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Chemical Transformations Induced by Triflic Anhydride

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1. Introduction

Trifluoromethanesulfonic (triflic) anhydride (**1**) has found a very broad application in synthetic organic chemistry, firstly as a reagent for the conversion of various compounds to the triflates.[1,2] The triflate group is one of the best leaving groups available, only the nitrogen molecule in diazonium salts or $PhI^{\oplus}$[3] in iodonium salts being more effective nucleophugs.[1] It is known, for example, that the relative rate of solvolysis of 1-phenylethyl triflate is approximately 3×10^3 times greater than that of the tosylate.[4] Moreover, triflate derivatives (and the acid itself) have a higher thermal stability than their closest analogues—fluorosulfonic acid derivatives. The Hammett substituent constants have been determined[5] for the triflate group and it has been shown that s_I of the triflate moiety is 0.84, and therefore OTf (OSO_2CF_3) is one of the most inductively strong electron-withdrawing groups which is comparable with $N(CH_3)_3^{\oplus}$. All these facts result in extensive applications of triflic anhydride in modern organic chemistry.

2. Reaction of Triflic Anhydride with O-Nucleophiles

The main thrust of the synthetic use of triflic anhydride is its reaction with oxygen nucleophiles—carbonyl compounds,

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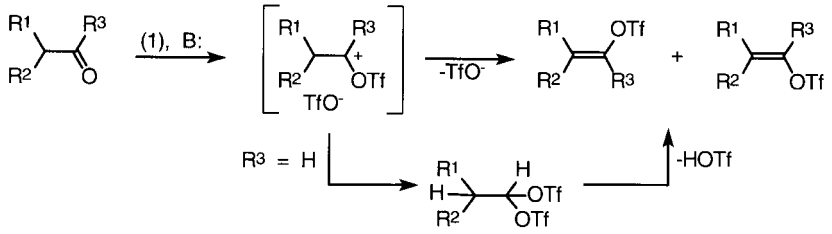
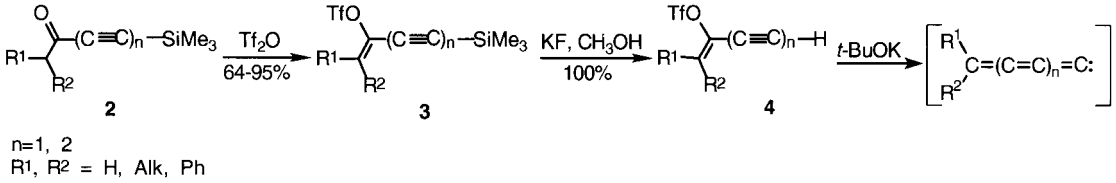


Scheme 1.



Scheme 2.

alcohols and phenols as well as oxides of phosphorous, sulfur and iodine. The compounds formed and their application in preparative organic chemistry are now discussed.

2.1. Reaction of triflic anhydride with carbonyl compounds

The reaction of triflic anhydride with carbonyl compounds consists of the electrophilic attack of the anhydride on the carbonyl oxygen, resulting in the formation of the trifloxycarbenium ion. Depending on the nature of the carbonyl compounds and the reaction conditions, this cation can undergo several synthetic transformations, namely: 1) proton abstraction leading to a vinyl triflate (in the case of ketones as the carbonyl source) or to a mixed anhydride (in the case of carboxylic acids), 2) cationic rearrangement (with bicyclic ketones), 3) trapping by the triflate counterion (aldehydes) and 4) reaction with an external nucleophile (amides, acids and esters as the carbonyl source).

2.1.1. Preparation and synthetic transformations of vinyl triflates (non-coupling reactions). Reaction of triflic anhydride with ketones in the presence of different bases such as pyridine, lutidine, Et_3N, and sodium or potassium carbonate gave the corresponding vinyl triflates;[1] the use of sterically hindered, non-nucleophilic 2,6-di-(*t*-butyl)-4-methylpyridine (DTBMP)[6,7] or *N*,*N*-di-*i*-butyl-2,4-dimethyl-3-penthylamine[8] as the base may significantly improve yields. In the case of aliphatic aldehydes, the initially formed *gem*-bistriflates underwent thermal decomposition to a mixture of *E*- (usually dominating) and *Z*-vinyl triflates, whereas for ketonic compounds no formation of *gem*-bistriflates was observed (Scheme 1).[9]

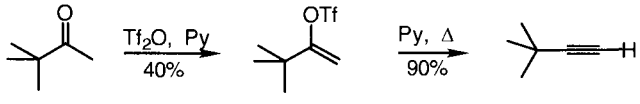
Primarily, vinyl triflates have been used for the solvolytic generation of vinyl cations,[10,11] and via α-elimination for the generation of alkylidene carbenes.[12,13] The application of vinyl triflates in preparative and synthetic organic chemistry has increased rapidly and numerous experimental methods have been developed for their preparation and handling after the discovery of cross-coupling reactions of vinyl and aryl triflates with different organometallic compounds. The literature up to 1982 has been reviewed in detail by Stang and Hanack,[1] and recently Ritter[2] has summarized the cross-coupling reactions of aryl and vinyl triflates. In this section only representative and recent examples of vinyl triflate transformations will be surveyed, the main emphasis being placed on non-coupling synthetic applications.

A series of alkynylvinyl triflates **4** was synthesized via a sequence[14,15] involving the reaction of acylalkynes **2** and Tf_2O in the presence of DTBMP, followed by desilylation with potassium fluoride. The triflates **4** can be utilized as precursors for extended unsaturated carbenes (Scheme 2).

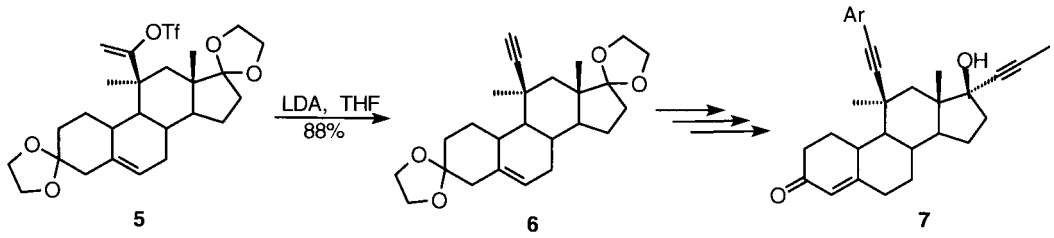
Triflic anhydride could be applied to the conversion of methyl ketones into terminal alkynes. For example, conversion of pinacolone into the corresponding triflate, followed by treatment with a base, has provided a simple route to *t*-butylacetylene.[16] Recently, a key intermediate **6** required for the synthesis of 11-disubstituted progestins **7**, has been prepared via LDA-initiated elimination of triflic acid from vinyl triflate **5** (Schemes 3 and 4).[17]

Some aldehydes can be dehydrated to terminal alkynes by the Stang protocol[18,19] provided that for the final detriflation step, potassium *t*-butoxide is employed as the base. However, when LDA is used as the base, this type of transformation is also successful.[20] Thus, Fleming[20] has reported a sequence involving the above strategy to prepare racemic or homochiral propargylsilanes **9** from the corresponding β-silylated aldehydes **8** (Scheme 5).

