglycemic
US 3625985	1971	Ad-carboxamido acids	Antibiotic
DE 1943404	1971	Ad-alkylamines	Antidepressant
US 3705194	1972	Ethoxyacetamido-Ad	Virostatic
DE 1941218	1972	Tromantadine	Antiviral
US 3789072	1974	Ad-carboxamides	Serotonoin inhibitors
US 3789073	1974	Ad-alkylaminobenzamides	Cardiacarrhythmia
US 3929888	1975	Phenyl-Ad-alkylamines	Parkinson's, antidepressant
US 4001223	1977	Ad-piperazines	Cerebral vasodilators
US 4016271	1977	Ad-carboxylate steroids	Immunological disorders
US 4051256	1977	Ad-guanidines	Rhinoviral infections
US 4122193	1978	Memantine	CNS, Parkinson's
US 4273704	1981	Ad-enkephalins	Analgesic
US 4288609	1981	Amantol	Antifungal, antibacterial
US 4331686	1982	Ad-(dimethylethyl)amines	Otitis externa
US 4515715	1984	Ala-IsoGlu-Ad	Immunostimulant
US 4448972	1984	Ad-ethanoylprolines	Kidney function, antihypertensive
US 4661512	1987	Pyroglutamide-Ad	Anticonvulsant
US 4692515	1987	Ad-spirolactams	Antimicrobial
US 4739074	1988	Ad-spiropyrrolidines	Carrageenan-induced edema
US 4751292	1988	Ad-purines	Cytokinin
EU 199636	1989	Adapalene	Antiacne, multiple sclerosis
US 4797489	1989	Ad-phenylpiperazines	Antidepressant, anxiolytic
US 5061703	1991	Memantine	Cerebral ischemia
EU 392059	1993	Memantine	Peripheral neuropathy, pain
WO 93/08182	1993	HT-90B	Antidepressant
US 5480905	1996	Ad-carboxamidobenzodioxanes	Antianxiety, antidepressant
US 5482940	1996	Ad-carboxamidopiperazines	Anxiolytic, addiction
EU 699438	1996	SR-48692	Anticancer, neuroleptic
US 5574070	1996	Ad-CF3phenylguanidines	Sigma receptor ligands
US 5650406	1997	N-Heterocyclic-Ad	Antischizophrenic
US 5731337	1998	Ad-aminooxazolines	Adrenergic blocking
WO 99/20599	1999	Acylguanidine-Ad	Neurodegenerative disorders
US 6057364	2000	Fluoro-substituted-Ad	Neurological disorders
US 6066652	2000	Memantine	Tinnitus
US 6384083	2002	Amantadine	Borna disease virus
US 6645968	2002	Ad-aminal	Potassiumchannelopener
WO 03/024401	2003	Ad-piperazinones	Chemokine receptor activity
US 6878736	2005	Ad-pyrrolidinylguanidines	Histaminic H3 inhibitor
US 7129246	2006	Nicotinamido-Ad	Immunosuppression, asthma
US 7145037	2006	Ad-amidines	Neuroprotective, antidepressant

Table 4. Adamantyl-containing drugs affecting group **B** properties

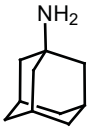
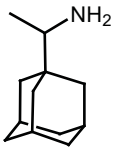
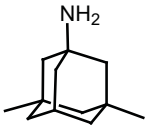
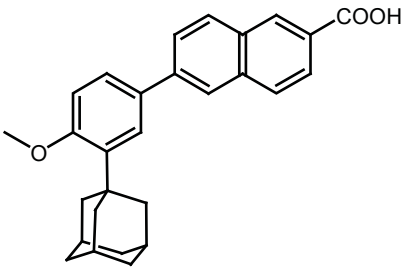
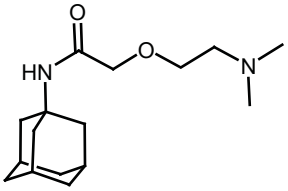
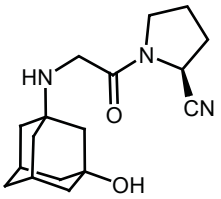
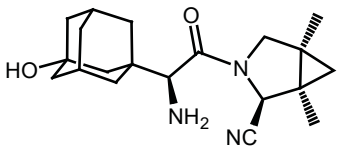
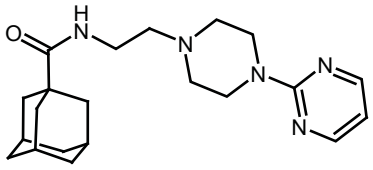
Property	Adamantane derivatives
ADME	
Hydrophobic binding	
Ion channel effect	
Molecular scaffold rigidity	

culosis, inflammatory conditions, and cancer, as well as on their adamantane-containing precursors.

The review considered 38 types of adamantane derivatives, and an attempt was made to elucidate the role of the adamantane fragment in pharmacological activity of these compounds. They included seven approved drugs used in clinical practice (compounds **I–VII**) and adatanserin (**VIII**).[2] An important characteristic of pharmacological agents is their lipophilicity. The review contains calculated octanol–water partition coefficients (*c*Log*P*) of compounds **I–VIII** together

[2] In this section of the review, bold Roman numerals **I–VIII** are used for the seven registered adamantane-containing drugs and adatanserin (**VIII**).

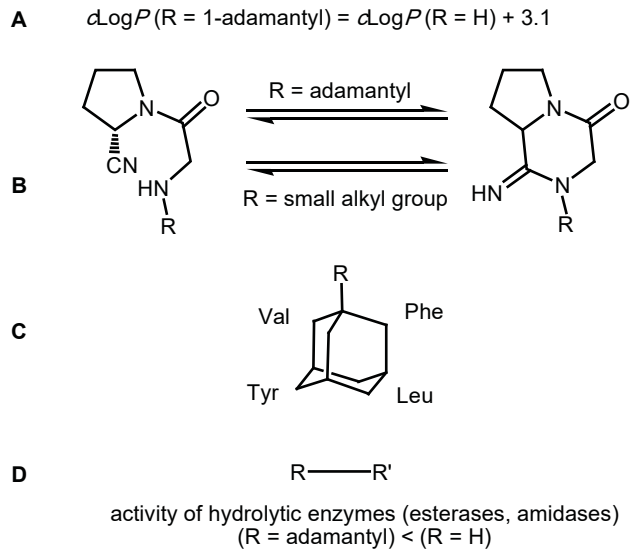
Table 5. Calculated *c*Log*P* values of adamantane-containing drugs **I**–**VIII**[a]

Drug	Structure	Activity (disease)	*c*Log*P*[a]	*c*LogP_{des}[b]
Amantadine (**I**)		Antiviral, Parkinson's disease	2.22	No data
Rimantadine (**II**)		Antiviral	3.10	–0.13
Memantine (**III**)		Alzheimer's disease	3.18	No data
Adapalene (**IV**)		Acne vulgaris	8.04	4.70
Tromantadine (**V**)		Antiviral	1.30	–1.88
Vildagliptin (**VI**)		Type 2 diabetes	–0.14	–1.50
Saxagliptin (**VII**)		Type 2 diabetes	–0.14	–1.65
Adatanserin (**VIII**)		Neuroactivity, antidepressant	2.65	0.45

[a] Calculated by ACD/Labs V11.01 and V12.01;

[b] Analogues containing no adamantane fragment: ethanamine, 2-[2-(dimethylamino)ethoxy]acetamide, 6-(4-methoxyphenyl)naphthalene-2-carboxylic acid, (2*S*)-1-(aminoacetyl)pyrrolidine-2-carbonitrile, (1*S*,3*S*,5*S*)-2-(aminoacetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile for compounds **II** and **IV**–**VIII**, respectively.

Scheme 38.



with $c\text{Log}P_{\text{des}}$ values of their analogues containing no adamantane fragment (Table 5). This data may be quite useful for drug design.

The authors [101] concluded that the presence of an adamantane moiety in the examined compounds affects their properties in four aspects (Scheme 38): (1) the $c\text{Log}P$ value increases by about 3 log units; (2) the relative concentration of cyclic amidine formed from N-substituted cyanopyrrolidine fragment decreases (as shown for vildagliptin **VI**; (3) favors interaction with hydrophobic amino acid residues on binding to proteins; (4) inhibits hydrolysis of adamantane-containing esters and amides with hydrolytic enzymes (esterases and amidases).

Our review [29] summarized data on pharmacological activity of adamantane-containing heterocyclic compounds synthesized from keto acids of the adamantane series (Table 6).

In 2013, L. Wanka, K. Iqbal, and P.R. Schreiner published a review [102] (870! references) with an amazing title "The Lipophilic Bullet Hits the Targets: Medicinal Chemistry of Adamantane Derivatives" and an equally amazing photo (Fig. 14) preceding the main text. The photo shows the chemical formulas of seven adamantane-containing drugs available in 2013 on the market. "Chicagoans refer to cloud gate as "the bean", and researchers at universities near "the bean" have contributed to the elucidation of the mechanisms of action of some of these drugs. Photograph taken by L. Wanka" [102].

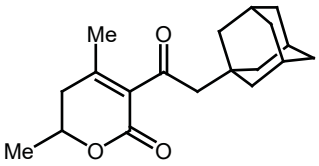
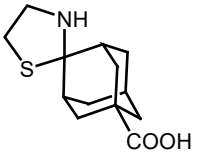
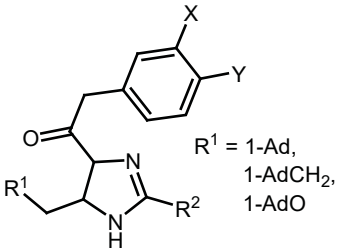
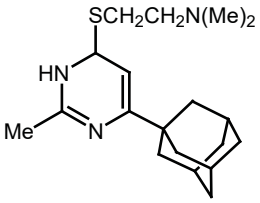
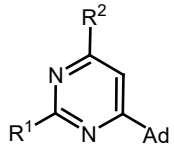
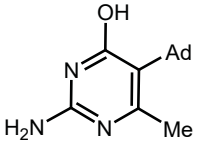
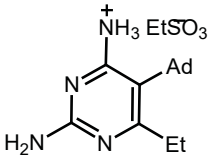
This review can be called an "encyclopedic medicochemical" review-manual for researchers working in these areas of adamantane chemistry. It contains formulas of 461 adamantane-containing compounds, provides a scrupulous analysis of the biological activity of each of them, discusses possible mechanisms of their action and structure–activity relationships, and puts forward hypotheses for further development.

The data given in the review are grouped into 10 large sections, including numerous and very specific subsections. The significance of adamantyl derivatives as antiviral and anti-infective drugs (influenza A, herpes simplex, hepatitis C, HIV, malaria, etc.), drugs for the treatment of the central nervous system (Parkinson's and Alzheimer's diseases), drugs for the treatment of cancer, and much more is considered. The conclusions contain a list of factors that, in the authors' opinion, can affect the biological activity of adamantyl-containing derivatives. These include: (1) the uniqueness of the adamantane structure, which "can only be compared with a methyl group"; (2) the size of the adamantyl-containing fragment and the nature of functional groups; (3) the orienting effect of the rigid adamantane platform on the functional groups responsible for the formation of hydrogen bonds; (4) "critical lipophilicity" of the drug; (5) "biocompatibility" of drugs, etc.

The review ends with the phrase "Adamantane may not be a magic bullet and adamantane-based pharmaceuticals certainly are not silver bullets, yet the lipophilic bullet can be expected to hit even more targets in medicinal chemistry in the years to come."

