Triflamides and Triflimides: Synthesis and Applications

Mikhail Y. Moskalik * and Vera V. Astakhova

Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russia
* Correspondence: moskalik@irioch.irk.ru

Abstract: Among the variety of sulfonamides, triflamides (CF$_3$SO$_2$NHR, TfNHR) occupy a special position in organic chemistry. Triflamides are widely used as reagents, efficient catalysts or additives in numerous reactions. The reasons for the widespread use of these compounds are their high NH-acidity, lipophilicity, catalytic activity and specific chemical properties. Their strong electron-withdrawing properties and low nucleophilicity, combined with their high NH-acidity, makes it possible to use triflamides in a vast variety of organic reactions. This review is devoted to the synthesis and use of N-trifluoromethanesulfonyl derivatives in organic chemistry, medicine, biochemistry, catalysis and agriculture. Part of the work is a review of areas and examples of the use of bis(trifluoromethanesulfonyl)imide (triflimide, (CF$_3$SO$_2$)$_2$NH, Tf$_2$NH). Being one of the strongest NH-acids, triflimide, and especially its salts, are widely used as catalysts in cycloaddition reactions, Friedel–Crafts reactions, condensation reactions, heterocyclization and many others. Triflamides act as a source of nitrogen in C-amination (sulfonamidation) reactions, the products of which are useful building blocks in organic synthesis, catalysts and ligands in metal complex catalysis, and have found applications in medicine. The addition reactions of triflimide in the presence of oxidizing agents to alkenes and dienes are considered separately.

Keywords: triflimide; triflamide; amination; heterocyclization; NH-acids; sulfonamidation; coupling; biological activity

1. Introduction

Over the past 2–3 decades, N-Trifluoromethanesulfonylamides (CF$_3$SO$_2$NHR, TfNHR) have found wide application in organic synthesis as reagents, catalysts, additives and as substituents that transform reactivity and biological activity in a wide range of substrates. The chemistry of triflamide and triflimide derivatives was the subject of several early reviews [1,2], which confirms the high interest in such compounds. Having a strong electron-withdrawing CF$_3$SO$_2$-group in their structure, triflamides are among the strongest NH-acids ($pK_a$ in H$_2$O) for TfNH$_2$ is 6.33, $pK_a$ (in H$_2$O) for Tf$_2$NH is 2.8 [1]). This property determines the use of triflamides in organic synthesis, in the production of biologically and pharmacologically active substances and in various industries. One of the most important properties of triflamide derivatives in terms of biological activity is their lipophilicity. Triflamides are widely used in the production of lithium–sulfur batteries, where N,N-dialkyl-substituted triflamide (dimethyl- or dipropyl-) is present as a solvent in the electrolyte [3]. In organic synthesis, catalysts containing a trifluoromethanesulfonyamide or imide moiety are used (Michael [4], Friedel–Crafts [5], Diels–Alder [6], Mannich [7] and many other reactions).
This review is devoted to the latest progress in the field of applications of triflimide in organic synthesis as an active catalyst. The review also includes the reactions of triflimide and its derivatives (metal salts). As a catalyst/co-catalyst based on the TfN-salts of metals (Au, Ag, Fe, Li, Ca), triflimide has found application in a wide range of addition reactions, cycloaddition, intramolecular cyclization, CH-amidation, etc. TfNH is often used as an additive to the reaction medium, for example, in the synthesis of spiroheteropolycyclic compounds [8,9] and nitrogen-containing heterocycles [10], in catalytic (3 + 2)-annelation [11], in the oxidative synthesis of hydrodibenzofurans [12] and in condensed 2,8-O,O- or O,N-bicyclo[3.3.1]nonanes [13]. The triflimide anion is a counterion for the production of low-melting ionic liquids, used to stabilize nanoparticles, which are used in various fields, including medicine, sensors, optics and the aerospace industry [14,15]. On the basis of triflimide, various types of extractants and ionic liquids with organic cations have been obtained, which are used to isolate lanthanides and actinides from liquid waste; for example, from spent nuclear fuel [16,17].

The triflimide moiety is introduced in organic molecules in two ways. The first way is the reaction of a substrate with the activated TfNH sulphonamide molecule. The second method is the treatment with trifluoromethanesulfonic acid anhydride or halides of the corresponding N-nucleophiles, which, as a rule, require low temperatures and the presence of additional bases.

2. Triflimide as a Catalyst in Organic Synthesis

Triflimide (TfNH) is used as a catalytic additive in the formation of C-C and C-heteroatom bonds, due to its strong acidity, as well as its good compatibility with various organic solvents [18]. It has been widely used as a Brønsted acid for the catalysis of Friedel–Crafts reactions [19–24] and cycloaddition reactions [25,26]. In addition, triflimide is used as a Brønsted acid, for example, to obtain various bis-arylated amides from vinyl azides in moderate to quantitative yields [27] or in the hydroalkylation of arylalkenes with activated alcohols [28]. In a series of works, Ye et al. proposed different approaches to the cyclization of ynamides initiated by TfNH, which were applied to the synthesis of functionalized heterocyclic compounds [29–33].

For example, the cascade cyclization of ynamides 2 having an allyl ether moiety in the molecule made it possible to obtain various highly functionalized 3-isochromanones 3 via intramolecular alkoxylation in good to quantitative yields (68–99%) under mild conditions (Scheme 1) [30]:

![Scheme 1](image)

Based on these works, it was proposed to activate simple alkynes and to synthesize a number of highly functionalized isoindolinones [34]. The intramolecular TfNH-initiated cascade cyclization of N-methoxybenzamides 4 gives rise to the formation of fused chromanes or isoindolinones 5 in good yields and with a high regioselectivity (Scheme 2). The reaction meets the requirements of green chemistry by providing an atom-economical alternative to transition metal catalysis.
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Scheme 2. Intramolecular cyclization of N-methoxybenzamides in the presence of Tf$_2$NH.

Frontier et al. [35] described a simple intermolecular reaction of the carboamination of alkenyls 6 with cyclic aminals 7 in the absence of metal-based catalysts. Acidic conditions (Tf$_2$NH) allowed it to stereoselectively synthesize ether-condensed cyclic enamines 8.

The proposed reaction mechanism involves the formation of aminals by combining alkenyls with aminals via the capture of iminium ions. Aminals give oxonium ions and vinyl cations, respectively, through the ring opening and subsequent reaction with alkyne. Finally, the intramolecular amination leads to the formation of cyclic enamines. Various bicyclic heterocycles were obtained in a good yield and with good diastereoselectivity (Scheme 3):

The one-pot assembling of the 9,10-dihydroacridine scaffolds 11 used in OLED devices was achieved by the selective ortho-C-alkenylation of diarylamines 10 with arylalkynes 9 followed by the intramolecular hydroarylation of the olefin formed as an intermediate. The reaction was carried out in hexafluoropropanol with triflimide as a catalyst which launched the reaction (Scheme 4) [36]:

Scheme 4. One-pot assembly of 9,10-dihydroacridine scaffolds.
Arylalkynes with electron-donating groups in the para-position give 9,10-substituted dihydroacridines in a 73 to 98% yield. Noteworthy, in the case of the nitrile and nitro groups, a complete conversion of the starting alkyne is achieved only at high temperatures of the reaction mixture. The effect of the diarylamine structure on the course of the reaction was also investigated, and it was shown that the presence of electron-donating or electron-withdrawing groups only slightly affected the yield, as the target products were obtained in 57–95% yields.