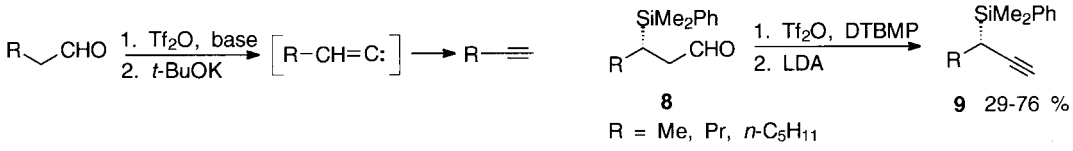
Bestmann et al.[21] have devised a method for the decomposition of β-ketoylides to alkynes in which the ylide **10** was



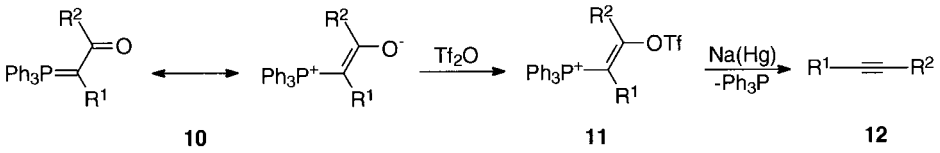
Scheme 3.



Scheme 4.



Scheme 5.



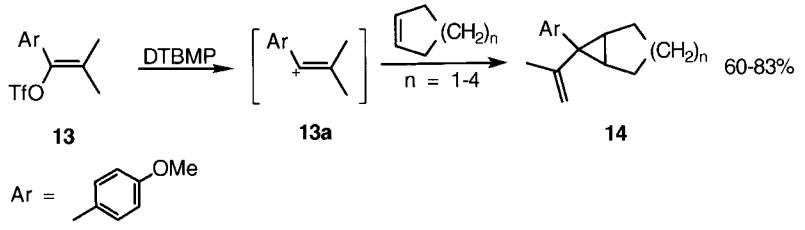
Scheme 6.

converted to a vinyl triflate **11** in high yield, and subsequent reduction of the latter with sodium amalgam in THF gave 47–80% yields of the alkyne **12** (Scheme 6).

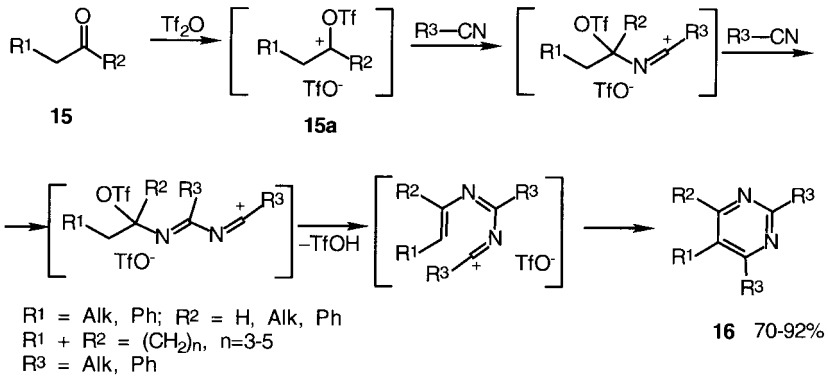
Vinyl cations **13a**, which are readily generated from the simple vinyl triflates **13**,[1,10] can undergo [2+1] cycloaddition reactions with different cyclic alkenes giving mostly the corresponding cyclopropane derivatives **14** (Scheme 7).[22]

The reaction of ketones with aliphatic and aromatic nitriles in the presence of Tf_2O offers a versatile route to the preparation of substituted and functionalised pyrimidines **16**.[23,24] The transformation apparently consisted of a cascade reaction of the trifloxycarbenium ion **15a** with two molecules of a nitrile followed by elimination of triflic acid and cyclization (Scheme 8).[23]

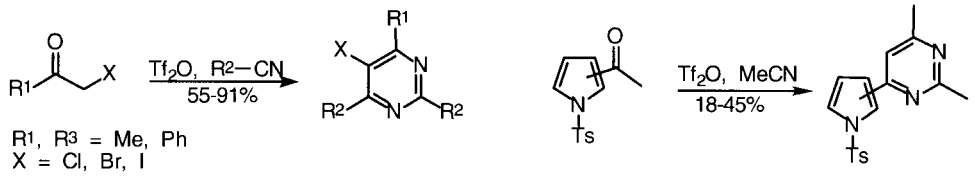
Application of this reaction to α-haloketones[25] or



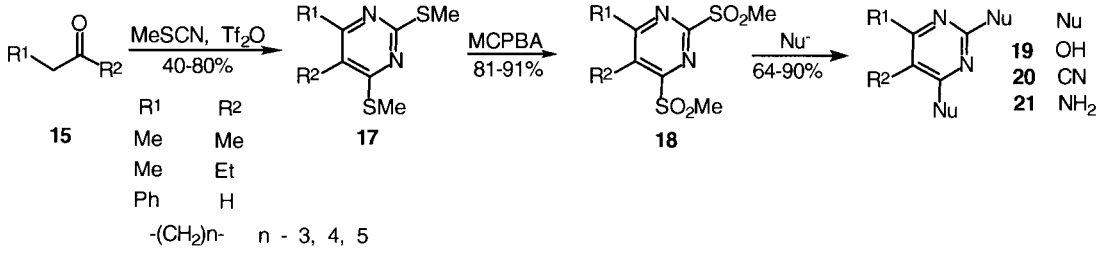
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

N-tosylacetylpyrroles[24] provided a convenient route to 5-halopyrimidines and 6-pyrrolylpyrimidines, respectively (Scheme 9).

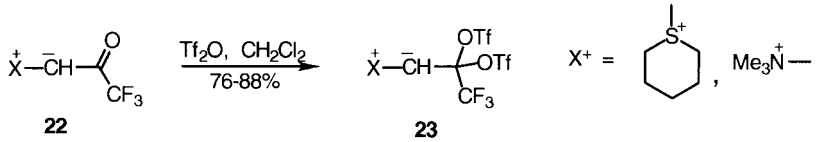
Similarly, 2,4-bis(methylthio)pyrimidines **17** can be prepared by the reaction of different aliphatic and aromatic ketones with Tf_2O and methylthiocyanate.[26] Oxidation of **17** with MCPBA to **18** followed by nucleophilic substitution of the methylsulfonyl group affords the uracils **19**, dicyanopyrimidines **20** or mono- and diaminopyrimidines **21** (Scheme 10).[24]

In a few cases, the triflate anion can act as a nucleophile toward a cation resulting from the reaction of Tf_2O with a ketone. Thus, trifluoroacetyl methylides **22** which cannot abstract an α-proton yield the corresponding *gem*-bistriflates **23**.[27] Treatment of azibenzils with Tf_2O affords the vicinal ditriflates **25a–b**, resulting from an electrophilic attack of the anhydride on the oxygen followed by nucleophilic displacement of nitrogen in **24** by the triflate anion (Schemes 11 and 12).[28]

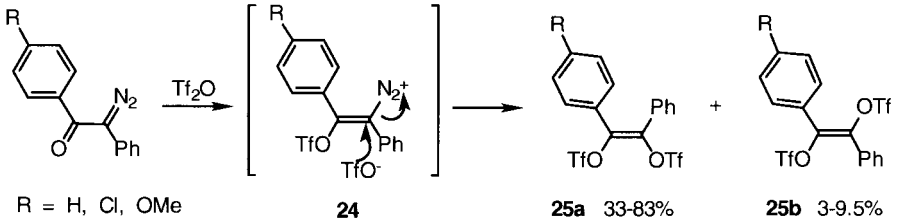
In contrast, however, triflation of *o*- or *p*-quinoid diazoketones gives *o*- or *p*-trifloxyarenediazonium salts **26**.[29] The stability of **26** compared with **24** may be explained by the higher energy of the corresponding aryl cations (Scheme 13).