In 2015, Stockdale and Williams (Australia) published a review [110] in which they analyzed literature

Table 6. Biologically active compounds obtained from keto acids of the adamantane series

Compound structure	Activity
	Inhibits the growth of *Dictyostelium discoideum* but does not affect their morphogenesis; inhibits the growth of K562 human leukemia cells [103]
	Radioprotective activity; antiviral activity against A/Bangkok/1/79 influenza virus [104]
 R^1 = 1-Ad, 1-AdCH_2, 1-AdO	Tested as orally active cholecystokinin 2 (CCK_2) receptor antagonists [105]
	Significant antitumor activity, especially against leukemia U937 cells; strong antibacterial activity [106]
 R^1 = SCH_2COOH, SH, NH_2 R^2 = OH, SH, NH_2	Pronounced activity against herpes-Kupka virus [106]
	Moderate inhibitory activity against sarcoma S180 in mice; exceptionally high activity against murine mammary adenocarcinoma TA3 [107]
	Antitumor activity (4 times stronger than the activity of methotrexate); stoichiometric inhibitor of dihydrofolate reductase from S180 cells [108, 109]

data on pharmaceuticals containing polycyclic hydrocarbon scaffolds. These compounds constitute less than 1% of the total number of drugs. A special section of the review was devoted to adamantane, where seven adamantane derivatives were discussed (Table 7), and detailed schemes of their synthesis and results of pharmacological tests were included. The data given in the review indicated that amantadine (**I**) and rimantadine (**II**) block M_2 ion channels as a result of hydrophobic interaction between the adamantane fragment and N-terminal gate [120]. Memantine (**III**) acts synergistically with appropriate acetylcholinesterase

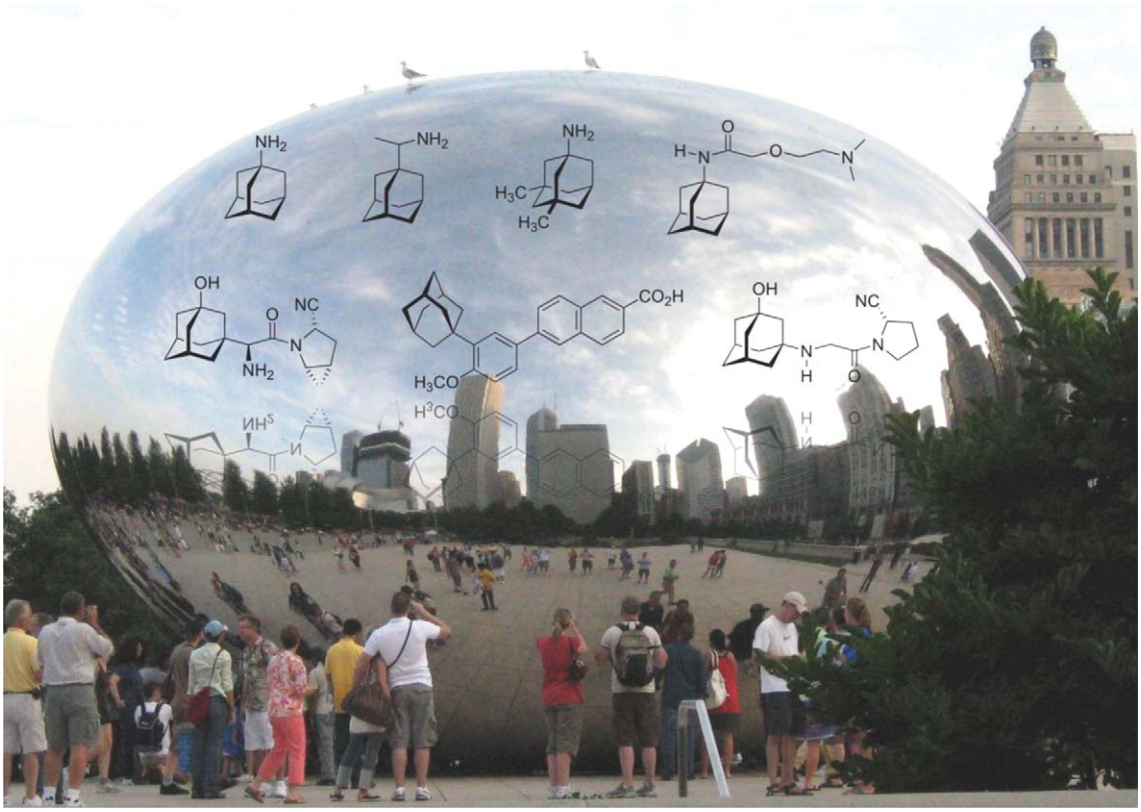


Fig. 14. Silver sculpture "Cloud Gate" with structures of adamantane-containing drugs applied thereto. Modified from [102].

inhibitors in moderate to severe stages of Alzheimer's disease [121].

Adapalene (**IV**)-based drugs under numerous trade names (e.g., Differin® and Epiduo®) proved to be very popular in the treatment of skin diseases such as acne [122, 123]. The SAR study showed that adapalene as a selective vitamin A inhibitor binds to RARβ but acts as an RARγ agonist [124, 125]. The mechanism of action of tromantadine (**V**) remains not completely clear, though numerous studies showed that this drug inhibits both initial and final stages of viral replication [126]. Vildagliptin (**VI**) can also be useful in the treatment of Alzheimer's disease [127].

The authors [110] distinguished five polycyclic hydrocarbon scaffolds, derivatives of which are used in clinical practice. These are the adamantane scaffold (5 compounds: amantadine, rimantadine, adapalene, tromantadine, and saxagliptin) and four scaffolds with bicyclo[2.2.1]heptane (5 compounds), bicyclo[2.2.2]-octane (2 compounds), bicyclo[4.4.1]undecane (one compound), and bicyclo[3.3.1]nonane skeletons (3 compounds) (Fig. 15).

The review by Spilovska et al. (Czechia) published in 2016 [128] was entirely devoted to seven adamantane derivatives **I**–**VII** that are widely used in medical practice. The authors focused on the mechanisms of action of these drugs, pharmacokinetics, pharmacodynamics, clinical trials, and possible side effects.

The review by Klimochkin et al. [129] entitled "Antiviral Properties of Cage Compounds. New Prospects" summarized and systemized literature data over the preceding 15 years. The authors used the term "cage compounds," though, in fact, the antiviral activity of a very large number of individual adamantane-containing compounds of different types was considered. Information on the activity against RNA and

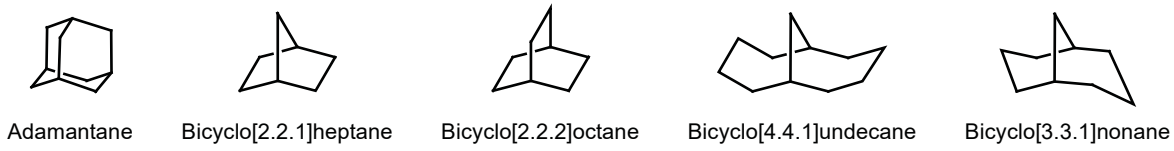


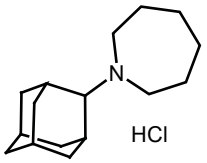
Fig. 15. Polycyclic hydrocarbon scaffolds underlying medically used drugs.

Table 7. Adamantane derivatives used in medical practice

Compound name, synthesis (initial adamantane -containing compound, number of steps)	Biological activity
Amantadine **I** (adamantane or 1-bromoadamantane, 2 steps)	Antiviral [111], analgesic, anti-Parkinson [112]; EC_{50} = 42 μM (influenza A H_2N_2), 6 μM (influenza A H_3N_2)
Rimantadine **II** (1-acetyladamantane, 2 steps)	Antiviral [111], analgesic, anti-Parkinson [112]; EC_{50} = 14 μM (influenza A H_2N_2), 0.4 μM (influenza A H_3N_2) [113]
Memantine **III** (1,3-dimethyladamantane, 3 steps)	IC_{50} (NMDA receptor) = 0.5–3.0 μM; IC_{50} (serotonin $5HT_3$ receptor) = 1 μM [114], 2.2–2.3 μM [115]
Adapalene **IV** (1-hydroxyadamantane, 3 steps)	K_i(RARα) = 1100 nM, K_i(RARβ) = 34 nM, K_i(RARγ) = 130 nM [116]; (RAR is retinoic acid receptor)
Tromantadine **V** (1-aminoadamantane, 2 steps)	Antiviral activity against herpes simplex virus and shingles [117]
Vildagliptin **VI** (3-amino-1-hydroxyadamantane, L-proline, 4 steps)	Antihyperglycemic activity (against type 2 diabetes); K_i (DPP-4) = 17 nM, IC_{50} (DPP-4) = 3.5 nM, IC_{50} (DPP-8) = 9 nM [118, 119]; (DPP is dipeptidyl peptidase)
Saxagliptin **VII** (methyl adamantane-1-carboxylate, 10 steps)	Antihyperglycemic activity (against type 2 diabetes); K_i (DPP-4) = 0.6 nM, IC_{50} (DPP-4) = 18 nM, IC_{50} (DPP-8) > 50 nM [118, 119]

DNA genome viruses, influenza A virus and its strains, hepatitis C virus, human immunodeficiency virus, herpes virus, cytomegalovirus, and orthopoxvirus was given. Particular attention was paid to the mechanisms of drug action, especially to the mechanism of inhibition of M2 ion channel protein.

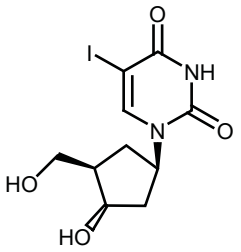
The review by Sayadyan and Shklovskii [130] published in 2017 was almost entirely devoted to the properties of memantine which, in authors' opinion, is the most known drug for the treatment of cognitive disorders in various pathological conditions. In 2003, memantine became the first registered drug for the treatment of severe Alzheimer's disease. The mechanism of its action was studied since 1990. The review analyzed and summarized the available data which allowed the authors to conclude that memantine (1) reduces the intensity of nonspecific inflammation (which is observed in Alzheimer's disease); (2) is the most effective non-competitive antagonist of NMDA receptor which plays an important role in the development of Alzheimer's disease; (3) permeates the blood–brain barrier and is excreted almost completely by kidneys. The effect of memantine on neurorehabilitation of stroke patients was studied, and the results confirmed its pronounced efficiency in the improvement of cognitive functions. The authors reported on the efficiency of another adamantane derivative, himantane **61** [*N*-(adamantan-2-yl)hexamethyleneimine hydrochloride] in the monotherapy of Parkinson's patients [131]. This drug reduced motor disorders such as tremor and exerted a corrective effect on emotional and personality disorders.



61

In 2016, a unique review by E. De Clercq and G. Li [132] was published in *Clinical Microbiology Reviews*. One of the authors, Prof. E. De Clercq (Belgium), is well-known in scientific circles of physicians, microbiologists, virologists, and specialists in related fields and the author of more than 2700 scientific publications. The second is a Chinese scientist who obtained his bachelor's degree in Applied Mathematics at Hunan University in 2006. In 2014 (two years before the publication of review [132]), he received his doctoral degree in Biomedical Sciences from the Faculty of Medicine, KU Leuven (Belgium). The review deals with antiviral drugs approved over the past 50 years.

Throughout human civilization, viral infections have caused millions of deaths, yet the first antiviral drug, idoxuridine [133], was approved only in June 1963 for clinical use in the treatment of hepatitis C. Between June 1963 and April 2016 (over 50 years), only 90 drugs were approved to combat 9 types of



Idoxuridine

human viral infections, despite the fact that by that time more than 200 viruses were known and thousands of antiviral inhibitors were discussed in the literature. The authors [132] distinguished the following viruses responsible for nine types of human infections known by 2016: (1) human immunodeficiency retrovirus (HIV); (2) DNA viruses including hepatitis B virus (HBV), cytomegalovirus (HCMV), herpes simplex virus (HSV), papillomavirus (HPV), and varicella zoster virus (VZV); and (3) RNA viruses: hepatitis C virus (HCV), respiratory virus (RSV), and influenza virus.

The review provides a full description of each virus, which included the date of discovery, origin, transmission routes, incubation period, particle size, and protein targets for the approved drugs. The epidemiology and pathogenicity of viruses and clinical complications of the disease were considered. Next, all 90 antiviral drugs approved by 2016 (including vaccines) were presented with extensive information on each drug, focusing on the molecular (chemical structure, mechanism of action) and therapeutic aspects.

Among the 90 drugs discussed in the review, the section "Influenza Virus Inhibitors" considered 8 compounds, including two adamantane derivatives, 1-aminoadamantane **I** (amantadine) and 1-(α-aminoethyl)adamantane **II** (rimantadine) [86, 134–141]. Amantadine was the first drug for the treatment of influenza A [86]; it blocks H^+ ion transport through the viral M2 (matrix 2) protein channels [134, 135], thus preventing the release of free ribonucleoproteins into the cytoplasm [142].

Review [132] was preceded by earlier publications in *Medicinal Research Reviews*, namely three review articles by De Clercq devoted to the discovery of antiviral drugs, parts A [143], B [144], and C [137]. The latter review discussed the available data on the antiviral activity of rimantadine and its 11 analogues, 1- and 2- monosubstituted and spiro adamantanes with nitrogen-containing 3-, 5-, and 6-membered heterocyclic fragments, against influenza A virus. On the whole, the given information provides a valuable guide for specialists in the field of antiviral drug therapy.

The results of biological testing of adamantylated heterocyclic nucleobases and related compounds described in Section 3.1.1 of the present review [52] were published in 2016 [53]. They included the data on the following types of biological activity: antiparasitic [against amastigotes and CRK_3/CYC_6 kinase of the bloodstream (BS) form of *Trypanosoma brucei*]; antitumor (TNF-α production in murine melanoma B_{78}/TNF/9 cells); antiviral (HIV-1, HSV-1, HSV-2) and on the effect on specific receptor functions [A_1, A_{2A}, A_2B, and A_3 adenosine receptors; histamine H4 receptor; glycogen synthase kinase 3 (GSK-3)].