An efficient method was developed for the nucleophilic introduction of a difluorinated carbanion (from 13) into α,β-enones with the formation of 2,2-difluoro-1,5-diketones 14, the regioselectivity of the reaction being determined by the TMSNTf₂ (silylbistriflimide) or Tf₂NH catalyst. It is the strong electron-withdrawing properties and bulky substituents in the TMSNTf₂ generated in situ that were responsible for the 1,4-addition route. 2,4,6-Triaryl-substituted 3-fluoropyridines 15 can be obtained by the one-pot method (Scheme 5) [37]:

![Scheme 5. Difluoroalkylation of α,β-enones in the presence of TMSNTf₂ or Tf₂NH.](image)

However, with other bulky catalysts, such as trimethylsilyl trifluoromethylsulphonate (TMSOTf) or tert-butylidimethylsilyl trifluoromethanesulphonate (TBSOTf), which are also effective in this reaction, 1,2-addition by-products are also formed as minor admixtures. The electronic effects of the substituents in α,β-enone do not affect the yield of the products. The yield is slightly reduced in the presence of bulky substituents.

Triflimide is used in some cyclization in Diels–Alder reactions of 4-oxopent-2-enoates [38], in Michael addition reactions to substitute 3-vinyl-1,2,4-triazines and the subsequent cyclization to tetrahydro-[1,6]-naphthylpyridines [39] and in the synthesis of 2,3-dihydro-1H-benzo[e]indoles and 2,3-dihydrobenzofurans using Tf₂NH. The yield of the latter was 64% (with Tf₂NH) but while using In(OTf)₃, the yield increased to 80% [40]. The synthesis of mono- and bis-γ-lactams by the Mannich method (the addition of 2,5-bis(trimethylsilyloxy)furan to imines) occurs in good yields in the presence triflimide [41]. The intramolecular hydroacyloxylation of non-activated alkenes proceeds well in hexafluoropropanol not only with triflimide, but also in the presence of Ca(NTF₂)₂·nBu₄NPF₆ [42]. The aromatization of dibenzonorcaradienes to dibenzo[f,h]isocoumarins proceeds with TfOH in yields up to 99%. Replacing the triflic acid with triflimide also showed excellent results, affording the products in a 95–98% yield [43]. Enantioselective (4 + 2)-cycloaddition in the presence of triflimide gives chiral 1,2-amino alcohols, 1,2-diamines and β-amino acids in yields of 92–98% [44].

The Tf₂NH-catalyzed (3,3)-sulfonyl rearrangement of vinyl sulfoxides 17 or 18 in the presence of ynamides 16 is an enantioselective and stereodivergent strategy for the synthesis of acyclic polysubstituted 1,4-dicarboxyls 19 or 20 (Scheme 6) [45]:
Scheme 6. Reaction of vinyl sulfoxides with ynamides in the presence of Tf₂NH in water.

The catalytic aldol reaction of silyl enol ethers is a universal method for C-C bond formation. Gati et al. [46] proposed the triflimide catalyzed syn-stereoselective aldol reaction for the synthesis of α,β-dioxyaldehydes 23 and 1,2,3-triols 24 from (Z)-tris(trimethylsilyl)silyl enol ethers 21 and aldehydes 22 (Scheme 7):

Scheme 7. Aldol reaction of (Z)-tris(trimethylsilyl)silyl enol ethers in the presence of triflimide.

Iodobenzene acts as a co-catalyst that stabilizes the silylenium cation formed in situ, because the additive seemed to be playing a critical role in affecting the rate of the reaction.

The Mukaiyama aldol reaction in the presence of “supersilyl” tris(trimethylsilyl)silyl enol ethers 26 with ketone 25 leads diastereoselectively to α,β-dioxyaldehydes, whereas the same reaction in the presence of Tf₂NH 1 (the reaction of silyketene acetal with ketones) leads to siloxycarbonyl compound 28 [47] (Scheme 8):

Scheme 8. Mukaiyama aldol reaction in the presence of Tf₂NH.

This efficient methodology allows for a rapid and stereoselective construction of mono-, bis- and tris-hydroxyaldehydes by mono-, double- and triple-cross-aldol processes, respectively, to produce polyketide-like scaffolds that are particularly useful for the construction of complex natural polyketides [47].

The Peterson olefination in the presence of triflimide 1 [48], as well as the synthesis of α-CF₃ and α-CF₃H amines 30 by the aminofluorination of gem-difluoroalkanes and monofluoroalkenes 29, respectively, was described (Scheme 9) [49]. Selectfluor was used as a source of electrophilic fluorine and acetonitrile as a source of nitrogen.
Scheme 9. Peterson olefination and aminofluorination of gem-difluoroalkenes and monofluoroalkenes in the presence of Tf\(\text{NH}\).

Triflimide 1 is used as a catalyst in the isoprenylation of aliphatic aldehydes via the (3,3)-sigmatropic rearrangement of N-Boc-N-(1,1-dimethylallyl)hydrazones [50], in the synthesis of amides from vinyl azides and alcohols [51] and in the rearrangement of N-(1-trimethylsilyl)allylhydrazones with the formation of the corresponding vinylsilanes and cyclopropanes [52]. In addition, triflimide activates the silylum catalyst in the reactions of the selective functionalization of azines with the formation of \(N\)-silylated dihydro- pyridines [53]. A number of works can be mentioned in which Tf\(\text{NH}\) was successfully used as a catalyst. These include the synthesis of poly-L-lactide in CO\(\text{2}\) under plasticization conditions [54], the nucleophilic C-arylation of halopurines leading to \(N7\)-substituted purine biaryls [55], reactions of the diastereoselective intramolecular hydride shift in the presence of alkenes [56], the preparation of amides from vinyl azides and alcohols [50], the synthesis of polysubstituted naphthalenes by the reaction of aryldiacetaldehydes with alkynes (benzylation reaction) [57,58], glycosylation reactions [59], three-component regioselective synthesis of tetrahydrofuro[2,3-d]oxazoles [60], etc.

3. Triflimide Derivatives in Organic Synthesis

3.1. AgNTf\(_2\)

The direct C–H amidation of substituted benzamides 31 with trichloroethoxycarbonyl azide (TrocN\(_3\)) 32 was reported in the presence of AgNTf\(_2\) 33 [61]. When cesium acetate is added, the reactions proceed efficiently and with high regioselectivity, affording various functionalized quinazoline-2,4(1H,3H)-diones 34, which are important building blocks and key synthetic intermediates from a biological and medical point of view. During the reactions, two new C-N bonds are formed by the successive rupture of the C-H and N-H bonds (Scheme 10).

![Diagram of reaction](image-url)

**Scheme 10.** Cyclization of ortho- and para-substituted benzamides 31 with trichloroethoxycarbonyl azide 32 in the presence of a complex based on silver triflimide 33.
N-Alkylated benzamides 31 with electron-withdrawing or -donating groups in the para-position of the phenyl ring cyclize to the corresponding products in good yields. In the same way proceeds the regioselective C-H amidation of meta-substituted benzamides 31. However, substituents in the meta position affect both the steric hindrances and electron density of the reaction center of the substrate [61]. Catalysis by chiral cyclopentadienyl complexes of iridium in combination with AgNTf₂:33 is used for CH-arylation of tetralone derivatives with arylboronic esters [63].

The diastereoselective synthesis of spirocyclic pyrrole-2-one-dienone systems was conducted in the presence of AgNTf₂:33 in combination with a gold-based complex [64]. A similar procedure was used for the synthesis of diarylmethine-substituted enones [65]. The combination of AgNTf₂:33 and the AuCl-based ligand was also successfully used in the cycloisomerization of 1,6-enzyme to 3-azabicyclo[4.1.0]heptene [66], as well as in the asymmetric synthesis of fused bicyclic N,O- and O,O-acetals [67]. The (C₆F₅)$_3$PAuCl/AgNTf₂ catalyzed cyclization of N-tosyl-protected 5-benzyl-6-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydropyridines obtained by the Sonogashira reaction in the presence of enol triflate lactam derivatives gives tetrahydrobenzo[g]quinolines, the skeletal framework of which is a recurring motif in natural products [68].