1,3-Diketones[30] and 1,3-ketoaldehydes[31] react with an equimolar amount of Tf_2O or an excess of this reagent to afford the corresponding vinyl or dienyl triflates. The reaction with dicarbonyl compounds proceeds probably through the enol form, since treatment of the formylcyclopentanone (**27**) with one equivalent of triflic anhydride leads to the formation of the keto monotriflate **28**, as well as ditriflate **29**.[31] Similarly, the reaction of the 1,2-diketone **30** with Tf_2O furnished the vinyl triflate **31** as the sole product (Scheme 14).[32]

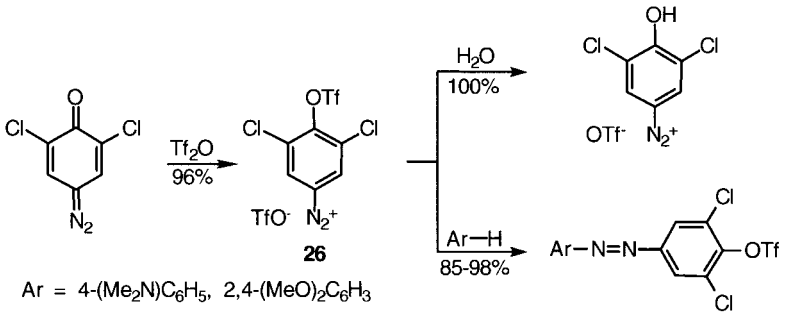
The bicyclic β-ketoesters **32** could be converted smoothly into the corresponding 2-carboxyvinyl triflates **33**.[33,34] Nucleophilic displacement of the trifloxy group by pyridines[34] or thiols[33] afforded a variety of C-3 substituted cephems and dethiacephems **34**, **35** (Scheme 15).



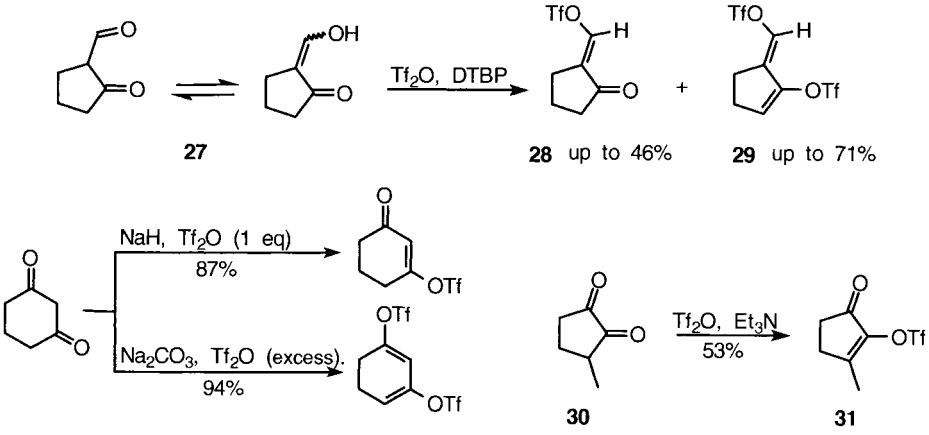
Scheme 11.



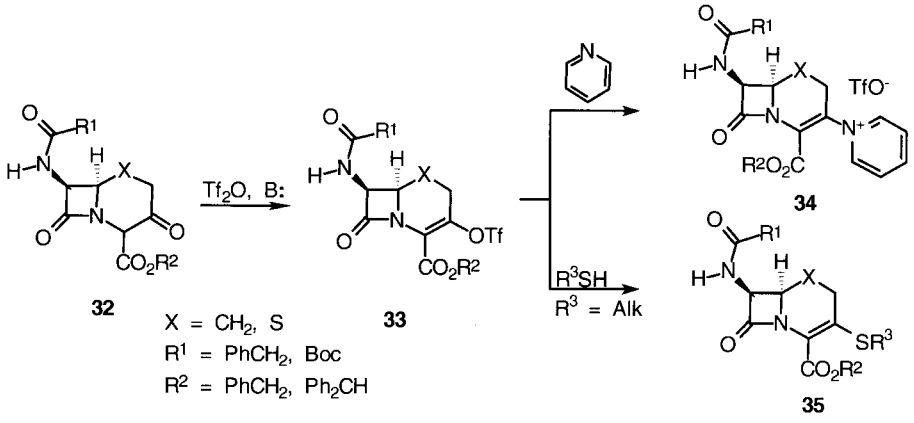
Scheme 12.



Scheme 13.



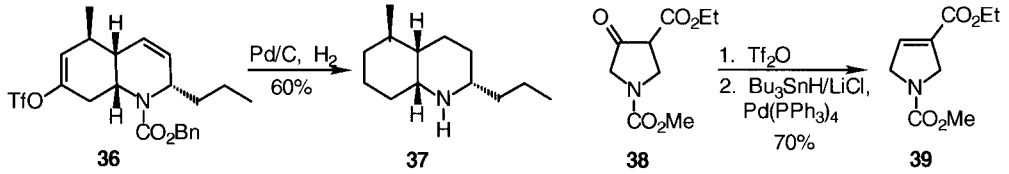
Scheme 14.



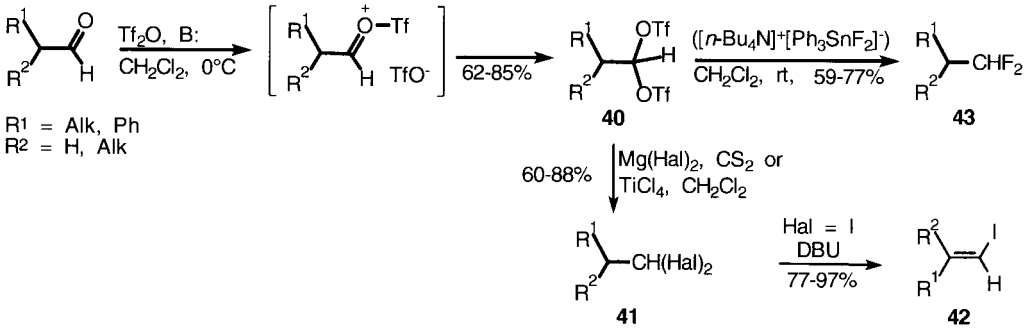
Scheme 15.

Finally, one of the useful chemical transformations of the vinyl triflates consists of their reduction to the corresponding alkanes and alkenes. Comins[35] and Dillard[36] have used the palladium/charcoal or platinum oxide-catalyzed hydrogenation of vinyl triflates to alkanes in the synthesis of pumiliotoxin C **37** from **36**. The vinyl triflates derived from 1,3-diketones[30] or β-keto esters[37] can be transformed smoothly into monoketones, alkanes and unsaturated ketones by means of various reducing agents; for example, the pyrrolidone **38** was converted into the unsaturated cyclic ether **39** via reduction of the corresponding triflate with tributyltin hydride in the presence of $Pd(PPh_3)_4$ as catalyst (Scheme 16).[37]