The design of selective ligands for specific receptors is now acquiring paramount importance [145, 146]. For example, it is known that activation of A_1A and A_3A receptors reduces the level of cyclic adenosine monophosphate (CAMP), whereas activation of A_2AA and A_2BA receptors increases it. Stimulation of A_1A receptors activates potassium and deactivates calcium channels, while stimulation of A_2AA receptors inhibits functioning of D2 dopamine receptors. Thus, a new large and poorly studied field of activity is opened, which is related to the design of novel drugs for the treatment of a wide range of diseases, including cardiovascular, oncological, neurological, mental, etc. [147, 148].

In addition to the data given above, the review [53] contained the subsection "Biological Screening" which included the results of testing certain, fairly large groups (types) of compounds for several activities rather than a single one. Most frequently, their antimicrobial, fungicidal, antimalarial, and cytotoxic activities were assayed.

The unique structure and chemical properties of adamantane have aroused the interest of researchers in the field of creation of drug delivery systems. Just this topic was the subject of the review by Štimac et al. (Croatia) published in 2017 [149]. The review analyzed two methods of using adamantane: as a building block bearing various functional groups (adamantane-based dendrimers; Fig. 16a) or as a part of self-assembled supramolecular systems where it is introduced due to its lipophilicity and strong host–guest interaction (cyclodextrins; Fig. 16b).

The data presented in the review confirmed the previously proposed concept of the possibility of using adamantane as an anchor in the lipid bilayer of liposomes for targeted drug delivery and surface recogni-

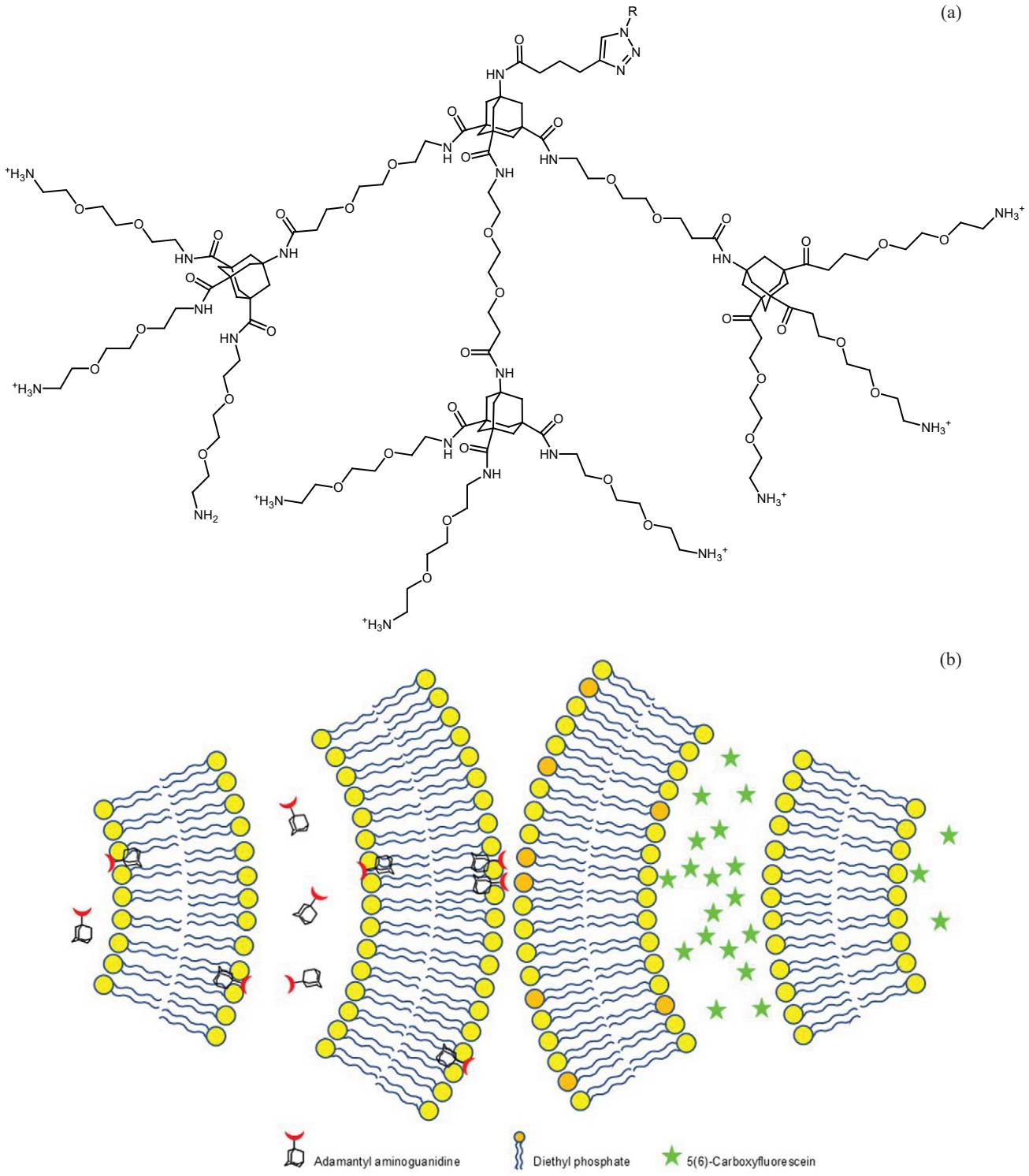


Fig. 16. (a) Adamantane-based polyammonium dendrimer; (b) Interaction of liposomes containing adamantylguanidines with complementary liposomes. Modified from [149].

tion. The authors noted that, apart from the structure and chemical properties of adamantane, this is favored by its biocompatibility, non-toxicity, availability, and low cost.

In 2020, Kitagishi et al. (Japan) [150] proposed a convenient and efficient method for intracellular delivery of relatively large biomolecules (such as GFP, β-gal, and IgG proteins with a size of ~100 nm) using

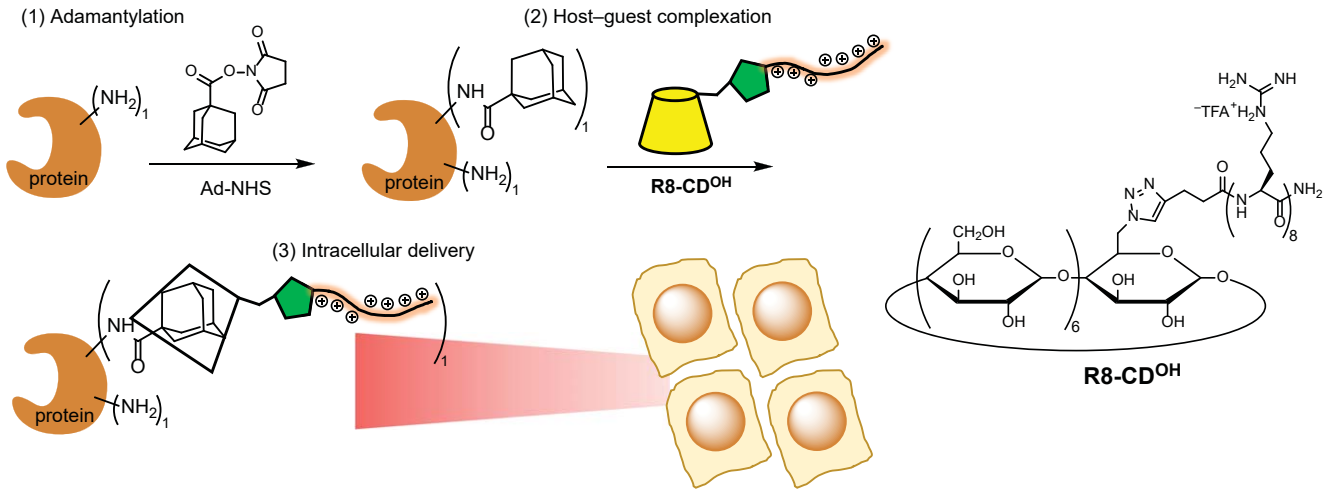


Fig. 17. Surface modification of a protein with Ad-NHS and its intracellular delivery by CPP-modified cyclodextrins. Modified from [150].

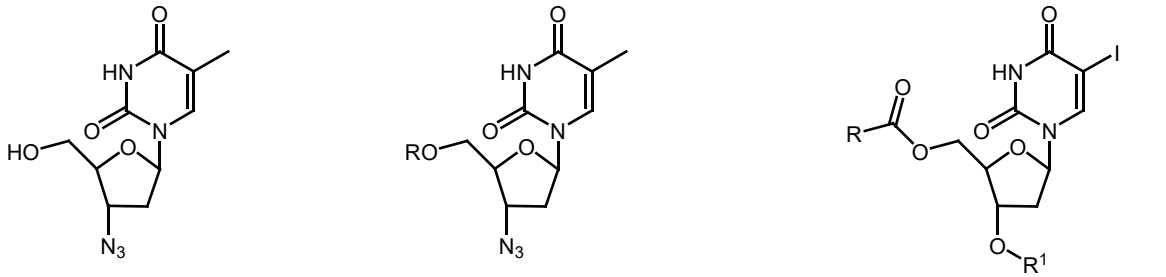
proteins modified with adamantane-1-carboxylic acid *N*-hydroxysuccinimide ester (AD-NHS). The mechanism of delivery of biomolecules is well explained by supramolecular host–guest interaction of adamantane derivatives with the internalized peptides [cell-penetrating peptides (CPPs)] modified with cyclodextrins R8-CD^{OH} (Fig. 17).

The authors noted that the proposed method is advantageous as it does not require any genetic manipulation, the procedure for chemical modification is very simple, and the size of the modified surface is minimal. The obtained results indicated that the method can be utilized in various bioengineering applications, such as protein therapy, cell programming, genome editing, etc.

4.1.1. QSAR analysis of adamantane-based drugs. The idea that the chemical structure of molecules and their biological activity are in a certain relationship was put forward more than 150 years ago [136, 151]. Subsequently, it led to the development of QSAR (quantitative structure–activity relation) program and computer software which make it possible to predict, with a certain degree of reliability, the presence or absence of pharmacological activity of natural and synthetic compounds [152].

In 2012, Bayat and Reyhani Yassavoli (Iran) [153] utilized two empirical QSAR methods, MLR (multiple linear regression) and GA-MLR (genetic algorithm–MLR) to study the possibility of using in HIV therapy nucleotides modified by adamantane-containing fragments, namely azidothymidine (AZT), five its derivatives **62**–**66**, and three 5-iodo-2′-deoxyuridine derivatives **67**–**69** (Fig. 18).

The authors substantiated their study as follows. Currently, the most promising agents for combating HIV infection are compounds belonging to 3 classes, nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Azidothymidine used for the treatment of AIDS patients belongs to the first class. It is believed that its antiviral activity is



AZT

R = 1-AdCO (**62**), 1-AdCH$_2$CO (**63**), 1-AdCONH(CH$_2$)$_n$CO (*n* = 1–3) (**64**–**66**)

R = 1-Ad, R^1 = H (**67**)
R = 1-AdNHC(O)(CH$_2$)$_3$, R^1 = H (**68**)
R = 1-Ad, R^1 = 1-AdCO (**69**)

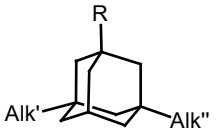
Fig. 18. Azidothymidine and adamantane-containing nucleotides **62**–**69**.

related primarily to its ability to penetrate the blood–brain barrier (BBB). On the other hand, it is known that introduction of an adamantane fragment into drug molecules increases their lipophilicity. This suggests the possibility of creating prodrugs on the basis of AZT modified by appropriate adamantane-containing fragments.

In 2020, during the pandemic, Dembitsky et al. [154] reported the results of QSAR analysis of more than 75 natural and synthetic adamantane derivatives with a view to finding out compounds capable of preventing and/or treating dementia, Alzheimer's and Parkinson's diseases, and other neurodegenerative disorders. The authors used the PASS (Prediction of Activity Spectra for Substances) program. The examined adamantane derivatives were divided into three groups: natural compounds, synthetic 1-R-3,5-dialkyladamantanes, and heteroadamantane derivatives in which the heteroatom is part of the adamantane core.