In 2019, an efficient and stereoselective method was developed for the synthesis of (Z)-β-halogenated enamides by the Ritter type Au-catalyzed reaction in the presence of BrettPhosAuCl and AgNTf₂:33 using haloalkynes as substrates [69]. The regioselectivity of the reaction was controlled by bulky substituents in the substrates. Other combinations of AgNTf₂: with Au⁺-based complexes also showed the efficiency in various processes, for example, in the [4 + 3]-annelation of anthranils with 1,5-enzyme to form tetrahydrobenzoazepine derivatives [70,71]. The chemoselectivity of the reaction depended on the type of the used alkyne. Silver triflimide AgNTf₂:33 was used in one of the stages of the synthesis of new fluorinated symmetric and asymmetric imidazolium salts, as well as of their complexes with various metals [72] and in the diastereoselective synthesis of benzo[5,6]oxepino[2,3-c]pyrroles via the [5 + 2]-annelation of the donor–acceptor type of arylinylidyazosuccinimide with ketones [73]. The iodination reaction of a wide range of arenes (derivatives of anisole, aniline, acetanilide and phenol) in the presence of AgNTf₂:33 and N-iodosuccinimide is known [74].

3.2. Gold Triflimide

Gold triflimides 35 are widely used in organic synthesis. Gold α-iminocarbene complexes have demonstrated good catalytic efficiency in the synthesis of N-heterocycles in the last few years [75]. [1,3]Dioxino[5,4-b]indoles 38 have been synthesized by the [4 + 2]-cycloaddition of the 3-indolylidene-Au-carbenium intermediate 39 to aldehydes 37 (Scheme 11). The reaction presumably occurs due to the presence of a hydroxyl group in the starting 3-(2-azidophenyl)prop-2-yn-1-ols 36. On the other hand, the presence of electron-withdrawing groups such as 3,5-dichloro or 3-cyano in the phenyl ring facilitates the reaction by excluding the competitive attack by the gold-activated alkyne:
Scheme 11. Preparation of [1,3]dioxino[5,4-b]indole derivatives.

A number of syntheses of the oxazino- [76] and pyrazinoindoles [77], pyrroloindoles [78], carbazoles condensed with benzofuran, 1,3H-dibenzo[a,h]carbazoles [79], pyridine derivatives [80], pyrroles [81–85], azipines [86] and other polycyclic compounds [87–93] are known in the literature. In contrast to intramolecular reactions, less is known about the intermolecular formation of gold carbene α-imino intermediates. Nevertheless, these reactions were applied to the synthesis of α,β-unsaturated amidines [94] or 2-amino-pyrroles [95] using highly polarized alkynes, for example, ynamides.

In the presence of Ph3PAuNTf2: 35, the regioselective functionalization of arenes and heteroarenes (derivatives of benzenes, phenols, ethers, indoles, pyrroles, furans and thiophenes) 43 with acetylenes 41 was performed using N-alkenoxypyridinium salt 42 as electrophilic alkylating agents for the synthesis of α-aryl- and heteroaryl ketones 44 (Scheme 12) [96]:

Scheme 12. Regioselective functionalization of arenes and heteroarenes to α-aryl- and α-heteroaryl ketones.

N-O bond cleavage might occur prior to the attack by the arene. After N-O bond cleavage, an electrophilic carbocation species is likely produced [96].

Using Ph3PAuNTf2: 35 makes it possible to synthesize the derivatives of 2-substituted 4-oxo-4-arylbutanal from alkynes and vinyl sulfoxide; five-, six- and seven-membered cycloalkyl-1-ones, for example, the derivatives of tetrahydrocycloalkyl[b]pyrrole, which are pharmaceutical structural units, were easily obtained from 1-cycloalkenyl sulfoxides [97]. The use of Ph3PAuNTf2: 35 allowed it to synthesize cyclohept[b]pyrroles from diynes and pyrroles [98] and to perform glycosylation reactions [99,100]. The combination of Ph3PAuNTf2: 35 with N-iodosuccinimide made it possible to develop a highly efficient synthesis of arenes labeled with radioactive iodine. The reaction represents the first example of the use of homogeneous catalysis in selective synthesis using radioactive materials.
The method was used to obtain meta-[\textsuperscript{\textsuperscript{[25]}\textsuperscript{I}]}iodobenzylguanidine, a radiopharmaceutical used for imaging and tumor therapy \cite{101}.

The synthesis of unsymmetrical esters using benzyl, \(t\)-butyl alcohols as alkylating reagents, also catalyzed by Ph\textsubscript{3}PAuNTf\(_2\): 35, was described \cite{102}. An interesting type of reactions proceeding in the presence of gold triflimides complexes are the so-called NT-reactions (\textit{Nitrene Transfer Reaction}). Among various NTRs, in a vast majority of studies, the azides, azirines, isoxazoles, anthranils, pyridinium azaylides and sulfilimines were used as the reagents. These reactions exhibit different activity and selectivity, depending on the chemical nature of the reactants. However, some of the NTRs have significant disadvantages. For example, azides are potentially explosive, and the ylides are poorly reactive in the gold-catalyzed reactions and are not easily available. Shcherbakov et al. \cite{103} have recently demonstrated the gold catalyzed nitrene transfer reaction from benzofuroxans 45 to \(N\)-allylynamides 46, resulting in the formation of various 3-azabicyclo[3.1.0]hexanes 47 (Scheme 13):

![Scheme 13. Synthesis of 3 azabicyclo[3.1.0]hexanes from benzofuroxans and \(N\)-allylynamides catalyzed by Au\textsuperscript{+}](image)

EWG = Ts, Ms, Bs, Ns, PhSO\(_2\), p-FC\(_6\)H\(_4\)SO\(_2\), R\(_1\) = H; 3,4-Me, 4-MeO, 4-Cl, R\(_2\) = Ph, p-MeC\(_6\)H\(_4\), p-MeOC\(_6\)H\(_4\), p-BrC\(_6\)H\(_4\), p-CF\(_3\)C\(_6\)H\(_4\), o-MeC\(_6\)H\(_4\), R\(_3\) = H, Ph

This highly selective annulation occurs under mild conditions (5 mol \% Ph\textsubscript{3}PAuNTf\(_2\), PhCl, 60 °C) and is applicable to substrates with various functional groups (21 examples, yield \(\leq 96\%)\) \cite{103}.

\[\text{3.3. LiNTf}_2, \text{Cat(NTF)}_2\text{, and Fe(NTF)}_2\text{)}\]

In the presence of LiNTf\(_2\): 48, various oxetanes are efficiently opened by C-nucleophiles; for example, silylketene acetics under these conditions give a spectrum of saturated 1,5-oxygen-containing molecules that are part of many natural compounds (for example, polyketides) \cite{104}. It should be noted that when LiNTf\(_2\) is replaced by TBSNTf\(_2\): (TBS = \textit{tert}-butyldimethylsilyl) as a catalyst, the reaction leads to the formation of 1,3,7-oxygen-containing products \cite{104}.

The formation of oxetane ethers 51–52 under the conditions of the Friedel–Crafts reaction between oxetanols 49 and phenols 50 in the presence of LiNTf\(_2\) was studied in detail by Bull et al. \cite{105}. The introduction of \textit{para}-substituents in the phenyl ring shows a direct dependence of the reaction course and the structure of the products on the nature of the nucleophile, namely, the formation of the kinetic products of O-alkylation versus the thermodynamic products of C-alkylation 53 (Scheme 14) \cite{105}:
Scheme 14. Friedel–Crafts reaction of oxetanols and phenols in the presence of LiNTf₂.