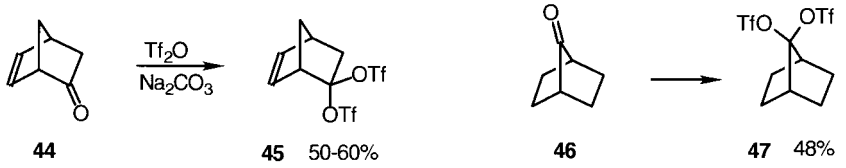
2.1.2. Reaction with aldehydes and bicyclic ketones. Synthesis of *gem*-bistriflates and skeletal rearrangements. In contrast to ketones, the reaction of aliphatic aldehydes with triflic anhydride, in the presence of acid scavengers such as DTBMP, leads to the formation of *gem*-bistriflates **40**.[9,38] Unfortunately, in most cases an aldol-type reaction successfully competes with *gem*-bistriflate formation, hence decreasing the yields of the



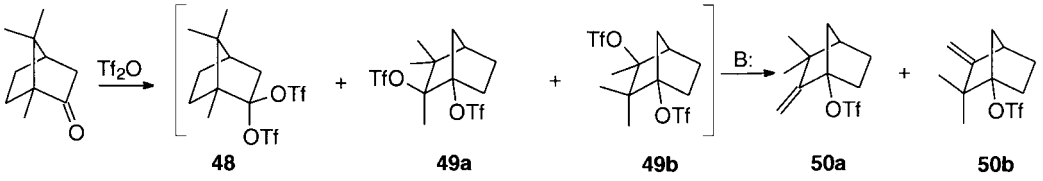
Scheme 16.



Scheme 17.



Scheme 18.



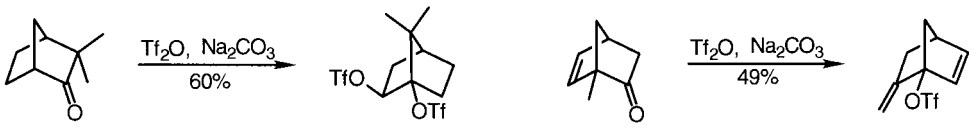
Scheme 19.

desired products.[9] There are few examples of synthetic applications of *gem*-bistriflates, since they are relatively unstable and rapidly undergo polymerization and decomposition to form the corresponding primary vinyl triflates.[38] However, triflate activation may be used for the displacement of an aldehyde oxygen by some nucleophiles; for example, Martinez et al.[39] have found that aliphatic aldehydes can be converted smoothly to 1,1-dihaloalkanes **41** by reaction of corresponding bistriflates with magnesium iodide and bromide or titanium tetrachloride. Similarly, good yields of the difluorides **43** were obtained using tetrabutylammonium difluorotriphenylstannane as a fluoride source.[40] Treatment of the in situ-prepared 1,1-diiodoalkanes with DBU furnished the corresponding vinyl iodides **42** in excellent yields and high stereoselectivity (Scheme 17).[41]

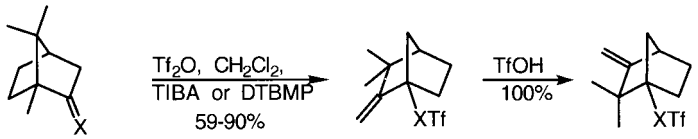
Stable *gem*-bistriflates e.g. **45** and **47** are available from the reaction of Tf_2O with non-enolizable and difficultly enolizable ketones such as **44** and **46** (Scheme 18).[42]

Bicyclic ketones in the terpene series give mainly rearranged triflates on treatment with triflic anhydride. Thus, camphor in the absence of a base yielded a mixture of the *gem*-bistriflate **48** and the rearranged triflates **49a** and **49b**.[43] During aqueous workup, compounds **48–49** underwent hydrolysis leading to camphor and bridgehead triflates **50a–b** (Scheme 19).

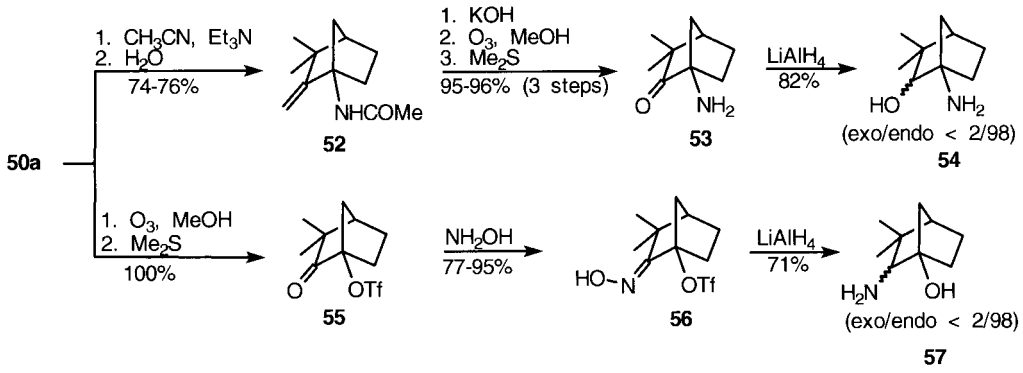
When the reaction with (+)-camphor was carried out in the presence of a hindered base such as DTBMP or Hünig's bases, the enantiopure triflate (−)-**50a** was the main reaction product.[43,44] The same Wagner–Meerwein rearrangement leading to predominant formation of bridgehead triflates[44,45] and thiotriflates[46] was observed for different bicyclic ketones and thioketones; representative examples are given below. Camphor derivatives (−)-**50a** and (−)-**51a** could be quantitatively isomerized to homochiral (−)-**50b** and (−)-**51b**, when treated with TfOH at −78°C through a Nametkin rearrangement.[46] The reaction of bridgehead triflates and thiotriflates with $LiAlH_4$



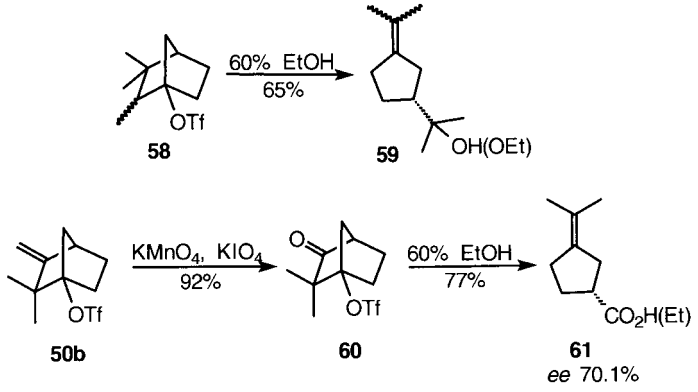
Scheme 20.



Scheme 21.



Scheme 22.



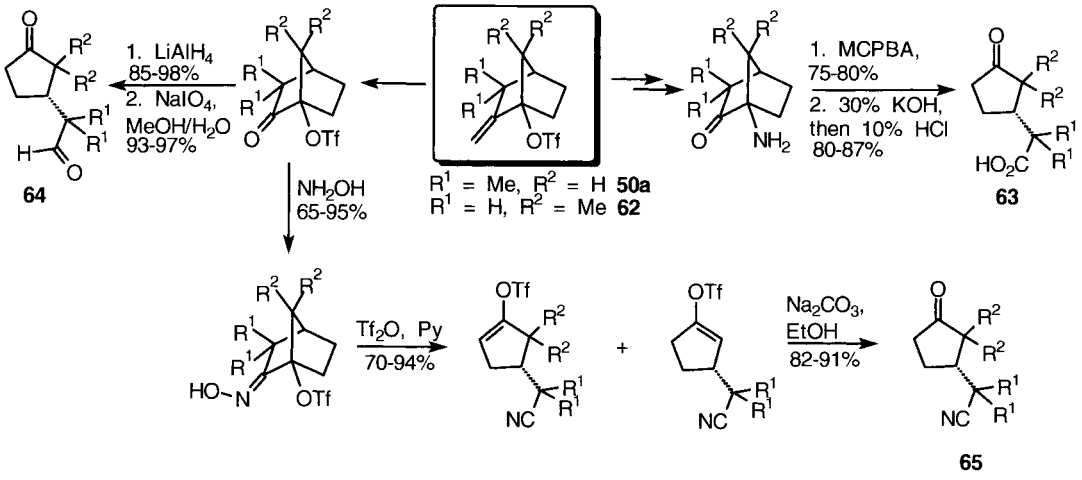
Scheme 23.

proceeds with X–S (X=O,S) bond cleavage, producing the corresponding homochiral 1-norbornyl alcohols[44] and thiols[46] in good yields (Schemes 20 and 21).