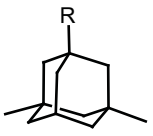
Natural compounds. The examined adamantane scaffolds included polysubstituted 2,2-dimethyladamantane-4,6,10-triones (9 compounds) and 2,2-dimethyladamantane-4,6-diones (2 compounds). In all cases, one CH and one CH_2 unit of the adamantane core remained unsubstituted. Their natural plant sources were *Hypericum sinaicum* [155], *Hypericum subsessile* [156], *Hypericum sampsonii* [157], *Hypericum hookerianum* [158], and *Garcinia multiflora* [159]. The authors [154] concluded that natural adamantane derivatives are more suitable for the treatment of malignant tumors than of neurodegenerative disorders. Seven compounds exhibited high antitumor activity. Two medications, Hookeriones **C** and **D**, were noted as the most interesting for the prevention and treatment of neurodegenerative diseases, and two drugs, RXC-189 and Hypersubone, showed high antiprotozoal activity (Fig. 19).

Synthetic adamantane derivatives. Amantadine, memantine, and trisubstituted 1-R-3,5-dialkyladamantanes **70** [R = F, Cl, Br, I, NH_2, NO_2, piperazin-4-yl, OH, OOH, SH, SeH, $OP(O)(OH)_2$, $P(O)(OH)_2$], more than 50 compounds in total, were subjected to comparative pharmacological analysis.



70

Alk′ = Alk″ = Me, Et, Pr
Alk′ = Me, Alk″ = $(CH_2)_4CMe_3$



R = $P(O)(OH)_2$ (**71**), F (**72**)

These synthetic adamantane derivatives were reported to have greater pharmacological potential in comparison to currently used amantadine and memantine. 3,5-Dimethyladamantan-1-ylphosphonic acid (**71**) and 1-fluoro-3,5-dimethyladamantane (**72**) were considered by the authors to be the most promising for the treatment of neurodegenerative diseases.

Heteroadamantane-based compounds. Small amounts of heteroadamantanes were found in natural sources, but most of the heteroadamantane derivatives discussed in [154] were of synthetic origin. In particular, among the 13 compounds, four compounds contained one nitrogen atom in the adamantane skeleton, 6 compounds contained two nitrogen atoms, one compound had an adamantane-like skeleton composed of four arsenic atoms (instead of tertiary carbons), three oxygens, and three carbons, and two compounds contained two skeletal oxygen atoms. These heteroadamantane derivatives were isolated from plants, bacteria, marine invertebrates, and some marine and river fishes (*Tetraodontidae*), in particular *Daphniphyllum humile* (alkaloid), *Daphniphyllum oldhamii* (leafs), *Acosmium panamense*, *Acosmium dasycarpum*,

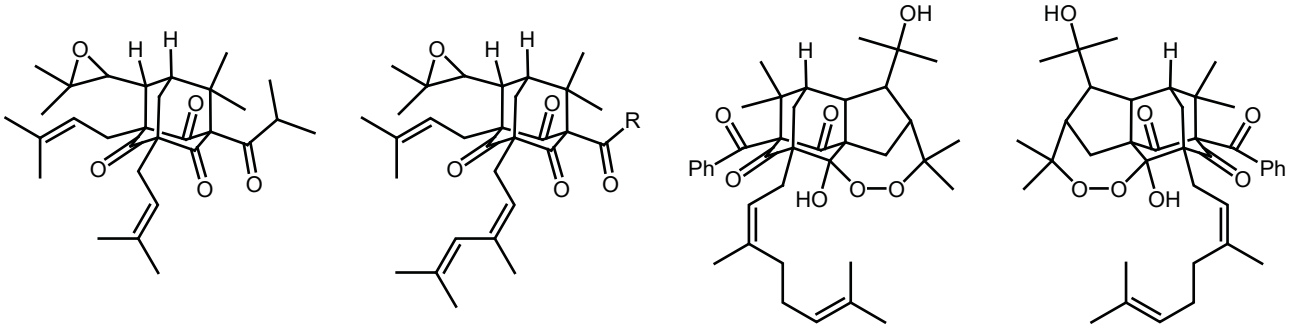


Fig. 19. Promising biologically active natural adamantane derivatives [154].

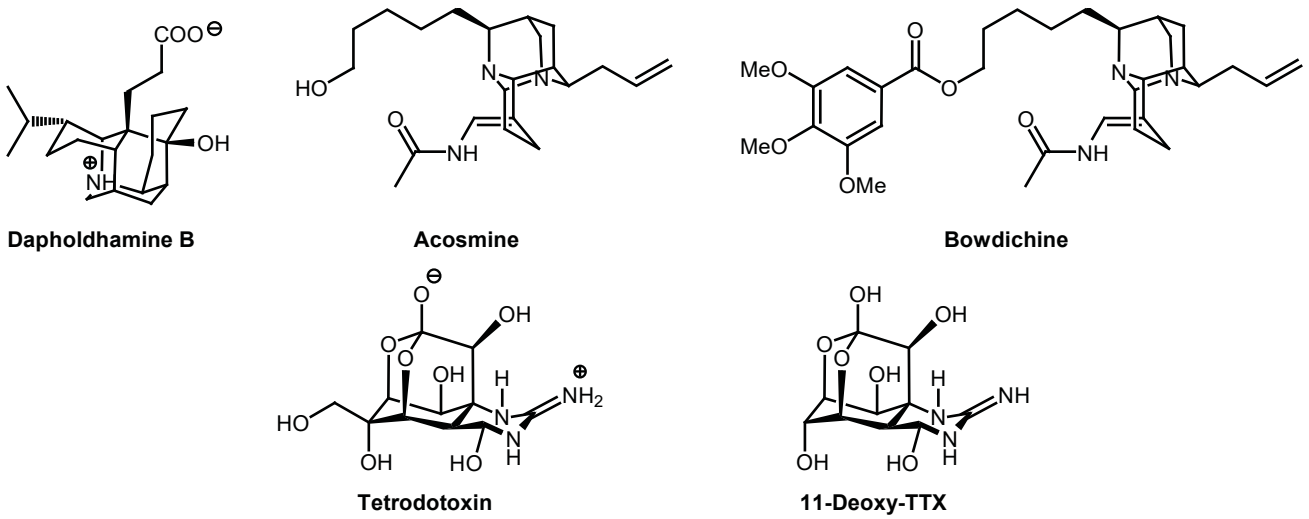


Fig. 20. Heteroadamantane derivatives promising for further study [154].

Bowdichia virgilioides (bark), *Echinochalina bargibanti* (marine sponge), *Fugupardalis* (poisonous fish), and *Acinetobacter*, *Aeromonas*, *Alteromonas*, *Bacillus*, *Micrococcus*, and *Moraxella* species (bacteria isolated from deep-sea sediments at a depth of more than 4000 m).

The conducted PASS analysis revealed five compounds promising for further pharmacological study (Fig. 20). Three of them, Dapholdhamine B, Acosmine, and Bowdichine were isolated from plants and were predicted to possess cardiotonic and antiarrhythmic activity. Their heteroadamantane scaffolds included one or two nitrogen atoms. Two compounds, Tetrodotoxin and 11-Deoxy-TTX isolated from deep-sea microbial species and containing oxygen atoms in the adamantane skeleton, may be active in multiple sclerosis.

4.2. COVID-19 Pandemic

Already in September 2020 (the very beginning of the pandemic), a review by Cortés Borra (Hospital Vall d'Hebron, Barselona, Spain) [160] appeared under the title "Adamantanes for the Prevention of COVID-19: A Review of Case Reports." The review included 14 references, ten of them dated 2020. The author stated that "Due to the short lapse of time since the appearance of SARS-CoV-2," only three case reports in this field were available (from Spain, Poland, Mexico, and Portugal). The author analyzed these case reports in order to shed light on the possibility of using amantadine and memantine for the prevention and/or treatment of COVID-19. Three groups of patients with Parkinson's disease, multiple sclerosis, and cognitive disorders were administered amantadine or memantine

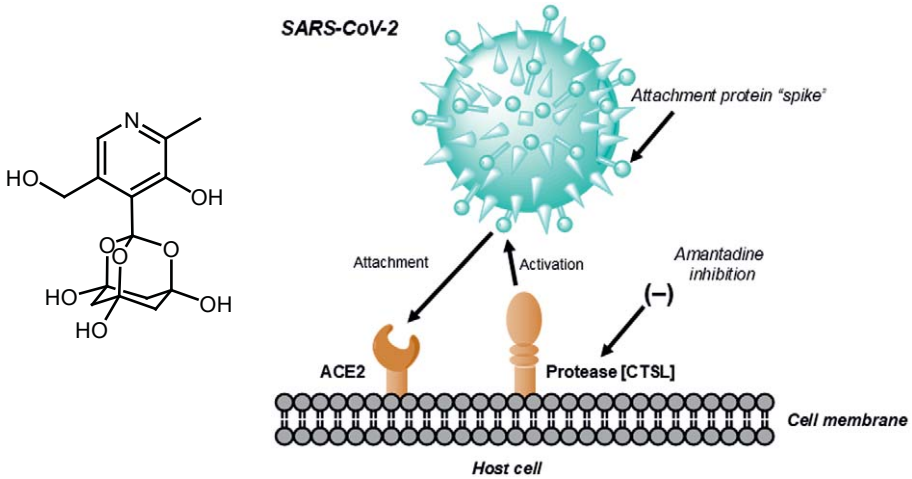


Fig. 21. (a) The simplest bananin, and (b) simplified scheme of the key steps and associated proteins involved in the invasion of the host cell by SARS-CoV-2. Modified from [161].

over a period of several weeks before COVID-19 infection. The author believed that a positive preventive effect of amantadine was observed.

At the same time, Butterworth (Canada) published a review [161] where he analyzed available data on the prospects of using adamantane derivatives for combating COVID-19. The in vitro and preclinical studies revealed the efficiency of amantadine, rimantadine, memantine, and bananins (Fig. 21a) against a number of coronaviruses, including SARS-CoV-2 which is responsible for COVID-19. Among other viruses, human coronavirus HCoV-0C43, bovine coronavirus, and severe acute respiratory syndrome coronavirus 1 SARS-CoV-1 were considered.

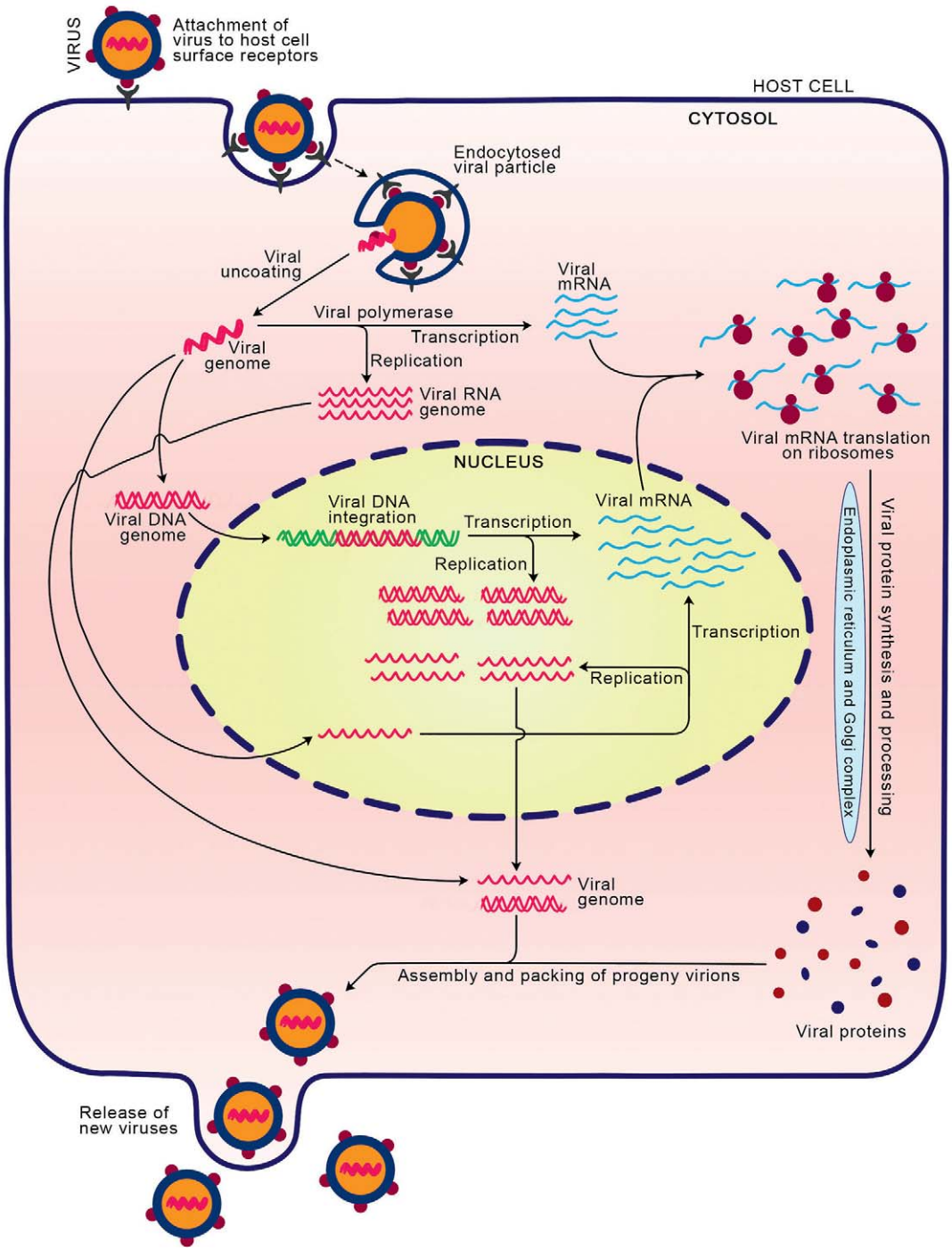


Fig. 22. Life cycle of viruses. Adapted from [162].