For electron-deficient 4-cyanophenol, the only observed product was the product of O-alkylation, while for \( X = \text{halogen and electron-releasing substituents, after 1 h, a mixture of C- and O-alkylated products was formed, and after 20 h, only the C-alkylation products were observed in the mixture. In addition, a number of oxetane ester derivatives were isolated, which are new potential bioisosteres for esters of carboxylic acids [105]. When the reaction was monitored using \(^1\)H NMR spectroscopy without a nucleophile present, a rapid degradation of the starting material occurred. A small amount of an aldehyde side product was identified; however, the majority of the material was unaccounted for. An insoluble precipitate was observed, indicating the possible formation of a polymeric species under the reaction conditions resulting from ring opening of the oxetane, promoted by the formation of the oxetane carbocation in the absence of a better nucleophile than the substrate itself [105].

The chemo-, regio- and stereoselective addition of triflimide (from LiNTf₂) to alkynes 54 is known. The reaction represents the second sample of the rare class of vinyl triflimides 55 in good yields (Scheme 15) [106]:

Scheme 15. Hydroaminosulfonation of phenylacetylene.

\( N \)-vinyl triflimides were first described in the work [107].

The reaction was performed by adding phenylacetylene to the dichloromethane solution of 1.5 eq. LiNTf₂ \( \text{48} \) and \( \text{Bu}_4\text{NNTf}_2 \) to increase the solubility of LiNTf₂. The regioselectivity of the addition is determined by the cation-stabilizing effect of the \( \alpha \)-aryl substituent [108]: (Scheme 16).

Scheme 16. Synthesis of bromvinyl triflimide.

A similar reaction of Si-substituted alkynes 59 and Tf\( \cdot \)NH \( \text{1} \) with the formation of vinyl triflimides 60 is known. The process proceeds in dichloromethane with slight heating and does not require the presence of additional catalysts (Scheme 17) [109]:
Scheme 17. Reactions of aryl-, vinyl-, alkyl- and silyl-substituted terminal alkynes with triflimide.

In the presence of calcium triflimide 66, the annulation reaction of an aldehyde 61, amine 62, alkene 63 and alkyn 64 takes place. The process proceeds with the formation of fused pyrrolo[1,2a]quinolones 65 with exclusive syn-diastereoselectivity and good yields (Scheme 18):

Scheme 18. Calcium triflimide-catalyzed stereoselective tandem of [4 + 2]- and [3 + 2]-annulation for the synthesis of ropyrrolo[1,2a]quinolines.

This tandem annulation process delivers products that generally comprise four or five rings fused in an angular fashion [110].

For example, in the reactions of furylcarbinol with amines under the action of Ca(NTf₂)₂, the Aza-Piancatelli rearrangement occurs, and after the addition of Et₃N to the reaction mixture, an intramolecular Michael addition proceeds with the formation of the corresponding tetrahydrobenzo[b]azepines in 33–93% yields [111]. The reactions of N,O-acetals with vinylboronic acids in the presence of Ca(NTf₂): lead to the formation of isindolinones in good to quantita tive yields [112].

Iron(III) triflimide salt 67 (formed in situ from FeCl₃ and AgNTf₂) is an efficient catalyst for addition reactions [113]. An alternative method for preparing Fe(NTf₂): that avoids the use of additional metal salts consists of dissolving FeCl₃ in a readily available and inexpensive ionic liquid [BMIM]-NTf₂ (1-butyl-3-methylimidazolium bis(trifluoromethanesulfon)imide). The combination of FeCl₃ with the ionic liquid resistant to air oxygen accelerates the reaction, and the FeCl₃+[BMIM]NTf₂ system has proven to be ideal for the direct iodination of aromatic compounds 67 in the presence of N-iodosuccinimide (NIS) with good yields (58–91%) [114] (Scheme 19):

Scheme 19. Fe(NTf₂):-catalyzed iodination of arrenes.
The reaction with N-chlorosuccinimide (NCS) proceeds similarly [100,115]. The yields of the corresponding chlorinated arenes (26 examples) ranged from 53 to 97%. The reaction was used for the mono- and di-chlorination of a number of target products, such as nitrofungin, the anti-bacterial agent chloroxylenol and the herbicide chloroxynil [115].

In the presence of Fe(III) and Cu(I), a regioselective reaction of the para-amination of the activated arenes 69 occurs via bromination with N-bromosuccinimide (NBS) (yields 51–95%) [116] (Scheme 20):

\[
\begin{align*}
    \text{R} = & \text{H, MeO, H$_2$N, AcNH} \\
\end{align*}
\]

**Scheme 20.** Strategy for regioselective CH-amination of arenes in the presence of Fe(NTf$_2$)$_3$/CuI.

The reaction involves the bromination of an aryl substrate in the presence of Fe(NTf$_2$)$_3$ followed by an N-arylation reaction catalyzed by Cu(I). A similar system was used for the synthesis of 2-arylbenzoxazoles and 2-arylbenzothiazoles from N-arylbenzamides. [117].

4. Synthesis of Biologically Active Triflamide Derivatives

Thrombosis is the main pathogenesis that causes the low curability of ischemic stroke and is often the cause of death and disability worldwide. Metformin 72, a biguanidine derivative, is a drug for the treatment of type 2 diabetes mellitus, which alleviates the course of ischemic stroke in patients with diabetes mellitus. Based on triflamide and metformin, a promising drug for the treatment of stroke was obtained [118] (Scheme 21):

\[
\begin{align*}
    \text{CF}_3\text{SO}_2\text{Cl} + & \text{NH}_2\text{NH}_{\text{NH}} \rightarrow \text{KOH,acetone} \rightarrow \text{rt, 3 h} \\
\end{align*}
\]

**Scheme 21.** Synthesis of N-trifluoromethanesulfonyl derivative of metformin.

The compound is prepared by the simple treatment of metformin 72 with trifluoromethanesulfonyl chloride 71 in anhydrous acetone in the presence of catalytic amounts of KOH. The target product was obtained in an 85% yield. The compound inhibits the formation of human platelets, including the reduction of platelet aggregation, adhesion and clot retraction, strongly inhibits the formation of blood clots in arteries, reduces the size and compactness of blood clots in stroke, reduces damage to nerve function and mortality and does not cause severe toxicity and tissue damage [118]. As shown later [119], this modified metformin exhibits selective biological activity against breast cancer cells (MFC-7). Together with its anti-thrombotic properties, which is very important in the treatment of cancer, the compound is a promising drug for the therapy of cancer [119,120].

N-Trifluoromethanesulfonyl-substituted anilines 75 proved to be effective substrates for biocatalytic hydroxylation with the formation of 4-aminophenols in the presence of a number of cytochromes of the P450BM3 family. The reactions proceeded with 100% conversion. Similar results were shown by N-trifluoroacetyl protection at the nitrogen atom of aniline. Ac- or Boc-derivatives of anilines showed only a 17 and 66% conversion, respectively [121] (Scheme 22):
Scheme 22. Biocatalytic hydroxylation of N-trifluoromethanesulfonyl substituted aniline.

P450-catalysed arene hydroxylation is accepted to occur via an NIH-shift within an iminium intermediate to give a dienone that re-aromatizes to phenol [121]. Biocatalytic hydroxylation reactions are used for the synthesis of drugs, agrochemicals and their metabolites. In the case of N-trifluoromethanesulfonyl derivatives, the reaction proved to be effective both in preparative and screening variants [121].

The reaction of 5-methyl-2-phenyl-4,5-dihydrooxazole 76 with trifluoromethanesulfonic acid anhydride 77 leads to the formation of trifluoromethanesulfonamido)prop-2-yl esters of phenyl-substituted derivatives of benzoic acid 78 [122] (Scheme 23):

Scheme 23. Ring-opening of the 5-methyl-2-phenyl-4,5-dihydrooxazole system by triflic anhydride.

The product yield varies from 56 to 88%. The reaction does not require the presence of bases. Derivatives with R = 4-Cl, 4-NO₂ and 4-CF₃ show high cytotoxicity against six human cancer cell lines (U251 (glioblastoma), PC-3 (prostate adenocarcinoma), K-562 (chronic myelogenous leukemia), HCT-15 (colorectal adenocarcinoma), MCF-7 (breast adenocarcinoma), SKLU-1 (lung adenocarcinoma) and the 4-CF₃ derivative was active against human gum cancer cells (FGH (gingival fibroblastoma) [122].