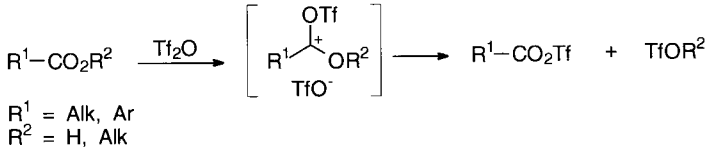
Martinez et al.[47] have developed an approach to the enantiospecific synthesis of the new homochiral β-amino-alcohols **54**, **57** from naturally occurring 2-norbornanones based on the high diastereofacial selectivity of the $LiAlH_4$ reduction of the bicyclic ketone **53** and oxime **56**. The former could be easily prepared via a sequence involving the solvolysis of the homochiral triflate **50a** in CH_3CN/Et_3N followed by amide hydrolysis and ozonolysis, whereas the latter resulted from the ozonolysis of **50a** to form **55** followed by reaction with NH_2OH (Scheme 22).[47]

In contrast to the unsaturated analogues **50a–b**, solvolysis of trimethyl substituted 1-norbornyl triflate **58** in 60% ethanol appears to proceed unusually via novel σ-bridged carbocations to form mainly the cyclopentane derivatives **59**, resulting from the $C_2–C_3$ bond cleavage.[48] This process has been successfully applied to the conversion of the triflate **50b** into the enantiomerically enriched cyclopentanecarboxylic acid **61**,[49] via the ketone **60** (Scheme 23).

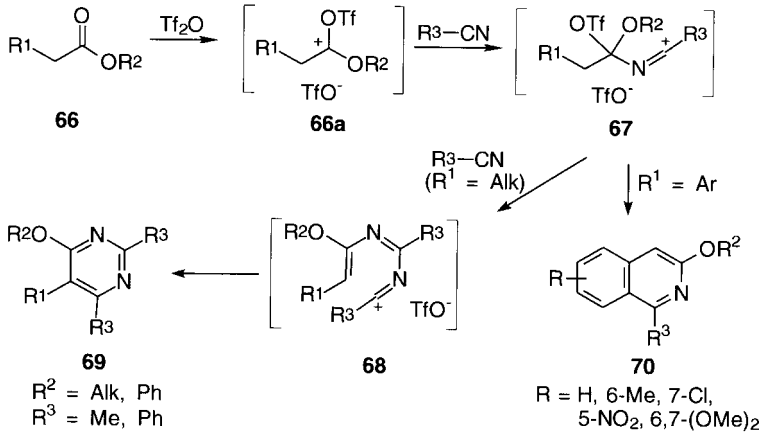
Cleavage of the $C_1–C_2$ bond in norbornane derivatives



Scheme 24.



Scheme 25.

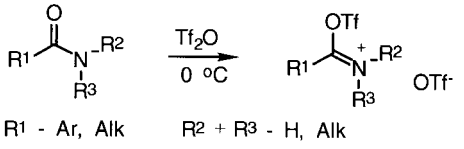


Scheme 26.

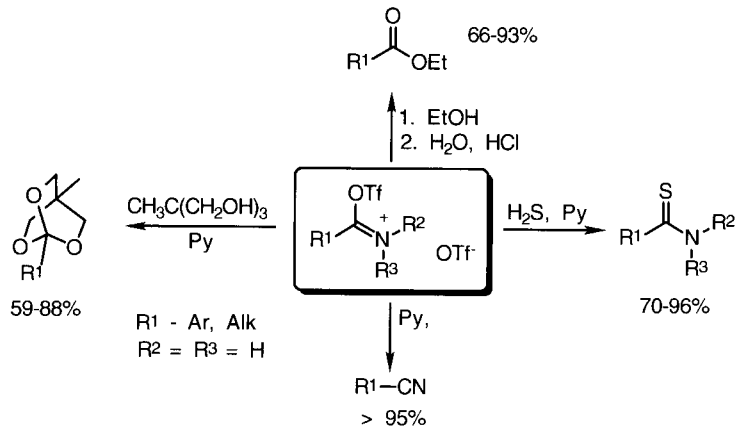
could be accomplished by base-promoted hydrolysis of α-nitroketones, periodate oxidation or triflic anhydride-induced Beckman rearrangement[50] of suitable precursors prepared from bridgehead triflates **50a** and **62**.[51] In all cases, the corresponding homochiral 3-substituted cyclopentanones **63–65** were obtained in excellent yields (Scheme 24).

2.1.3. Reaction with carboxylic acids and esters. The reaction of carboxylic acids and esters with Tf_2O also proceeds via the formation of the trifloxycarbenium cations which then lose triflic acid (or alkyl triflate) giving the trifluoromethanesulfonic carboxylic anhydrides.[52,53] These anhydrides may be utilized as highly effective acylation agents[54] which even react with nonactivated aromatics (benzene, toluene) without Friedel–Craft catalysts to yield aryl ketones (Scheme 25).[53,55]

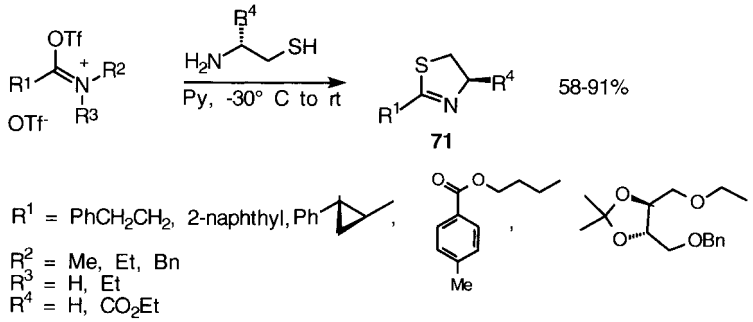
In the presence of a nitrile, the cations **66a** derived from aliphatic esters **66** (R^1=Alk) behave similarly to those formed from ketones and Tf_2O,[23] affording substituted



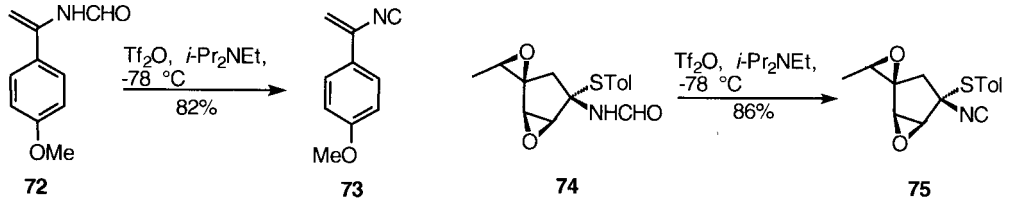
Scheme 27.