The available data indicated that amantadine could block the viral protein E channel, thus impairing viral propagation. Furthermore, amantadine analogues could inhibit virus penetration into the host cell by increasing the pH of endosomes and hence inhibit host cell proteases (e.g., cathepsin L) necessary for virus replication (Fig. 21b).

"Binding of the SARS-CoV-2 spike to ACE2 is followed by action of the endosomal cysteine protease Cathepsin L [CTSL], resulting in fusion of viral and host cell membranes and release of the viral genome into the host cell cytoplasm. Amantadine has the potential to disrupt the process by downregulation of CTSL by increasing the pH of endosomes, resulting in impaired viral entry and replication" [161].

The available data on the effect of various compounds (466 in total) on the expression of Cathepsin L showed that amantadine is the fifth most active agent. According to the author, "these findings constitute a good experimental evidence base and rationale for further study with a view to repurposing adamantane antiviral agents as anti-SARS-CoV-2 agents." It was also noted that amantadine and memantine could be useful for the treatment of neurological complications of COVID-19, including characteristic CNS symptoms of "long COVID-19." This is confirmed by the available data and those given in the review.

In 2021, Tompa et al. (India) published a review [162] on FDA (Food and Drug Administration)-approved antiviral drugs for the treatment of HIV, hepatitis C and B, influenza, herpes simplex, human papilloma, respiratory syncytial, human cytomegalovirus, and varicella-zoster infections. The list included all drugs from the first one approved in 1963 to those approved in 2019. A special section of the review was devoted to the major pandemics of the 21st century, namely swine flu, Ebola fever, and coronaviruses. As noted by the authors, the infection caused by each virus is individual; nevertheless, they considered typical, common for all viruses, infection and replication stages (Fig. 22), as well as the mechanisms of action of particular drugs.

Initially, a virus attaches to host cell receptors through its surface proteins, which facilitates its internalization. The internalized virus releases its genome into the cytosol for the purposes of replication (RNA in the cytosol and DNA in the nucleus), transcription, and translation with the formation of major viral proteins. The viral components are collected together to develop into new viruses that are released into the extracellular fluid through lysis of the host cell or budding.

Small molecule drugs (103 compounds) predominated in the drug list given. The section "Influenza Virus Infections" considered only 9 compounds, two of which were adamantane derivatives, amantadine (1966) and rimantadine (1969). Both these exhibit anti-influenza activity which is attributed to their ability to block M2 proton channels [142, 162, 163].

5. ADAMANTANE AND DIAMONDOIDS IN VARIOUS FIELDS OF SCIENCE AND TECHNOLOGY

In the 21st century, the intensity of the development of adamantane chemistry has not decreased; moreover, new trends in the conducted research have emerged. This fact is similar to that how the discovery of the antiviral activity of amantadine and rimantadine in the past century caused an explosion of research, which has not weakened until now, and the creation of a large area "Adamantane and Medicine." In our opinion, the "cornerstones" of the research in the last two decades are two types of compounds, 1,3,5,7-tetrasubstituted adamantanes and compounds with a diamond-like structure (diamondoids). These compounds attract interest not only from chemists. Physicists and specialists in materials science of a wide profile (nanotechnology, polymer nanocomposites, self-organized monolayers, liquid crystals, catalytic sensors, photoluminescence, biotechnology, etc.) come to the fore. The number of relevant publications grows exponentially, as follows from the data given in this section.

5.1. Adamantane (Diamondoid)-Containing Materials

In 2013, Robello (Eastman Kodak Company) [164] reported the synthesis and properties of polymers with pendant adamantane and diamondoid fragments. The initial compounds were adamantan-1-yl and diamantan-1-yl acrylates and methacrylates (Fig. 23) and 1-vinyladamantane. The polymerization conditions (initiator, solvent, time, temperature, yield) and characteristics of the obtained polymers are given.

The synthesized polymers exhibited an unusual combination of moderately high refractive indices and low optical dispersion, which was especially clearly seen for polymers with pendant diamondoids. Their refractive indices were significantly higher than that of poly(methyl methacrylate), whereas the optical dispersions were comparable. These properties, in combination with purely physical characteristics (solubility,

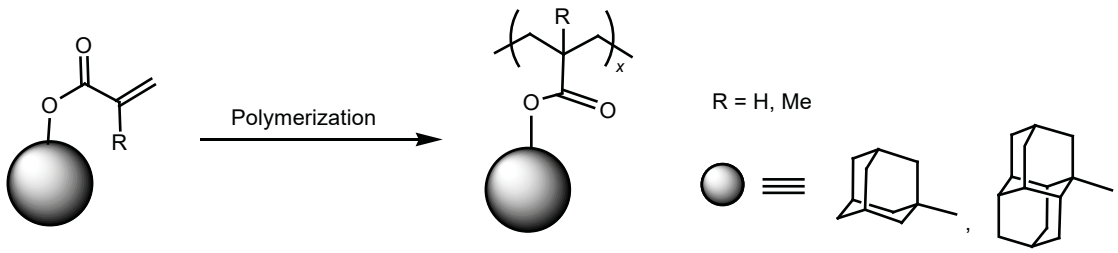


Fig. 23. Adamantane- and diamantane-containing acrylic and methacrylic polymers [164].

achromaticity, easy preparation of thin films), make the synthesized "polymers valuable as specialty optical plastics despite their undoubtedly high cost" [164].

In 2018, Ishizone and Goseki (Japan) wrote a review [165] under a similar title, "Synthesis of Polymers Carrying Adamantyl Substituents in Side Chain." The review covered both typical methods for the introduction of adamantane fragments to the existing polymers and polymerization of monomers containing adamantyl substituents, such as terminal olefins, acetylenes, (meth)acrylates, (meth)acrylamides, vinyl ethers, 1,3-dienes, and styrenes. Well-systematized and carefully analyzed data available in the literature on the synthesis of the starting monomers, conditions of various types of their polymerization, and properties of the resulting polymers can certainly serve as a reliable guide for specialists working in this field.

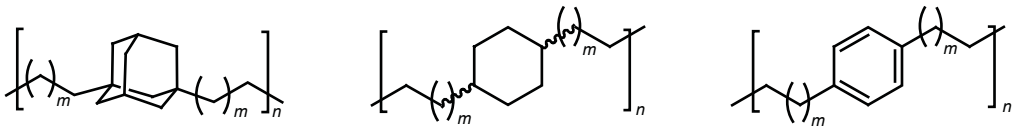
The review by Baranov et al. [22] published in 2022 (see Section 3.1.1 of the present review) discussed new methods of synthesis of unsaturated adamantane derivatives and their polymerization reactions. Referring to the review [165] "which describes in detail modern methods of synthesis and areas of practical application of various adamantane-based polymers," considered only some of the main aspects of the problems and the results of new studies. The latter included four publications in 2017–2019 and 2021 [166–169].

Spohn et al. [166] studied cationic polymerization of 1-vinyladamantane under different conditions (temperature, catalyst). The synthesized polymers were used to obtain nanodiamonds, very small (<10 nm) and medium-sized ones (10–20 nm). The results of cationic oligomerization of 2-methylideneadamantane (a dimer was formed) and cationic, anionic, and radical polymerization of 2-allylideneadamantane were given in [167]. Tyborski et al. [1680 reported the electronic and vibrational properties of oligomers based on adamantane and diamantane interconnected with double bonds and oligomers of dienes with a 1,3-adamantane fragment.

In 2019, Friebel et al. [169] were the first to synthesize poly(1,3-adamantylene alkylene)s **73** with 10, 16, 18, and 20 methylene units between the adamantane fragments via acyclic diene metathesis polymerization. In all cases, the resulting saturated adamantane-containing polymers showed excellent thermal stabilities (452–456°C) which were significantly higher than the thermal stability of structurally related analogues **74** and **75** with cyclohexane or phenylene units (Fig. 24).

In 2020, Yeung et al. [98] reviewed literature data on the potential use of adamantane and diamondoids in the creation of nanostructured systems for various purposes. The review included Introduction, 7 sections, and Conclusions. The first section was devoted to the fundamental characteristics of diamondoids, and it contained data on the synthesis, chemical properties (functionalization), and physical properties (electronic structure, photoluminescence, optical and vibrational characteristics) of these compounds.

Two sections considered polymer nano- and metallonanocomposites with adamantane and diamantane fragments. Such polymers were obtained from



73 **74** **75**

m = 10, 16, 18, 20

Fig. 24. Poly(1,3-adamantylene alkylenes) **73** and their cycloaliphatic (**74**) and aromatic (**75**) analogs [169].

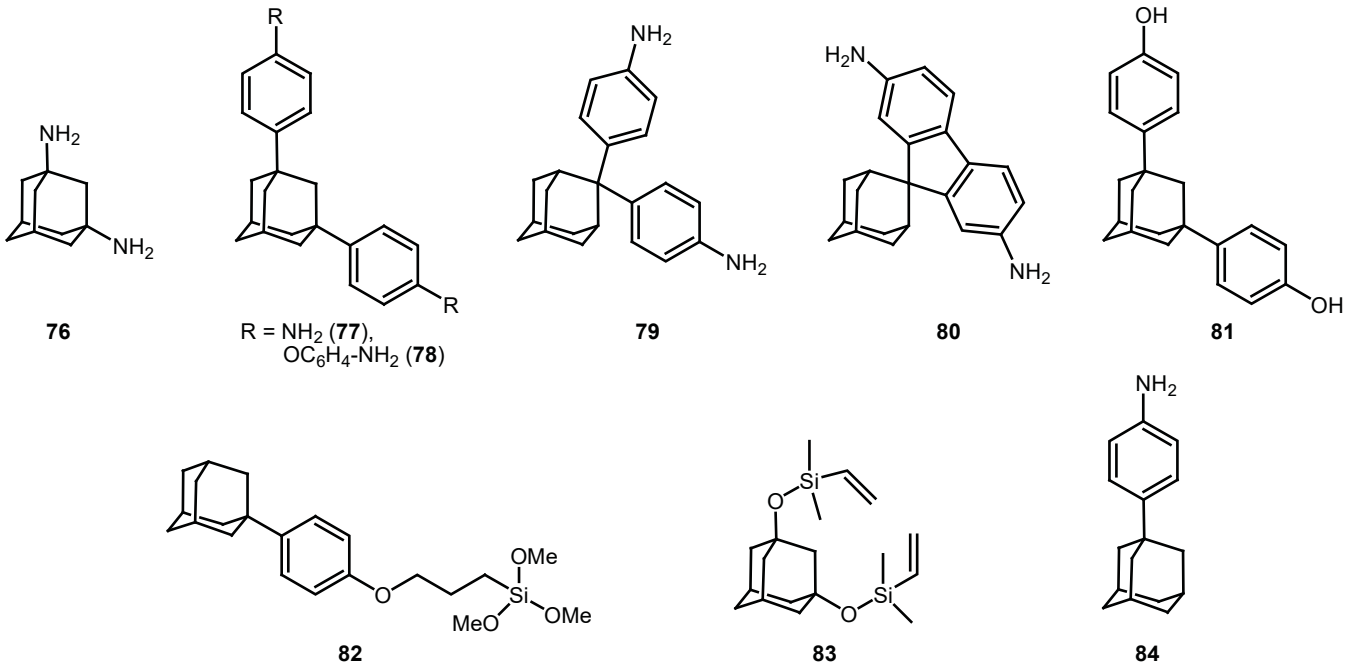


Fig. 25. Adamantane derivatives used in the synthesis of polymer nanocomposites [98].

mono- and disubstituted adamantanes with amino and oxygen-containing groups (Fig. 25). Polyimides based on 1,3-disubstituted adamantanes (diamines **76**–**78**), porous polyimides derived from 2,2-disubstituted derivatives **79** and **80**, epoxy resins based on 1,3-bis(4-hydroxyphenyl)adamantane (**81**), and polymeric materials obtained from silicon-containing derivatives **82** and **83** and 4-(adamantan-1-yl)aniline (**84**) were discussed. The dielectric constants (ε) of these polymers suggest prospects of using them in optoelectronics and semiconductor industry.