A triflamide derivative of diphenylpyrimidine 82 is known, which exhibits excellent activity against the proliferation of pancreatic carcinoma cells (AsPC-1, Panc-1, BxPC-3), lymphoblastic leukemia cells (Ramos) and some lung cancer cells (Scheme 24):
4-Aminephenol was converted to N-phenyl triflamide 80 intermediates under the action of trifluoromethane sulfonic anhydride. Then, 80 were reacted with 4-fluoronitrobenzene to form the intermediate, which were conveniently converted to the amine derivative 81 by using the Fe-NH₄Cl reduction condition. Additionally, under the action of the p-toluenesulfonic acid reagent, 81 was reacted with the 2-chlorine pyrimidine derivative to generate the title molecule 82 [123].

On the basis of triflamide 83, a derivative of oseltamivir 84, an anti-viral drug used to treat various types of influenza, was obtained (Scheme 25):

Coupling reactions of acid 84 with triflamide 83 were carried out, followed by the removal of the Boc protecting group with TFA, to afford acyl triflamide 85. The amino group in 85 was further elaborated to the guanidino group by treatment with 1,3-di-Boc-2-(trifluoromethylsulfonyl)guanidine to afford GOC-sulfonamides 86 after the removal of the Boc groups. The compound 86 exhibited high inhibitory activity against the H1N1 influenza virus, with the final yield of the product being 39% [123,124].

Type 2 diabetes mellitus is a progressive metabolic disorder characterized by high blood glucose and high endogenous insulin levels. Diabetes mellitus causes serious
vascular complications, heart disease, kidney failure and blindness [125]. Glucagon-like peptide-1 (GLP-1) is a potent anti-hyperglycemic hormone that induces the glucose-dependent stimulation of insulin secretion while simultaneously inhibiting glucagon secretion. However, active GLP-1 is rapidly degraded by the dipeptidyl peptidase-4 (DPP-4) enzyme. Therefore, the inhibition of DPP-4 is a new approach to the treatment of type 2 diabetes. Based on triflamide, a DPP-4 inhibitor 90 in the low micromolar range was obtained, the pharmacokinetic profile of which was suitable for clinical use (Scheme 26):

Scheme 26. Synthesis of DPP-4 inhibitor.

Compound 90 was synthesized according to Scheme 26. The condensation of 87 with 88 provided compound 89, which was then reduced by H₂ and condensed with sulfonyl chloride and was followed by the deprotection of Boc by treatment with TFA in CH₂Cl₂, which provided target compound 90 [125].

Triflamide derivatives have been obtained that exhibit anti-diabetic activity as inhibitors of aldose reductase (ALR2), aldehyde reductase (ALR1) and antioxidant activity. These N-acyl triflamide derivatives 94 are obtained on the basis of the quinoxalinone 91 framework [126] (Scheme 27):

Scheme 27. Synthesis of quinoxalinone-based triflamide derivatives.
3-Chloro-quinoxalin-2(1H)-one 91 was alkylated with methyl bromoacetate to form methyl ester 92 as a key intermediate. Then, 92 was subjected to the Heck coupling reaction with the corresponding styrenes and then to hydrolysis with lithium hydroxide, and the carboxylic acid 93 was afforded. Finally, 93 was treated with triflamide 83 in the presence of EDC·HCl and DMAP to obtain the desired compound 94.

The yield of the final reaction products was 57–70%. The product 94 with R = 3,4-(OH)2 exhibited the highest inhibitory activity. It also exhibited extraordinary antioxidant activity, which was even higher than that of the commercial drug Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), a water-soluble analogue of vitamin E [126].

The triflamide derivative of indomethacin 97 is known, which is promising in the treatment of prostate cancer, showing high selectivity and good inhibitory properties in the treatment of this disease. The yield of the product was 70% [127] (Scheme 28):

![Scheme 28. Synthesis of indomethacin triflamide analogues.](image)

Scheme 28. Synthesis of indomethacin triflamide analogues.

Compound 96 was obtained from 4-chloro-N-(4-methoxyphenyl)-benzohydrazide hydrochloride (obtained from 95) by the refluxing with slight excess of 4-oxobutanoic acid in AcOH, respectively. Then, 96 and triflamide 83 were dissolved in 2 mL of 1,2-dichloroethane (DCE) under stirring to obtain compound 97.

Triflamide has been used to synthesize the selective inhibitor of matrix metalloproteinase-12 (MMP-12) 100. The inhibition of the reactions of this enzyme often plays an important role in the treatment of lung, inflammatory and cardiovascular diseases [128] (Scheme 29):

![Scheme 29. Synthesis of triflamide-containing selective matrix metalloproteinase-12 (MMP-12) inhibitor.](image)

Scheme 29. Synthesis of triflamide-containing selective matrix metalloproteinase-12 (MMP-12) inhibitor.
Diarylsulfide derivative 100 was prepared as reported in Scheme 29. Compound 98 was protected as an ethyl ester by treatment with thionyl chloride (SOCl₂) in ethanol. This step was necessary to improve the subsequent cross-coupling reaction, which exhibited a poor yield if conducted on carboxylic acid. A palladium-catalyzed cross-coupling reaction (under Suzuki conditions) of protected aryl bromide 98 with 4-methoxyphenylboronic acid afforded biphenyl derivative 99. Compound 99 was converted into sulfonamide 100 by condensation with triflamide 83, respectively, in the presence of N-(3-(dimethylamino)propyl)-N′-ethylcarbodiimide (EDC) and 4- dimethylaminopyridine (DMAP) using dichloromethane as a solvent.

The yield of the target product 100 was 80%. A similar sulfone was also obtained, but its selectivity and inhibitory activity were much lower [128].

Chiral complex 103 was obtained on the basis of N-trifluoromethanesulfonyl substituted amino acids 102 and Au(I). The complex 103 exhibited in vitro cytotoxicity against breast cancer cells with limited toxicity to healthy epithelial cells [129] (Scheme 30):
Scheme 31. Synthesis of non-steroidal anti-inflammatory drugs-derivatives of triflamide.

The synthetic pathway for compound 109 can be summarized as follows: 3-bromopyridine 104 is first oxidized by a mixture of acetic acid and hydrogen peroxide to afford 3-bromopyridine N-oxide 105, which is then nitrated at the 4-position by a nitric and sulfuric acid medium to provide the key intermediate 3-bromo-4-nitropyridine N-oxide 106. The NH-bridge is achieved by the reaction of intermediate 106 with properly substituted anilines 107. The 4-aminopyridine intermediates 108 are obtained after the simultaneous reduction of the nitro and the pyridine N-oxide moieties using iron in an acetic acid and water medium. The pyridine analogs of nimesulide 109 are obtained by the reaction of the aminopyridine intermediates 108 with trifluoromethylsulfonyl chloride in acetonitrile in the presence of potassium carbonate. The products 109 were obtained in a 35–77% yield [130].

Triflamide derivatives exhibit biological activity as progesterone receptor antagonists. The product 113 presented in Scheme 32 is a potentially effective drug in the treatment of diseases of the female reproductive system, including endometriosis [131] (Scheme 32):

Scheme 32. Synthesis of trifluoromethanesulfonyl-based antagonists of the progesterone receptor.

The synthetic route towards compound 113 is described in Scheme 32. The deprotonation of cyclohexanol 111 with NaH in THF followed by the addition of fluorobenzonitrile 110 furnished cyclohexylamine 112 in a good yield. Compound 113 was synthesized by the triflation of cyclohexylamine 112 using triflic anhydride and triethylamine in DCM at −60 °C. The yield of the final product 113 was 92%. The product 113 also inhibited drug metabolism by cytochromes P450, CYP 2C [131].