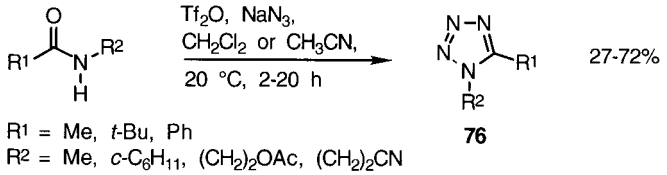
Scheme 28.



Scheme 29.



Scheme 30.



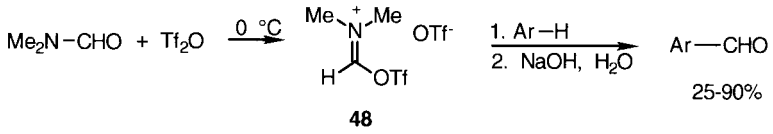
Scheme 31.

4-alkoxypyrimidines **69** in good yields via the intermediate **68**.[56] In contrast, the reaction of nitriles with arylacetic esters in the presence of Tf_2O furnished 3-alkoxyisoquinolines **70** via intermolecular cyclization of the intermediate nitrilium cation **67** (Scheme 26).[53]

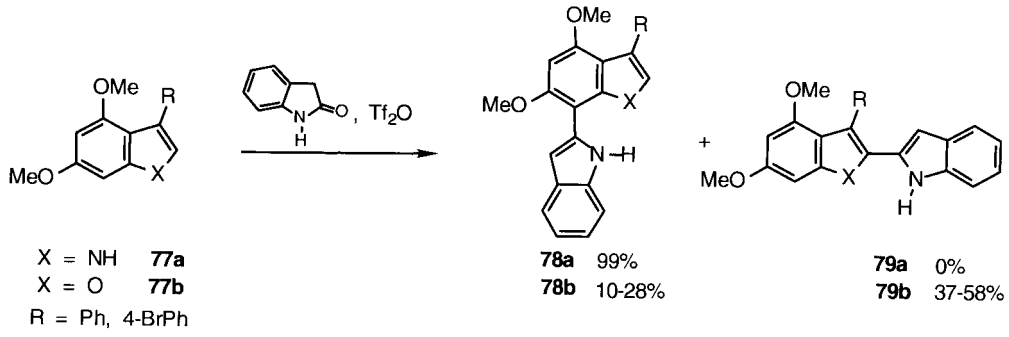
2.1.4. Reaction with amides and vinylogous amides. Treatment of tertiary and secondary amides with triflic anhydride at low temperatures gives rise to iminium and imino triflates, respectively (Scheme 27).

These salts are versatile reagents which can react with various N-, O- and S-nucleophiles and so may be used for the transformation of an amide function into other carbonyl functions. Thus, secondary and tertiary amides were subsequently treated with Tf_2O, pyridine (or a less nucleophilic base such as 2,6-lutidine or 2,6-di-*t*-butylpyridine) and alcohols[57–59] or hydrogen sulfide[60] to afford the corresponding esters[57,58] orthoesters[59] and thioamides.[57,60] The primary amides were quantitatively dehydrated to nitriles under these conditions (Scheme 28).[58]

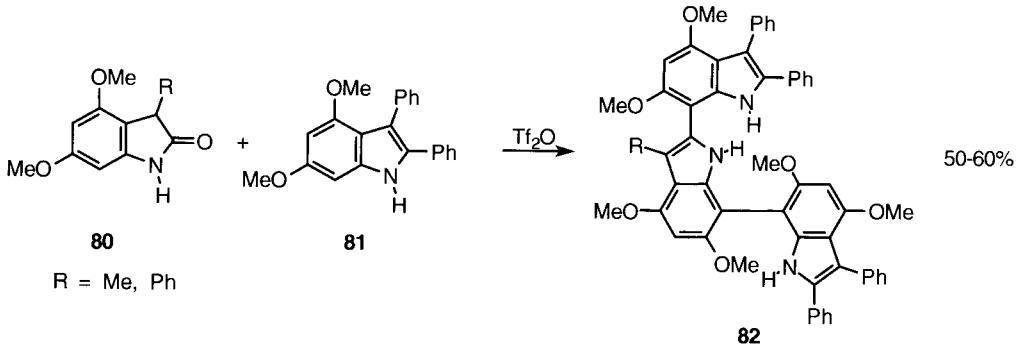
Addition of 2-aminothiols to the iminium triflates resulted in the formation of the corresponding thiazolines **71**.[61] This



Scheme 32.



Scheme 33.



Scheme 34.

reaction was found to tolerate the presence of chiral centers and various functional groups such as benzoate, silyl ether, benzyl ether and acetonide (Scheme 29).

Triflic anhydride was found to be far superior to phosgene or any of the related reagents in the dehydration of formamides **74** and vinylformamides **72** to isonitriles **73, 75** (Scheme 30).[62,63]

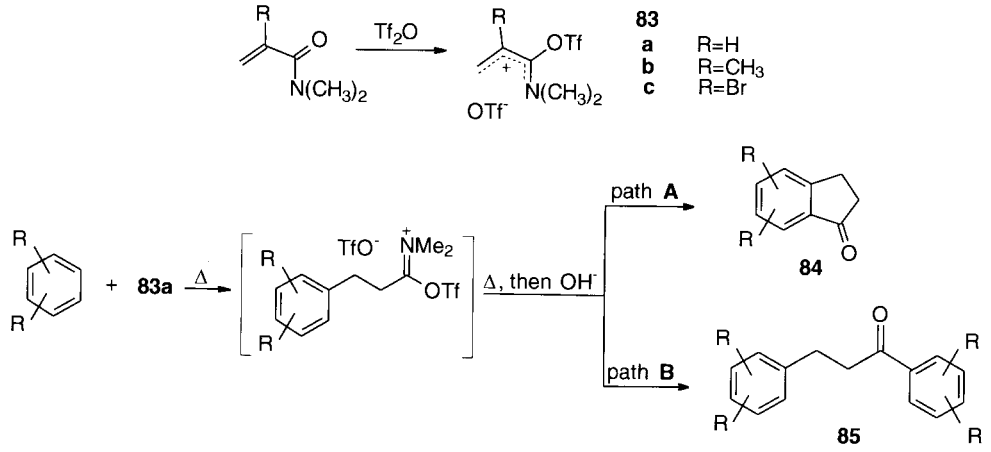
Thomas[64] devised a simple one-step method for the conversion of secondary amides to tetrazoles **76** employing triflic anhydride and sodium azide. A 1*H*-unsubstituted tetrazole was also synthesized by this method from an amide substituted with a cyanoethyl protecting group (Scheme 31).