In addition to adamantane-containing polymers, the authors [98] considered polypropylene (RR) and polycarbonate (RS) nanocomposites with diamondoid fragments, which can be used as electron emitters, catalytic sensors, light-emitting materials, as well as in biotechnology, medicine, etc.; two examples are shown in Scheme 39 and Fig. 26. Scheme 39 shows disubsti-

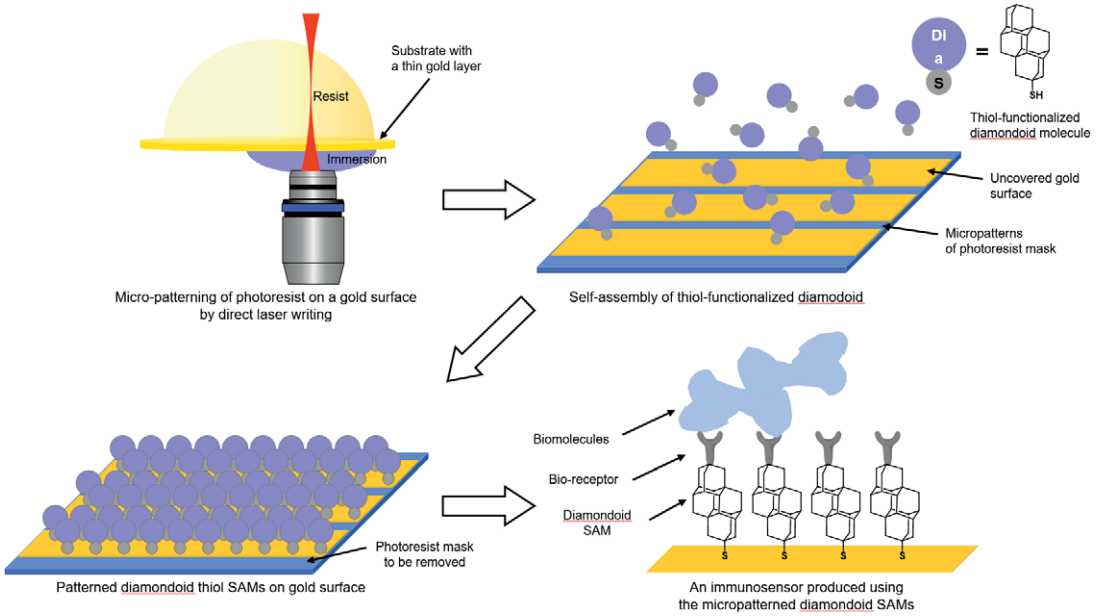
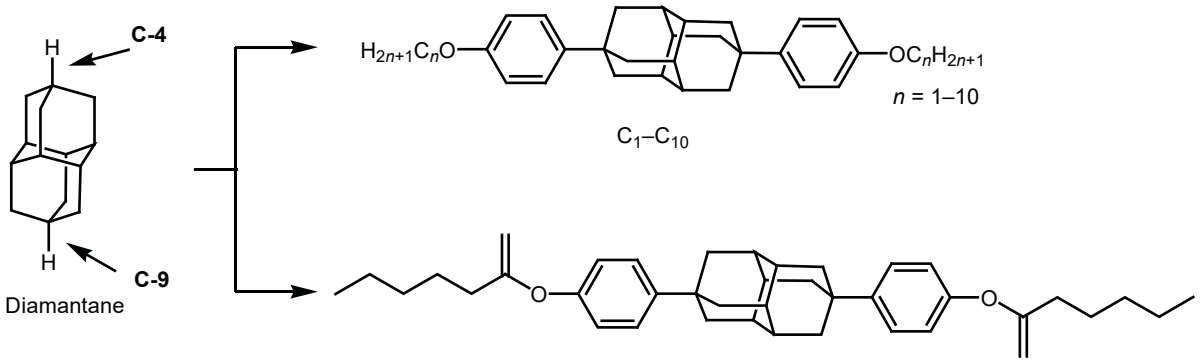


Fig. 26. Design of an immunosensor (**IS**) using micropatterned diamondoid SAMs. Modified from [98].

Scheme 39.



tuted diamantanes exhibiting thermotropic liquid crystal properties with excellent thermal stability. Figure 26 illustrates self-assembly of SH-functionalized [121]tetramantane and design of an immunosensore (**IS**) with the use of microstructured diamondoid self-assembled monolayers (SAMs).

5.2. Polyfunctional 1,3,5,7-Tetrasubstituted Adamantanes. Prospects for Practical Applications

In 2022, Belz et al. (Germany) [170] reported on adamantane derivatives as white-light emitters. It is known [171, 172] that materials based on adamantane-containing molecular cluster exhibit nonlinear optical properties whose origin is not clear. Several mechanisms have been proposed to explain this phenomenon by inter- and intramolecular interactions in the cluster. It was shown that transient Coulomb forces and selective functionalization of adamantane derivative with bromine could significantly affect intramolecular structural transformations and intermolecular rearrangements in the crystal. In this connection, the authors [170] studied the effect of electron and laser irradiation on the structure and nonlinear optical properties of 1,3,5,7-tetraphenyladamantane $AdPh_4$ and bromophenyladamantanes $AdBr_xPh_{4-x}$ (x = 0–4). Electronic excitation is a direct consequence of the arrangement of matter in real space, which in itself is determined by fundamental electromagnetic interaction (Coulomb force). Unshielded Coulomb interaction takes place under irradiation with (free) electrons.

The authors [170] observed the same behavior of tetraphenyladamantane regardless of the irradiation type, and its original intramolecular structure remained intact. In the case of bromo derivatives, Coulomb forces lead to a change of the intramolecular structure due to debromination. The polycrystalline intermolecular arrangement becomes disordered (amorphous) upon both electron and laser irradiation. As a result, nonlinear optical properties change: depending on the number of C–Br bonds, a transition from second-harmonic generation to continuous broadband radiation is observed. These findings are very important from the technological point of view for the design of structured white-light emitters, including clusters with inorganic cores.

Ligands with a molecular tripod structure, such as rigid 1,3,5,7-tetrasubstituted adamantanes containing three similar substituents at positions *1*, *3*, and *5* and a functional anchoring group, are capable of binding to various surfaces, e.g., metals (Ag, Au), metal oxides (TiO_2, ZrO_2), proteins, etc. As a result, self-assembled monolayers can be formed on a solid surface.

The chemistry of adamantane-based tripods (synthesis, properties, and possible uses) was the subject of an entire section of review [35] (2012). Figure 27 shows adamantane derivatives of two types, **A**, **B** and **C**, **D**, with different anchoring and chromophoric groups.

Compounds **A** and **B** were studied as potential electron carriers. Spectroscopic, electrochemical, and photoelectrochemical properties of their ruthenium complexes were studied in acetonitrile solution, as well as after aplying them onto medium-pore anatase (TiO_2) films and medium-pore colloidal ZrO_2 particles. It was found that fast and effective electron pumping to the TiO_2 surface occurred in the excited state. Photoelectrochemical study revealed the ability of complexes formed by tripods **A** to convert light into electrical energy [40, 41]. Tripods **C** and **D** covalently anchored through S–Au bond on a gold surface acted as sharp and stable stationary molecular probes whose configuration can reversibly change under irradiation with visible light (Fig. 28).

The data on specific interaction between the functional groups R in the *trans*-configured molecular

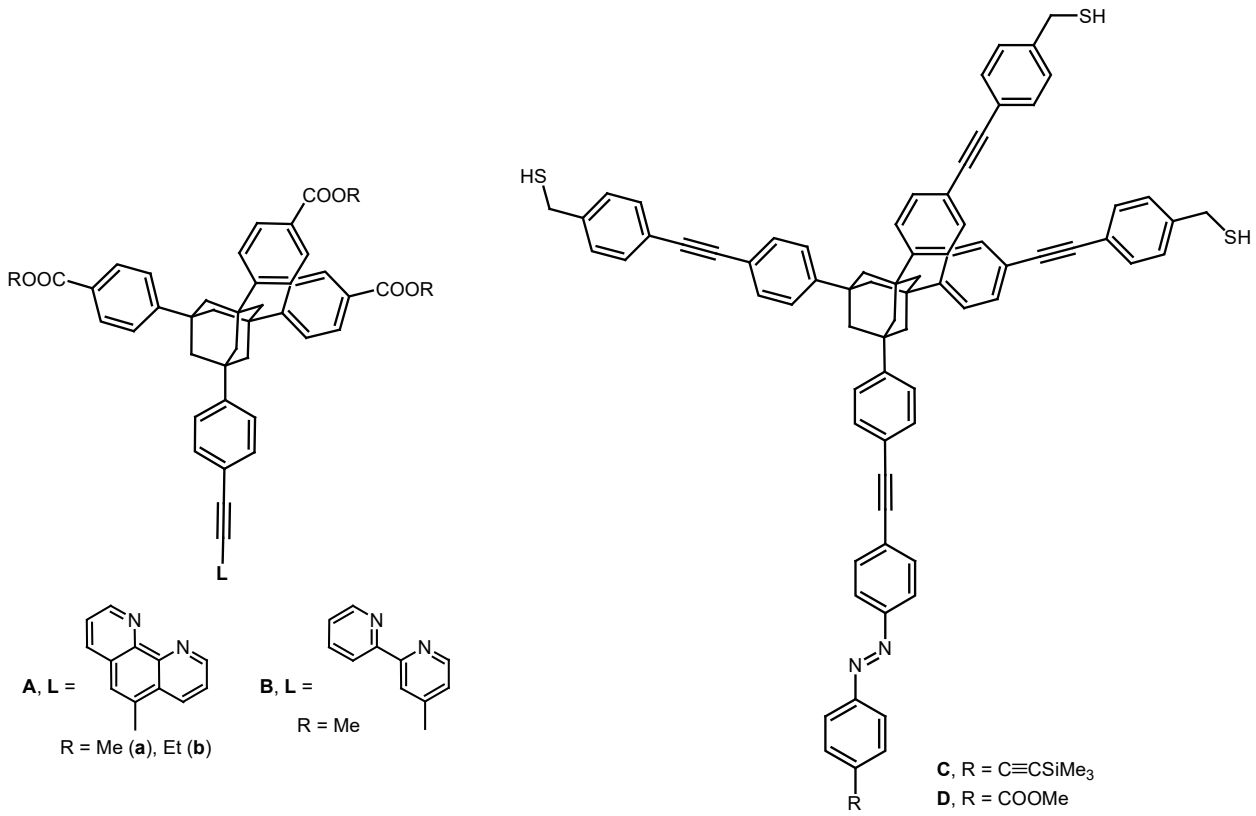


Fig. 27. 1,3,5,7-Tetrasubstituted adamantanes with a molecular tripod structure.

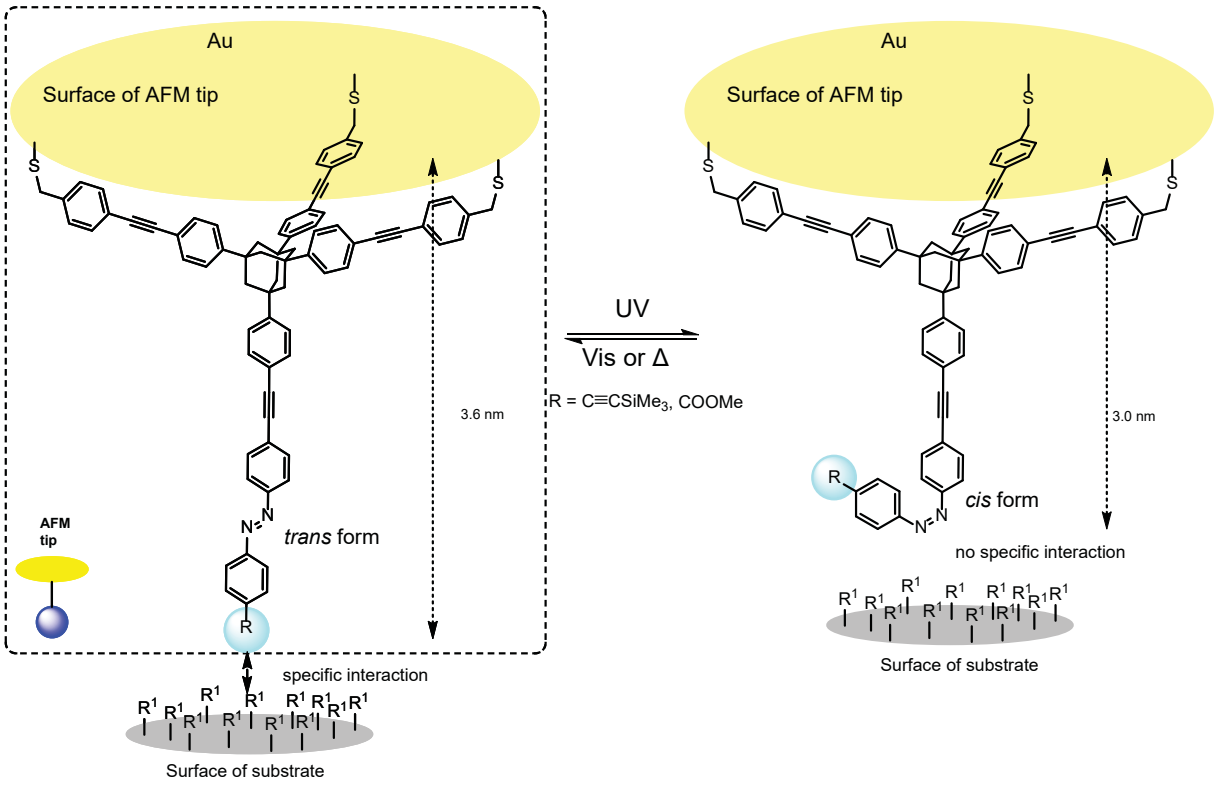


Fig. 28. Design of photoswitchable molecular probe for atomic force microscopy (AFM) [35].