N-Trifluoromethanesulfonyl-substituted derivatives 117 were obtained, exhibiting anti-mycobacterial activity, and could potentially become new anti-microbial drugs, including for the treatment of tuberculosis [132] (Scheme 33):
Scheme 33. Synthesis of N-glycosyl triflamide.

The synthetic route towards compound 117 is presented in Scheme 33. Acetyl chloride was added to a solution of 114 in methanol under nitrogen. The reaction was stirred for 3 h at room temperature. Sodium hydride and benzyl bromide were added. The reaction was cooled in an ice bath, quenched by the addition of methanol and then concentrated in vacuo. Then, the residue was dissolved in a mixture of water and acetic acid to afford hemiacetal 115. Compound 115 and triflamide 83 were stirred at room temperature in dry diethyl ether in the presence TMSOTf to give compound 116. Compound 117 was obtained by reduction with 10% activated Pd/C. The N-furanosyl triflamide 117 was obtained in a 44% yield [132]. Compound 117 was configurationally stable in aqueous solutions, in contrast to its other analogues obtained from alkylsulfonamides. N-Acyltriflamides also exhibited anti-mycobacterial activity [133].

Triflamide derivatives exhibit biological activity against the causative agent of sleeping sickness (African trypanosomiasis) [134]. Currently, there are five drugs for the treatment of this disease, including suramin, pentamidine, melarsoprol, eflornithine and nifurtimox [135]. However, their use is accompanied by a number of serious side effects and difficulties: (1) high toxicity; (2) the necessity to be injected intramuscularly or intravenously, which creates difficulties in an epidemic area with limited medical resources; (3) a narrow antitrypanosomal spectrum of action; and (4) high cost. In general, these drugs are not effective in treating the disease, and there is an urgent need to develop more effective and inexpensive chemotherapeutic agents for the treatment of trypanosomiasis. The treatment of this disease involves blocking the processes of polymerization/depolymerization of the tubulin protein, which is necessary for the division of pathogen cells and their movement. On the basis of the triflamide derivative, a selective tubulin inhibitor 121 was obtained, which can be used to treat sleeping sickness [134] (Scheme 34):

Scheme 34. Synthesis of trifluoromethanesulfonyl-based tubulin inhibitor.
Triflamide derivative 119 was prepared from aryl-substituted 2-amino-5-nitrophenol 118 by adding it with trifluoromethanesulfonic chloride in anhydrous DCM and K₂CO₃. Compound 119 was dissolved in acetone; then, Zn and FeCl₃ were added into the solution. When the reaction completed, the corresponding benzoyl chloride was added and product 121 was collected by filtration and purified by recrystallization in ethanol/water. The yield of the final product 121 of the reaction was 47% [134].

The derivative of triflamide 126 is known to exhibit biological activity and act as an inhibitor of the transporter derivatives of uric acid (hURAT1). In medicine, there are only three options for drugs of this kind, although they are extremely necessary in the treatment of hyperuricemia, which subsequently causes many diseases, such as gout, arterial hypertension, chronic kidney disease and some cardiovascular diseases [136] (Scheme 35):

![Scheme 35. Synthesis of triflamide-containing hURAT1 inhibitor.](image)

Triflamide compound 126 was synthesized by following Scheme 35. Bis(pinacolato)diboron reacted with 122 under the catalyst of Pd(dppf)Cl₂, which gave compound 123. Further Suzuki coupling of 123 with 4-amino-3-bromopyridine 124 provided 125, which subsequently reacted with CF₃SO₂Cl under the conditions of Et₃N in DCM to afford compound 126 [136].

Based on triflamide, a promising inhibitor of the α-amylase enzyme 130 was obtained [137] (Scheme 36):

![Scheme 36. Synthesis of triflamide-containing α-amylase enzyme inhibitor.](image)
Sulfonohydrazide-substituted indazole 130 was synthesized by a multi-step reaction. In the first step, 4-oxyindazole 129 was formed by reacting dimedone 127, dimethylformamide dimethylacetal (DMF-DMA) and phenylhydrazine 128 in the presence of a catalytic amount of CuCl2 in ethanol for 3 h. In the next step, 4-oxyindazole 129 was treated with a sulfonohydrazide derivative in ethanol in the presence of pyridine as a catalyst and was refluxed for 2 h to obtain the desired sulfonohydrazide-substituted indazole 130 (Scheme 36). Reducing the activity of the α-amylase enzyme is one of the best treatments for type 2 diabetes. For example, acarbose, voglibose and miglitol are commercially available α-amylase enzyme inhibitors used to treat type II diabetes mellitus. However, these agents have some side effects such as flatulence, diarrhea and abdominal discomfort, so other anti-diabetic agents are always recommended for greater effectiveness [137].

Triflamide derivatives are used for the synthesis of inhibitors of biochemical processes by introducing peptidomimetics into biochemical reactions. A triflamide-containing component of the proteasome complex 133 was obtained, exhibiting activity similar to chymotrypsin. Similar compounds are used for cancer therapy. The product 133 yield was 80% [138] (Scheme 37):

\[ \text{Scheme 37. Synthesis of triflamide-containing peptidomimetic.} \]

The synthesis of the target compound is presented in Scheme 37. The treatment of compound 131 with hydrazine generated compound 132, which was treated with trifluoromethylsulfonyl chloride in a basic media to generate sulfonamide 133 over two steps [138].

Scheme 38 shows a simple synthesis of a compound 137 exhibiting high anti-retroviral activity. The compound showed good activity against HIV at nanomolar concentrations, being an effective inhibitor of HIV-1 replication [139] (Scheme 38):

\[ \text{Scheme 38. Synthesis of triflamide-containing anti-retroviral agent.} \]

The synthesis of triflamide derivative 137 was achieved from the key intermediate, N-(4-amino-2-methylphenyl)-4-chloro-phthalimine 136, which was synthesized from 4-chlorophthalimine 135 and 4-chloro-3- methylaniline 134. Further, 136, when treated with appropriate CF3SO2Cl in the presence of TEA and DCM at room temperature, gave the respective sulfonamide 137.
The resulting isoindolindione 137 gave a good performance in overcoming the hematomaencephalic barrier. Obtaining such drugs is important because there is a demand in medicine for drugs for highly active anti-retroviral therapy, which is necessary to curb the progression of HIV disease and increase the survival of HIV-infected patients, as well as due to the high resistance of retroviruses [139].

5. Triflamide Derivatives in Organic Synthesis

Arylbenzyltrifluoromethanesulfonamides 139 are starting compounds for the synthesis of phenanthridine derivatives 140, which are among the most important basic nitrogen-containing heteroaromatic structures. Phenanthridine fragments are part of natural compounds and have powerful anti-bacterial and anti-tumor activity [140]. O-Arylbenzyltrifluoromethanesulfonamides 139 are obtained by the reduction of the corresponding CN-diaryls 138 followed by treatment with triflic anhydride [140] (Scheme 39):

![Scheme 39. Preparation of phenanthidine from N-(o-arylmethyl) trifluoromethanesulfonamides with 1,3-diodo-5,5-dimethylhydantoin.](image)

Then, the product undergoes intramolecular oxidative cyclization at the aromatic ring in the presence of DIH in 1,2-dichloroethane under irradiation with a tungsten lamp with the formation of 5-trifluoromethanesulfonyl-5,6-dihydrophenanthridine, which, by the action of t-BuOK in THF, gives the target phenanthidine 140 (79%) [140].