Application of triflic anhydride as a mild and effective activation reagent in the Vilsmeier–Haack reaction is the subject of increasing interest. It has been reported that less nucleophilic aromatics can be formylated when the classical Vilsmeier–Haack reagent is replaced by DMF/triflic anhydride. The iminium salt **48** which is formed even reacts with naphthalene and mesitylene (Scheme 32).[65]

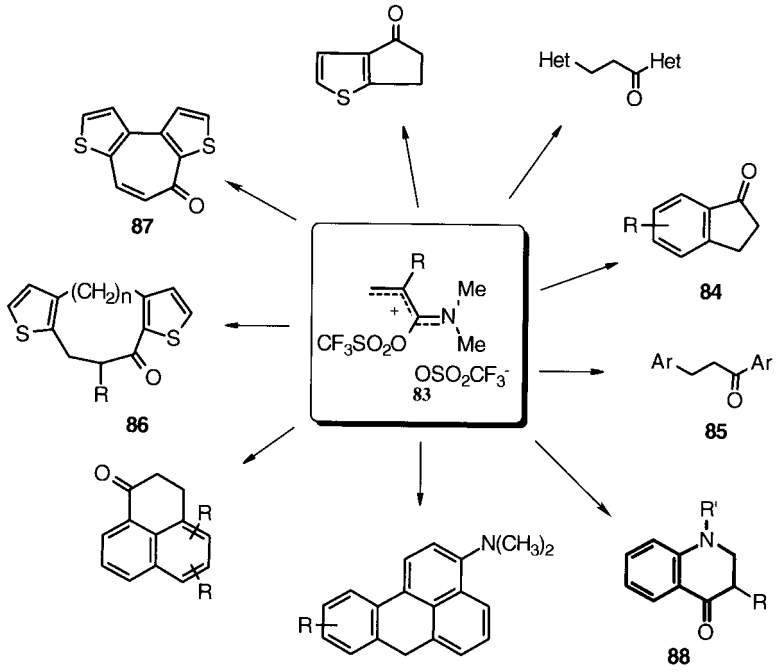
Using similar conditions indolin-2-one was shown to convert 3-aryl-4,6-dimethoxyindoles **77a** into the 2,7′-bisindolyl compounds **78a**.[66] In contrast, reaction of the indolin-2-one/triflic anhydride complex with 3-aryl-4,6-dimethoxybenzofurans **77b** gave 2-substituted indolobenzofurans **79b** as the major products; the 7-substituted products **78b** were obtained in low yields due to the higher reactivity of C_2 over C_7 in the 3-aryl-4,6-dimethoxybenzofuran series.[67] In all cases, no reaction took place when phosphoryl chloride was used for the activation of indolin-2-one (Scheme 33).[66,67]

Indolin-2-ones **80** react with the 2,3-disubstituted indole **81** in the presence of two equivalents of Tf_2O forming predominantly the 7,7′:2,7′-terindolyls **82**.[68] The reaction mechanism involves the initial reaction of the iminium salt with the indole **81** to produce 2,7′-bisindolyl system, which then undergoes oxidative coupling with a further equivalent of **81** (Scheme 34).

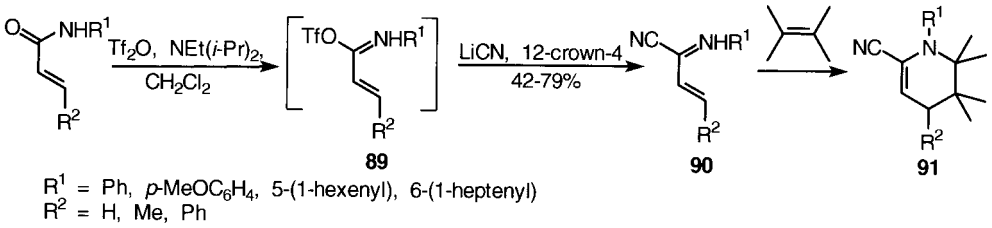
α,β-Unsaturated iminium triflates **83** derived in situ from the corresponding amides and triflic anhydride were found to react with electron-rich aromatics[69,70] and heteroaromatics[71,72] yielding the corresponding cyclic ketones **84** and/or 1,3-diaryl(hetaryl)propanones **85**. The mechanism envisaged for this reaction involves the initial alkylation of the aromatic substrate followed by either intra- (path



Scheme 35.



Scheme 36.



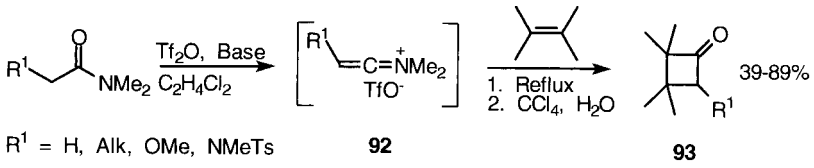
Scheme 37.

A) or intermolecular (path B) Vilsmeier acylation (Scheme 35).[70]

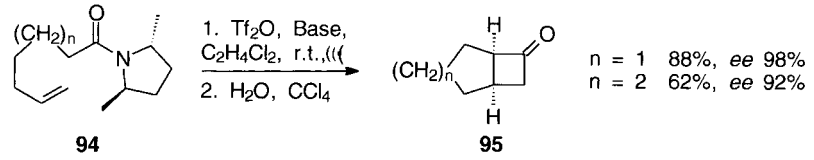
The use of appropriately substituted and activated bis-aromatic compounds with different bridge lengths would provide an efficient and concise route to a number of fused seven- and eight-membered cyclic ketones **86**, **87**.[73]

Secondary aromatic amines can react with **83a**,**b** to afford the corresponding 1,2,3,4-tetrahydroquinolones **88**.[74] Some representative examples reported by the authors[69–74] are shown in Scheme 36.

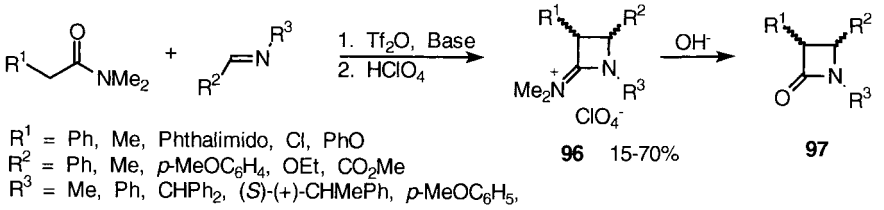
Unsaturated imidoyl triflates **89**, prepared in situ from the secondary acryloyl amides and triflic anhydride in the



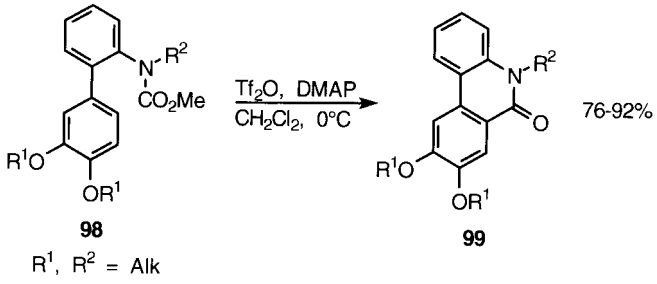
Scheme 38.



Scheme 39.



Scheme 40.



Scheme 41.

presence of a Hünig's base, on treatment with a suspension of lithium cyanide and 12-crown-4 were converted into 2-cyano-1-azabutadienes **90**.[75] The Diels–Alder reaction of the heterodienes **90** with a complete range of electron rich, electron poor, and neutral dienophiles provides a potentially powerful method for the construction of structurally defined polyfunctionalized tetrahydropyridines **91**;[75,76] an intramolecular version of this reaction has been used successfully for the preparation of indolizine and quinolizine ring systems (Scheme 37).[77]

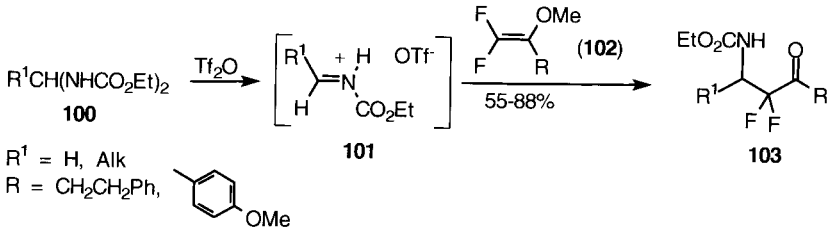
Ghozes et al.[78–80] observed [2+2] cycloaddition reactions of keteniminium triflates **92** generated from N,N-disubstituted amides and triflic anhydride. These salts turned out to be ideal reagents due to their high reactivity in cycloaddition reactions to form cyclobutanones **93**, even with nonactivated alkenes. An intramolecular version of this reaction provides a practical synthesis of cyclobutanones fused to carbo- or heterocyclic rings **95** (Scheme 38).[78,81]

Asymmetric versions of this reaction employing amides **94** derived from chiral amines were also investigated.[82,83] The highest induction and excellent chemical yields were formed for amides with C_2-symmetrical chiral pyrrolidines such as 2,5-dimethylpyrrolidine using ultrasound irradiation (Scheme 39).