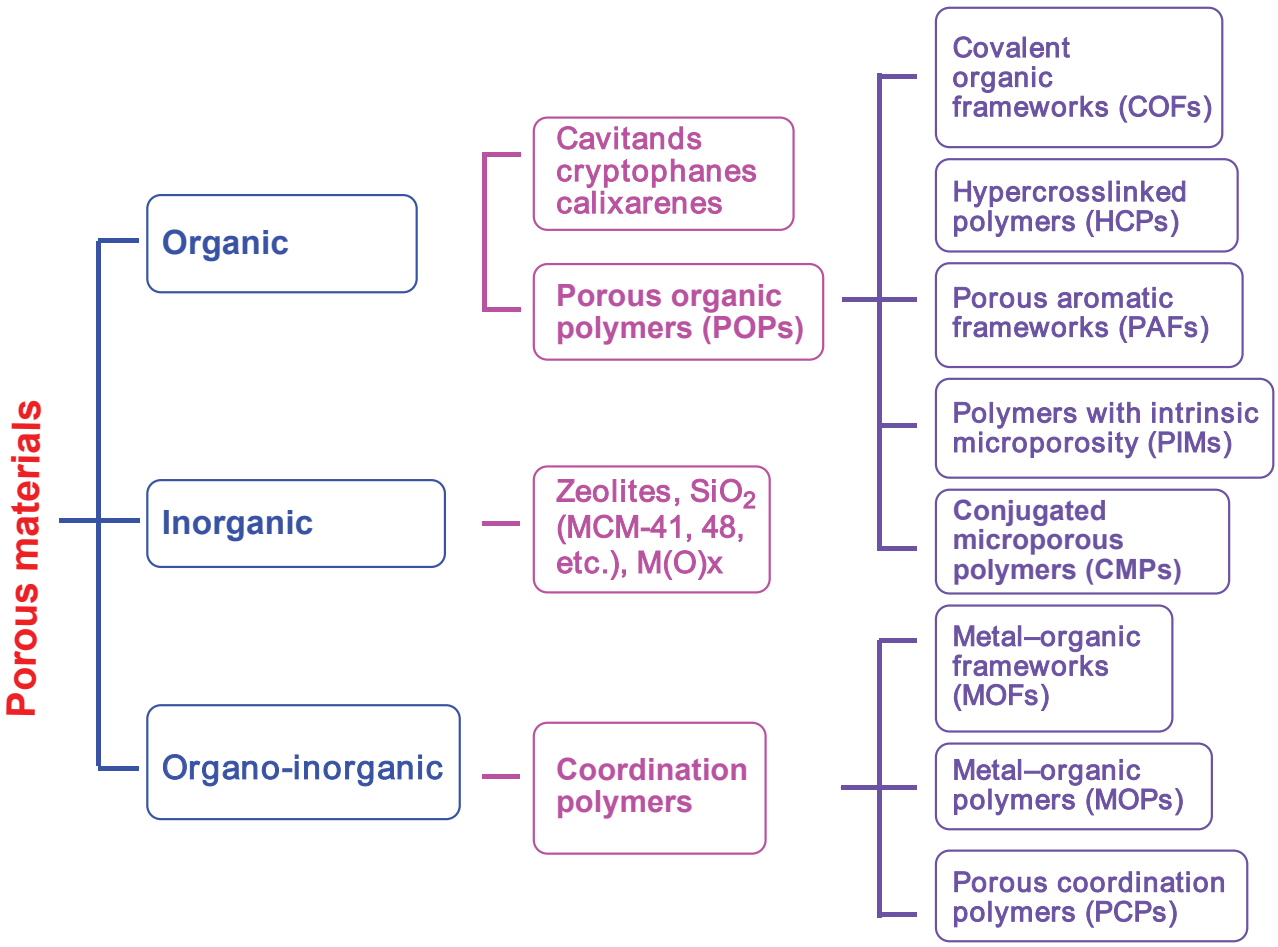


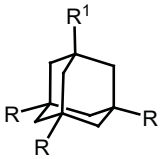
Fig. 29. Classification of porous materials according to the nature of building units. Depending on the pore size, microporous (<2 nm), mesoporous (2–50 nm), and macroporous materials (>50 nm) are distinguished. Adapted from [176].

probe and functional groups R^1 of the substrate surface may be useful for studying chemical properties of surfaces and ligand–receptor molecular recognition. Such interactions are the most important component of biological processes, including genome replication and transcription, enzymatic activity, immune response, initiation of infection, etc. Studies of these interactions are exceptionally important for the design of bioanalytical and biomedical equipment and various biosensors [173, 174].

In 2019, Nasrallah and Hierso (France) published a review [175] in which they considered synthetic approaches to three-dimensional (3D) porous supramolecular structures and nanomaterials (purely organic or within metal hybrid frameworks) based on polyhedral, mainly tetrahedral polyfunctional 1,3,5,7-tetrasubstituted adamantanes. The authors' classification of porous materials is presented in Fig. 29.

Review [175] is a well-systematized presentation of specific data available by 2018 on the synthesis of porous materials based on 3D-Td-adamantane scaffolds, 1,3,5,7-tetraamino- and 1,3,5,7-tetrakis(R-phenyl)adamantanes (Fig. 30) with ethynyl, ethenyl, and phenyl linkers and σ-donor coordinating phosphorus-containing groups in the aromatic moiety. Attention was drawn to the effect of the nature of functional substituents in the initial scaffold on the properties of porous material obtained therefrom (surface area, porosity, catalytic activity in homogeneous and chemo- and enantioselective reactions).

The unique geometry and high reactivity of the selected adamantane scaffolds opened wide prospects



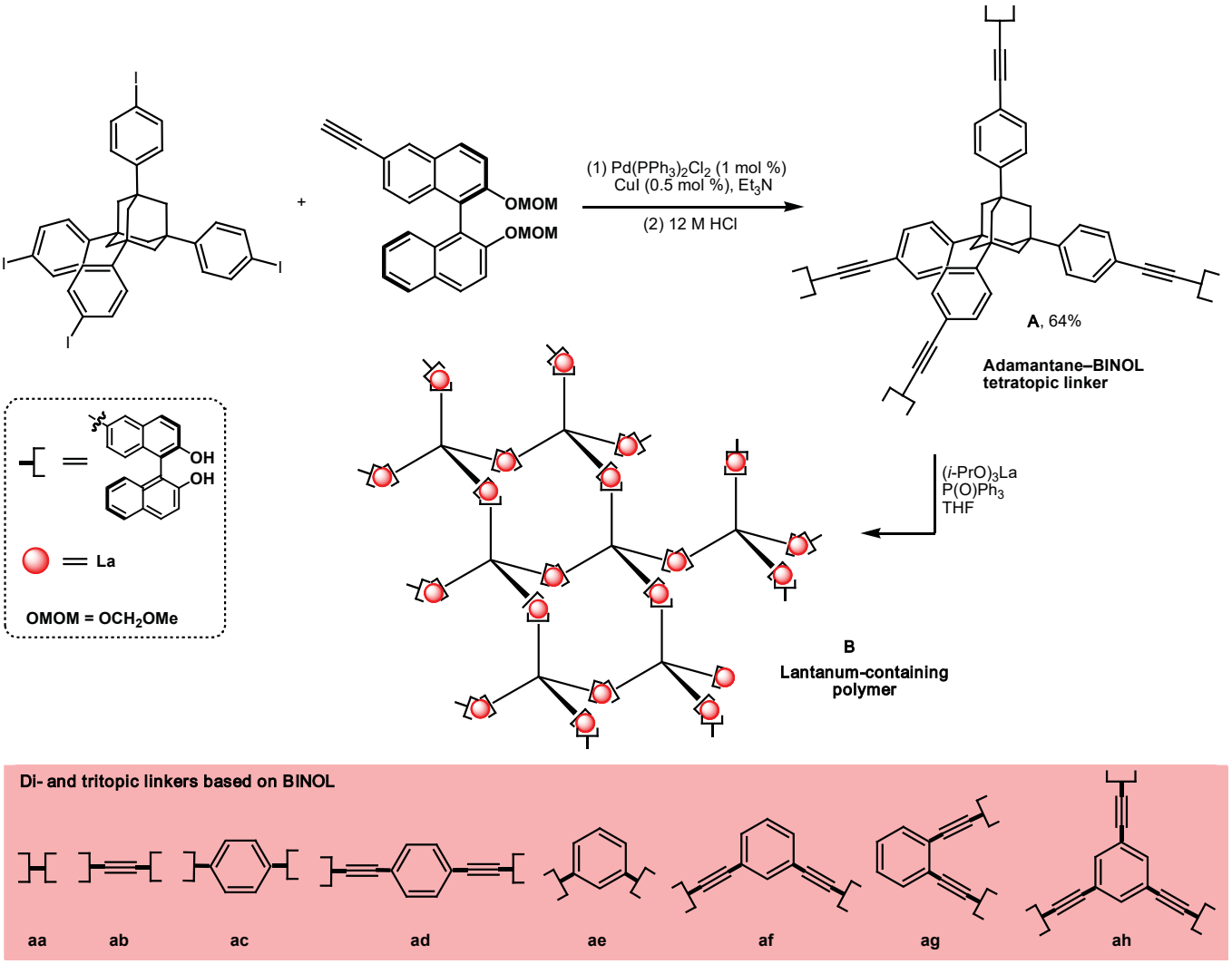
R^1 = H, R = Br, OH, COOH, NH_2, $\equiv$—CH_2OH, $(CH_2)_2CN$, $(CH_2)_2COOH$, $(CH_2)_2NH_2$, $(CH_2)_2OH$

R^1 = R = Br, NH_2, CN, COOH, Ph

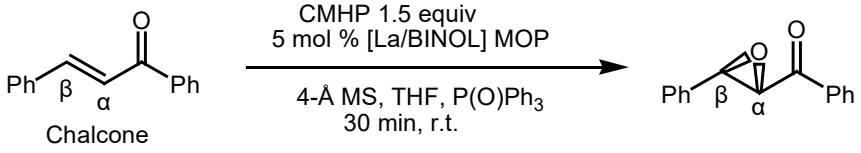
R^1 = R = 4-$R^2C_6H_4$ (R^2 = I, Br, NO_2, CHO, $COCH_3$, SO_2Cl)

Fig. 30. 1,3,5-Tri- and 1,3,5,7-tetrasubstituted adamantanes.

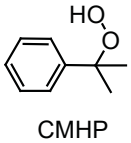
Scheme 40.



Scheme 41.