An olefination reaction of 2-methylquinoline in the presence of triflamide was shown to proceed in the presence of aldehydes under the action of microwave radiation with the formation of 2-vinylquinolines 144 [141] (Scheme 40):

![Scheme 40. Microwave-assisted synthesis of 2-vinylquinolines in the presence of TfNH₂.](image)

Not only derivatives of aliphatic aldehydes or benzaldehydes 142, but also heteroaromatic aldehydes (pyridinecarboxaldehyde and thiophene-carboxaldehyde) can be involved in the reaction. Triflamide 83 is added in the excess of 20% with respect to the aldehyde. As seen in Scheme 40, the microwave irradiation of TfNH₂: 83 gives the corresponding aldimine in situ. The corresponding alkene 144 is formed by the elimination of
the triflamide molecule from 143. Some of the obtained alkenes have high anti-malarial biological activity [141].

Various triflamide compounds are widely used as organyl catalysts that show high stereoselectivity and asymmetric transformations [142–149].

Triflamide derivatives 147 are used in the enantioselective cross-coupling of glycine derivatives with ketones and aldehydes 146 [143] (Scheme 41):

\[
\begin{align*}
\text{O} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{145} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{146} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{148} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{149} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{150} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

Scheme 41. Asymmetric Mannich-type reaction for the C–H Alkylation in the presence of TfNH-containing organyl catalyst.

The photoinduced process includes the oxidation of glycine derivatives to an imine intermediate, which enters the asymmetric Mannich reaction with an enamine 149 intermediate adduct formed in situ from a ketone or aldehyde 145 and a chiral TfNH-containing organic catalyst 147. The method allows one to create a new C–C bond with the formation of new stereocenters without the additional functionalization of the substrates [143].

Similar to organic catalysts, 2-(trifluoromethanesulfonamidoalkyl)pyrrolidines and their D-prolinamides were used in the addition of aldehydes to β-nitroalkenes at room temperature. The reaction in this case proceeded without additional reagents and catalysts and led to the formation of γ-nitroaldehydes in a quantitative yield and high enantio- and diastereoselectivity [144].

N-Propyltriflamide 151 reacts with activated alkenes 152 in the presence of an Ir(III) complex as a photocatalyst and a base (quinuclidine) [150] (Scheme 42):

\[
\begin{align*}
\text{Et} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{151} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{Et} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{152} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{Et} \quad \text{H} \quad \text{HN} \quad \text{Ar} \\
\text{153} \quad \text{R}_1 \quad \text{R}_2
\end{align*}
\]

Scheme 42. C–H Alkylation of N-propyl substituted Triflamide.
The more stable nitrogen-centered radical present on triflamide acts as an intermolecular hydrogen-atom abstractor to the deprotonated triflamides in the solution, which possess highly activated α-CH bonds due to their anionic character. This pivot in reactivity allows for the selective functionalization of both α- and δ-CH bonds depending on the installed nitrogen protecting group. The presence of a trifluoromethanesulfonyl group at the nitrogen atom ensures the complete deprotonation of the NH bond and makes the α-C-H bond more "hydride” and susceptible to hydrogen-atom transfer (HAT) under the action of quinuclidine and a photocatalyst. The reaction allows for the formation of a new C-C bond due to the combination of α-amino radicals and electron-deficient alkenes. The yields of 153 vary from 32 to 63% [150].

The reaction of 2H-azirine 154 with a slight excess of TfO in chloroform leads to the formation of the N-acetophenone derivative of triflamide 157 [151] (Scheme 43):

![Scheme 43](image)

**Scheme 43.** Formation of N-Triflyl acetophenone derivative.

2H-Azirine 154 is activated by a nucleophilic attack by the lone nitrogen pair on the highly electrophilic TfO, resulting in the formation of the triflate of the N-triflylazirinium cation 155. In the presence of water in the reaction medium, the iminium ion is hydrolyzed to N-triflyl α-aminoacetophenone 157 (71%). In anhydrous medium, when 2-chloropyridines are added, this 2H-azirine reacts in the presence of TfO to give imidazo[1,2-a]pyridines [151].

A unique one-pot reaction of the radical trifluoromethanesulfonylation and trifluoromethylation of imines 158 is known, which proceeds with the formation of CF₃-substituted N-vinyl triflamides 159 [152] (Scheme 44):

![Scheme 44](image)

**Scheme 44.** One-pot synthesis of CF₃-substituted vinyl trifluoromethanesulfonamides from imines and triflic anhydride.

The reaction starts with the formation of N-vinyltriflamides, which are the sources of the CF₃ group. In this case, the N-vinyltriflamides obtained at the first stage of the reaction further react as bifunctional reagents, acting as both sources of trifluoromethyl radicals and acceptors of these radicals. The yields vary from 34 to 61% [152].

Based on the triflamide derivatives, a new class of block of polystyrene-block-poly(ethylene oxide-co-hydroxyethyl glycidyl ether) diblock copolymers 163 is developed [153] (Scheme 45):
The resulting materials are currently being used to produce the next generation of single-ion-conducting polymer electrolytes (SICPEs) that are capable of competing with known Tf-NLi-based materials. In solid single-ion-conducting polymer electrolytes, the anion is covalently attached to the polymer and, ideally, only the cation contributes to the conductivity. The use of these electrolytes effectively eliminates many of the current safety and performance issues of the current liquid and salt-in-polymer electrolytes.

N-Phenethylenetriflamides 164 react with 1,3-dienes 166 in the presence of catalytic amounts of Pd(OAc)₂ and Cu(OAc)₂/O₂ as an oxidizing agent [154] (Scheme 46):

\[
\text{R}^1 = \text{H, 2,3-MeOC}_{10} \text{H}_4, 3-\text{ClC}_{10} \text{H}_4, 2-\text{MeOCC}_{10} \text{H}_4, 2-\text{MeOCH}_{10} \text{H}_4, 2-\text{ClC}_{10} \text{H}_4, 2-\text{MeOCH}_{10} \text{H}_4
\]

The reaction proceeds chemo-, regio- and diastereoselectively with the formation of 2,3,4,5-tetrahydro-1H-benzo[d]azepines 166. The use of O₂ as a co-oxidant makes it possible to reduce the amount of the oxidizing agent (Cu(OAc)₂). 3-Benzazepines are present in a wide variety of natural products and important pharmaceuticals. These compounds are among the most convenient in terms of structural proximity and selectivity for dopamine D₁ receptors, which regulate cell growth and development. As drugs for the treatment of CNS diseases, dopaminergic 3-benzazepines have the selective agonist or antagonist properties of dopamine D₁ receptors, which have led to the development of pharmaceutical drugs against Parkinson’s disease, leukemia, cocaine addiction and obesity [154]. Triflamide derivatives 166 containing a 3-benzazepine moiety can be used to treat Alzheimer’s disease [155]. It should be noted that the synthesis of the N-alkyl-substituted triflamides presented in the scheme above is carried out by the reaction of TfNH₂ with the corresponding alcohol in the presence of Cs₂CO₃ and an Ir-centered catalyst [156]. Such substituted sulfonamides exhibit a number of different types of biological activity (e.g., anti-inflammatory activity) [156].
With the participation of triflamide 83, the rhodium(III)-catalyzed intermolecular reaction of the C–H amination of ketoxime 167 in the presence of iodosobenzene diacetate takes place [157] (Scheme 47):

![Scheme 47. Catalyzed oxidative annulation of ketoximes with sulfonamide.](image)

In this case, under the conditions of an oxidative reaction, triflamide acts as a source of nitrogen during amination. The product 168 is formed in a 51% yield [157].

In the presence of NaOCl, the C–H amination reaction of 3-substituted indoles 169 with chiral triflamide-containing amino acids 170 proceeds. A feature of the reaction is the formation of a new class of atropisomers 171 [158] (Scheme 48):

![Scheme 48. NaClO-promoted amination of 3-substituted indoles with TfNH-containing amino acid derivatives.](image)

The yield of the product 171 is 50–92%. Indoles are among the most important heteroarenes that are present in natural products and pharmaceuticals. The compounds are of great interest in the field of synthetic and medicinal chemistry [158].

A unique property of triflamide derivatives is the ability to aminate non-activated C–H bonds, which is a great advantage in the synthesis of N-containing molecules due to the high efficiency and atom economy of such methods. A very unusual reaction of selective intramolecular amination at the C–H bond in the presence of silver salts resulting in functionalized heterocyclic products was published [159] (Scheme 49):

![Scheme 49. Silver-catalyzed direct amination of unactivated C–H bonds.](image)

The method is effective for the transformation of non-functionalized groups in organic molecules and for the creation of complex structural units in natural and bioactive molecules; the reaction is most effective in the amination of primary sp³ carbon atoms as the reactions proceed chemo- and regioselectively in comparison with the existing methods of direct amination (the Hoffmann–Löffler–Freitag reaction and the nitrene insertion reaction) [159].
Over the past few years, the reactions of triflamide with alkenes and dienes in the presence of oxidizing agents have been thoroughly studied in our group. Triflamide 83 reacts with styrene derivatives 174 and NBS in acetonitrile to form a product 175 with two different amine functional groups, N-trifluoromethanesulfonyl and acetamide. Obviously, solvent molecules (CH$_3$CN) are involved in the reaction in this case [160] (Scheme 50):

**Scheme 50.** Amination of styrenes with TfNH$_2$ in the presence of NBS.

Product yields are 76–94%.

With alkenes 176–178 that do not have aryl groups, the reaction proceeds with the formation of N-sulfonylamidines 179–181 in quantitative yields [160] (Scheme 51):

**Scheme 51.** Amination of vinylcyclohexane, hexa-1,5-diene and cyclohexa-1,4-diene with TfNH$_2$ in the presence of NBS.

Amidines 179–181 and acetamides 175 can be formed independently from the common intermediate bromonium ion 182, which could be opened via either the CH$_2$–Br or CH–Br bond splitting, leading, respectively, to amidines 179–181 or the products of hydrolysis (acetamides) 175 [160] (Scheme 52):

**Scheme 52.** Formation of amidines or acetamides from alkenes and TfNH$_2$ in the presence of NBS.

Unexpectedly, triflamide 83 reacts with norbornene 185 in acetonitrile with the insertion of the solvent and skeletal rearrangement, leading to the formation of iodine-containing acetamide 186 and the tricyclic product 187 [161] (Scheme 53):
If NBS or NIS are used as the oxidizing agent, only halogen-amidines are formed, similar to those presented in Scheme 51 [161].

The reaction of triflamide 83 with 1,5-hexadiene 188 was also studied. Two products were obtained in the total isolated yield of 91%; the corresponding pyrrolidine 189 and 3,8-bis(trifluoromethanesulfonyl)-3,8-diazabicyclo[3.2.1]octane 190 formed in the ratio of 3:2 [162] (Scheme 54):

\[
\text{TfNH}_2 + \text{188} \rightarrow \text{189} + \text{190}
\]

Scheme 54. Reaction of 1,5-hexadiene 188 with Tf NH\(_2\) in the presence of t-BuOCl + NaI in CH\(_3\)CN.

We have also proposed a simple one-pot synthesis of the 3,6-diazabicyclo[3.1.0]hexane framework based on the reaction of triflamide 83 with 2,3-dimethylbuta-1,3-diene 191 and 2,5-dimethylhexa-2,4-diene 193 in the presence of the t-BuOCl + NaI system [163]. The reaction with 2,3-dimethylbuta-1,3-diene 191 leads to a single product 192 in an 80% yield (Scheme 55):

\[
\text{TfNH}_2 + \text{191} \rightarrow \text{192}
\]

Scheme 55. Heterocyclization of 2,3-dimethylbuta-1,3-diene and 2,5-dimethylhexa-2,4-diene with Tf NH\(_2\) in the presence of t-BuOCl + NaI in CH\(_3\)CN.

A similar reaction of triflamide with 2,5-dimethylhexa-2,4-diene 193 carried out at – 30 °C afforded the corresponding bicyclic product 194 in a 37% yield and a 1:1 mixture of pyrrolidine diastereomers 195 in a 54% yield. The mechanism of the reaction of triflamide 83 with dienes 191 or 193 is supposedly heterocyclization to 3-pyrrolines and the subsequent aziridination of 3-pyrrolines and results in 3,6-diazabicyclo[3.1.0]hexanes 192 or 194. Pyrrolidines 195 in this case are formed by the nucleophilic attack of the aziridine ring by Cl\(^–\) or I\(^–\) anions, presented in the reaction mixture, which is accompanied by the opening of the aziridine ring in the bicyclic product [163].
6. Conclusions

To summarize, triflimide is a unique reagent in organic synthesis. Possessing strong acidity and low nucleophilicity, it is successfully used for the design of new organic molecules, making it possible to form new C–C and C–heteroatom bonds. Given the low electron density of the nitrogen atom in Tf₂NH and the steric hindrances around the nitrogen atom, it is a weak nucleophile for addition reactions. Due to these properties, the Tf₂N⁻ ion is actively used as a harmless counterion for cationic catalysts based on various metals to create substances that are important from a biological, pharmaceutical and industrial point of view. It is the ease of use, small loads and mild reaction conditions that make it possible to use triflimide both as a direct reagent in various reactions and as a catalyst/co-catalyst. Triflimide itself, as well as its derivatives, are effective in cascade cyclizations, cycloadDITION, olefination, iodination, amination, etc. All these reactions lead to a huge number of new synthetically and biologically important objects, which undoubtedly make a significant contribution not only to fundamental organic chemistry but also in many additional applications.

Some triflamides demonstrate high anti-diabetic activity, high cytotoxicity for human cancer cell lines, anti-mycobacterial activity and anti-HIV activity. Triflamide derivatives are used as non-steroidal anti-inflammatory and anti-viral drugs, drugs for the treatment of hyperuricemia and effective drugs in the treatment of the female reproductive system diseases.

The introduction of a triflamide in aryl-containing molecules makes the modification of such substrates for biocatalytic hydroxylation possible; some triflamide compounds possess extraordinary antioxidant activity. Various triflamide compounds are widely used as peptidomimetics, organic catalysts showing high stereoselectivity and asymmetric transformations. The oxidative addition of triflamide to unsaturated substrates is a convenient method for amination and further heterocyclization under mild conditions.

Triflamides in all their various forms have certainly influenced most areas of synthetic organic chemistry in the last 10 years. Special physical and chemical properties of triflamides are used very widely, especially in medicine and pharmaceuticals for the development and synthesis of drugs and prodrugs containing the triflamide group as a key structural unit that determines biological activity, which will certainly be widely used in the future. In addition, in recent years there has been a growing interest in the use of triflamides as powerful electrophiles in a wide range of reactions. Triflamides are used as a hydrophobic solvent in lithium–sulfur batteries. It can be easily argued that the most promising field of application of triflamides are electrochemical energy storage systems. Triflamides can greatly influence the reactivity of chemical reactions compared to alkyl- and arylsulfonamides. Thus, this modifying effect will be widely used in synthetic organic chemistry and catalysis.

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Abbreviations

DMEDA 1,2-Dimethylethylenediamine
DMAP 4-Dimethylaminopyridine
HBTU Hexafluorophosphate Benzotriazole Tetramethyl Uronium
EDCI EDC-1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBr Hydroxybenzotriazole
dIH 1,3-Diiodo-5,5-Dimethylhydantoin
dF-CH3-ppy 2-(2,4-difluorophenyl)-5-methylpyridine
dbppy 4,4′-Di-tert-butyl-2,2′-dipyridyl
TTBP Tri-Tert-Butylphenol
TFA Trifluoroethanol
phen phenethylamine
DCE 1,2-Dichloroethane
HFIP Hexafluoropropanol
XPhos Dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane
DCM Dichloromethane
TEA triethanolamine
Dppf 1,1′-Bis(diphenylphosphino)ferrocene
Bpy 2,2′-Bipyridine

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