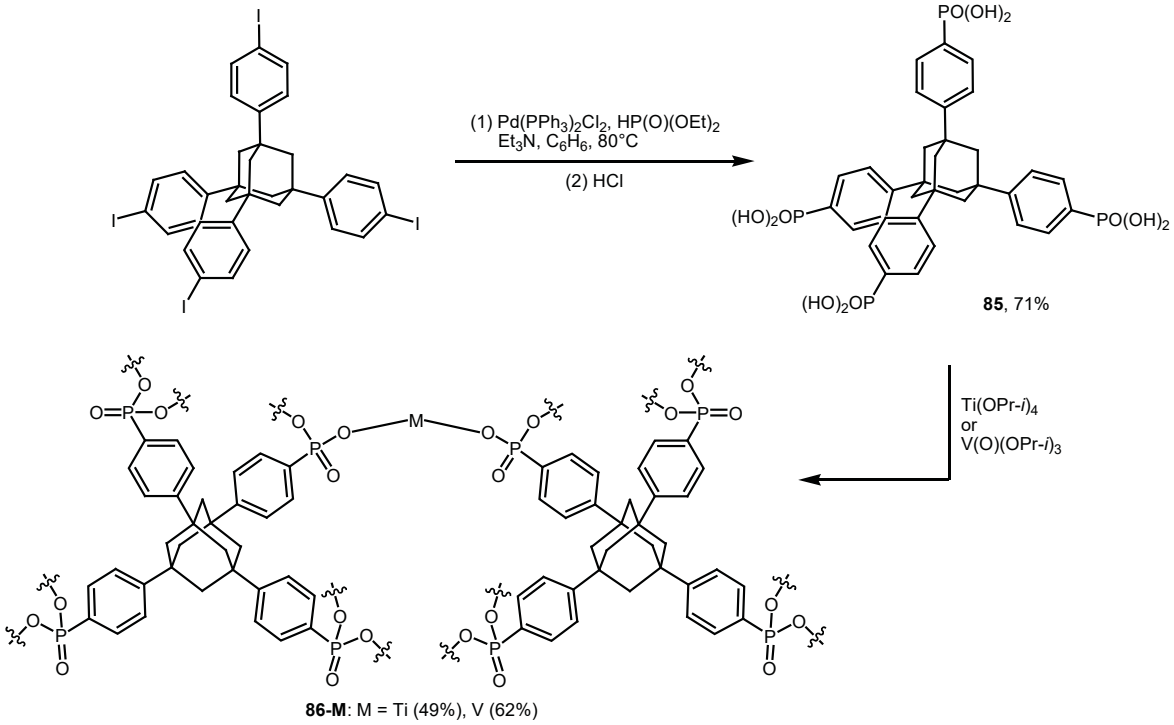


No.	Linker	Yield, %	*ee*, % (*R*,*S*)
1	**b**	99	95.0
2	**aa**	99	83.7
3	**ab**	99	82.9
4	**ac**	99	95.5
5	**ad**	99	97.6
6	**ae**	99	93.3
7	**af**	99	95.1
8	**ag**	99	84.2
9	**ah**	99	91.5

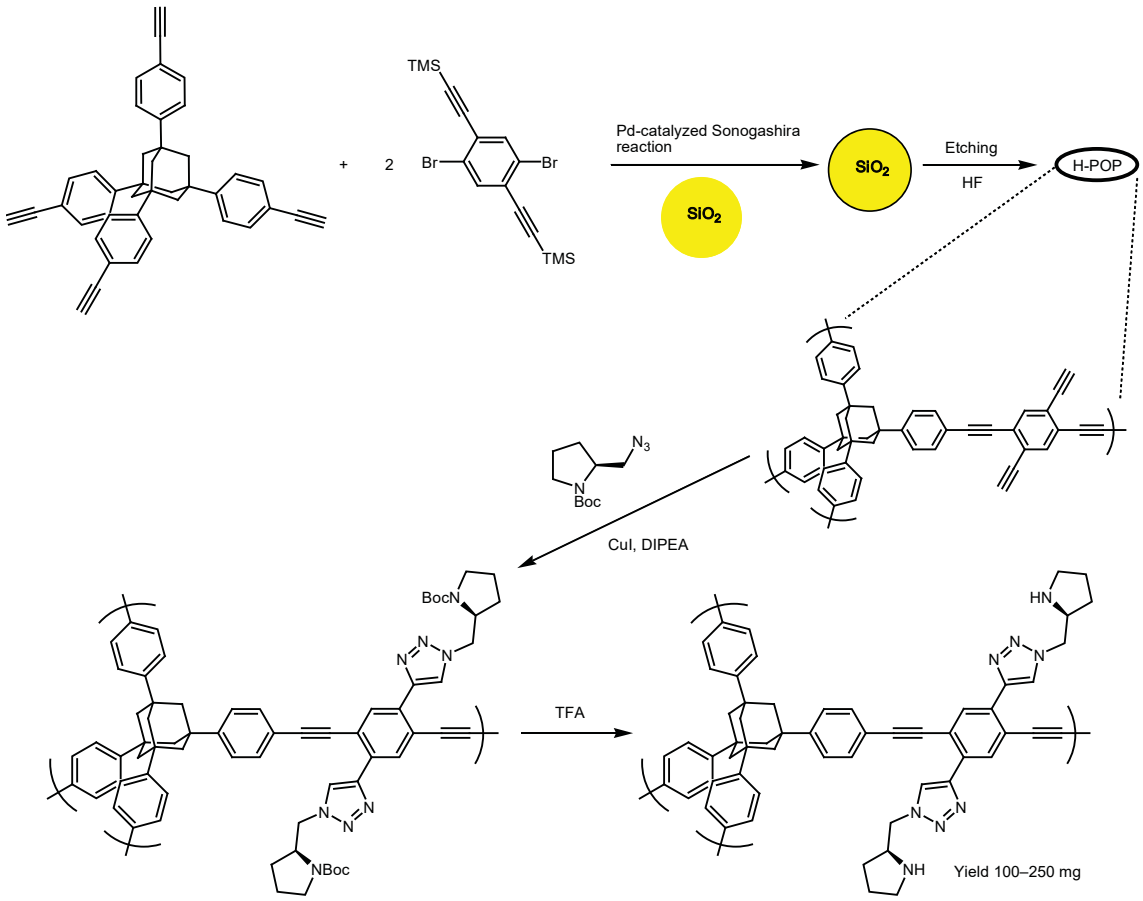


CMHP

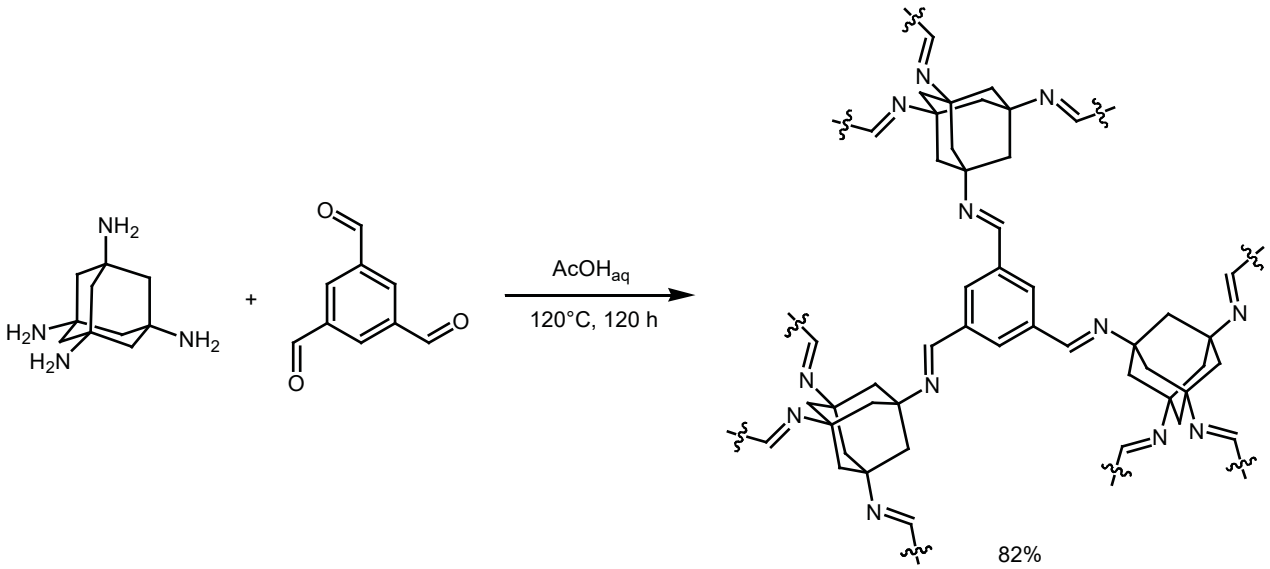
Scheme 42.



Scheme 43.



Scheme 44.



for obtaining porous materials. The latter can be prepared via efficient cross-coupling processes, including Sonogashira, Suzuki, Heck, and Ullmann reactions, as well as cobalt- and copper-catalyzed cycloadditions, coupling with peptides, radical cycloadditions, and reactions with polytopic linkers (benzenetrithiol, norbornadienediyl bistrifluoromethanesulfonate, phenylenediboronic acid, triformylbenzene, etc.)

As an example, Scheme 40 illustrates the synthesis of porous materials based on the tetraphenyladamantane scaffold with ethynyl linkers [177]. In particular, adamantane–BINOL linker (**A**), analogous derivatives with other di- and tritopic linkers (**aa**–**ah**), and the simplest lanthanum-containing polymer (**B**) are shown.

Scheme 41 shows the results of enantioselective epoxidation of chalcone (α,β-unsaturated ketone) with cumene hydroperoxide (CMHP) catalyzed by the synthesized La-containing polymer.

The authors [175] considered three families of porous materials derived from 3D-Td-adamantane ketones, which can be used as recyclable and reusable catalysts. The key points of the synthesis of some representatives of these families are shown in Schemes 42–44. Scheme 42 illustrates the synthesis of coordination polymers (CPs) with metal linkers. Depending on the method used, insoluble polymer **86-Ti** with a Ti/P ratio of ~1:1 to 1: 3.4 or **86-V** with a V/P ratio of 1:1 was obtained from tetrahedral ada-

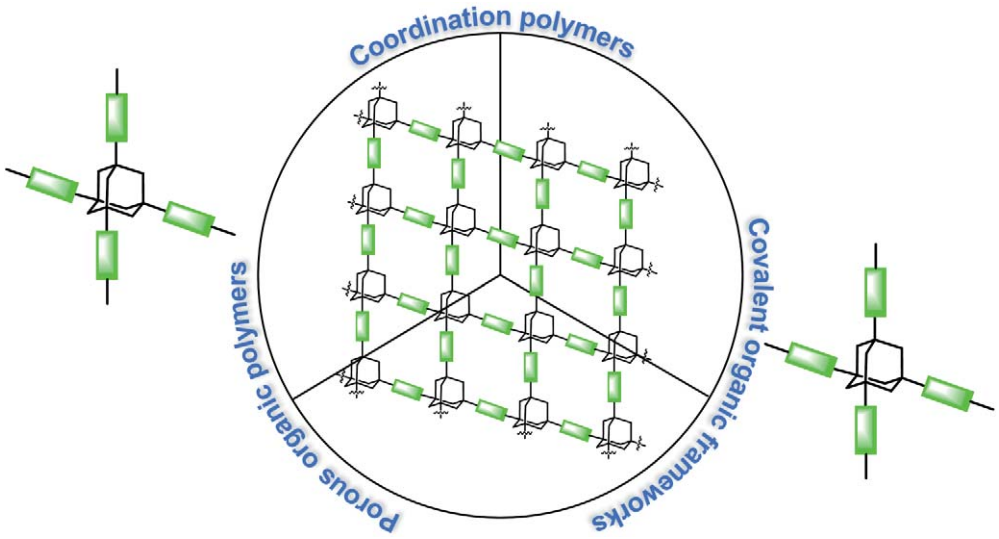


Fig. 31. Types of adamantane-based porous materials. Modified from [175].

mantane linker **85**. The second family included hollow porous organic polymers (POPs) which can be immobilized by metal complexes or encapsulated in metal nanoparticles; their synthesis is outlined in Scheme 43. The third family is represented mainly by well-defined covalent organic frameworks (COFs, Scheme 44).

Physical and chemical characteristics of adamantane-based porous materials were given, and prospects for their use were considered. The material presented in the review allows one not only to read it but, due to its specificity, punctuality, and completeness, to reproduce the entire process from adamantane to the desired product. The graphical abstract of the review is shown in Fig. 31.

CONCLUSIONS

The presented review is a jubilee one. Hundred years have passed since the scientific world heard the name of a compound that no one had seen – adamantane (from ancient Greek "diamond"). Ninety years ago, adamantane was found in oil and more than 20 years later it was obtained on an industrial scale. Since then, as before, adamantane has not ceased to amaze researchers with the unpredictability of its behavior, opening up new prospects for its use. The chemistry of adamantane is a subject of study not only by chemists, but increasingly by researchers in other fields: medicine, biology, physics, technology, etc. We hope that the presented review confirms this.

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FUNDING

This review was written according to state assignment "Petrochemistry and Catalysis. Rational Use of Hydrocarbon Raw Materials" (project no. 121031300092-6).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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