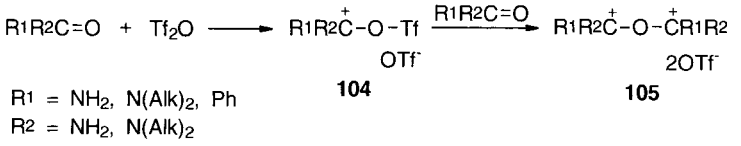
Battaglia et al.[84] indicated that annulation of aldimines with keteniminium salts (chlorides and triflates) may constitute an attractive alternative route to that of the Staudinger reaction for the synthesis of polysubstituted β-lactams **97**. In contrast to α-chloroiminium chlorides, keteniminium triflates show a preference for the *cis*-products (Scheme 40).[84]

The combination of triflic anhydride and 4-(N,N-dimethylamino)pyridine effects Bischler–Napieralski cyclization of β-phenethylcarbamates and β-phenethylamides under mild conditions, while $POCl_3$ in some cases did not achieve the cyclization (Scheme 41).[85]

Treatment of the biscarbamates **100** with Tf_2O allowed the



Scheme 42.

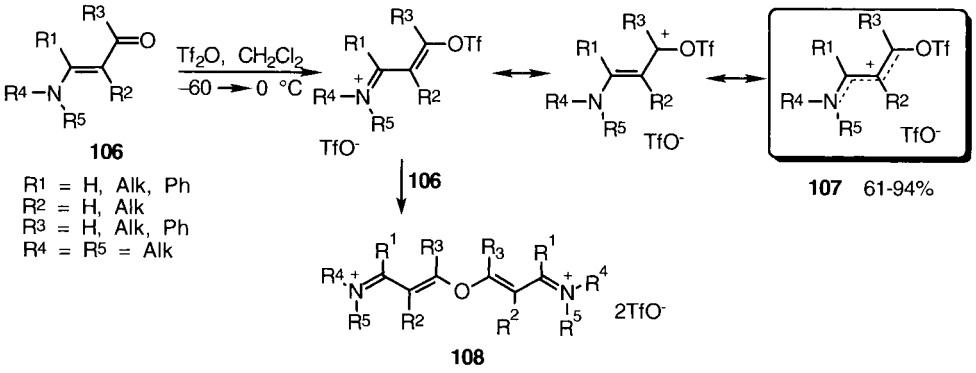


Scheme 43.

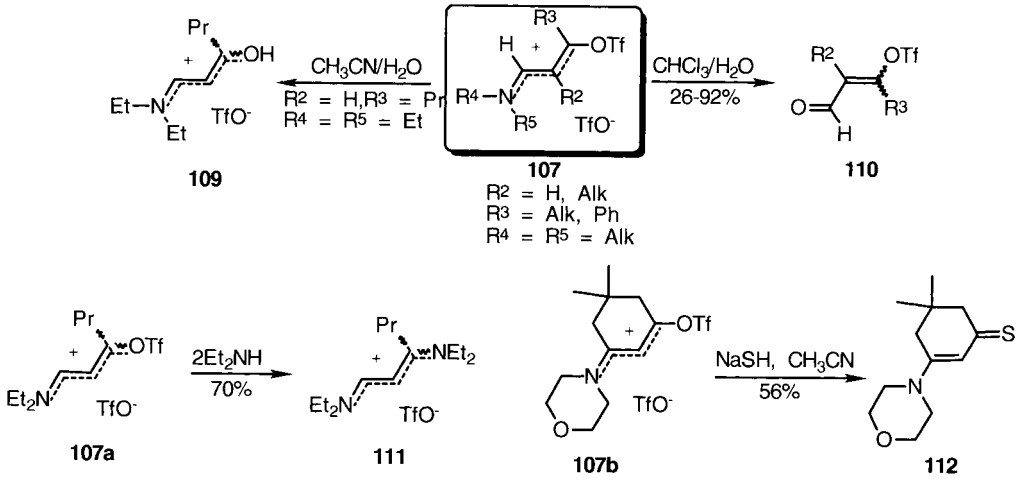
generation of N-protonated N-acyliminium salts[86] which can react with vinyl ethers **102** to give β-amino-α,α-difluoroketones **103** (Scheme 42).

Treatment of ureas, pyridones[87] and amides[88] with triflic anhydride led to the formation of stable dicarbonium salts $R_1R_2C^+–O–C^+R_1R_2\cdot 2TfO^-$ **105**. It seems probable[88] that this reaction proceeds initially via the formation of the electrophilic monocarbonium salt **104** which is then attacked by another molecule of the carbonyl compound. Some reactions of the dications obtained in this manner with various nucleophiles such as pyridines,[89] diazophosphoryl compounds,[90] ketoenolates and ketonitriles[91] have been investigated (Scheme 43).

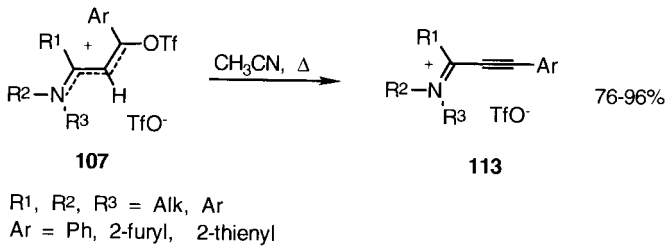
Stable conjugated dication ether salts **108** were formed from



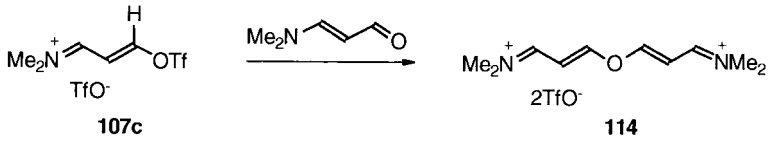
Scheme 44.



Scheme 45.



Scheme 46.



Scheme 47.

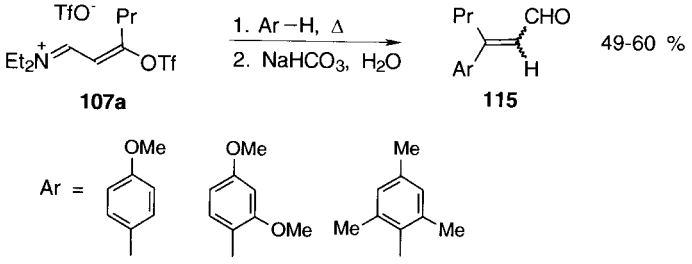
the reaction of triflic anhydride with two equivalents of vinylogous amides **106**.[92] With a 1:1 molar ratio, the 3-trifloxypropeniminium triflates **107** were obtained (Scheme 44).

Reaction of the iminium salts **107** with nucleophiles may occur at carbon atoms C-1 or C-3. Maas and co-workers[93] have shown that 3-trifloxypropeniminium triflates, in contrast to the 3-chloropropeniminium salts, reacted with nitrogen and sulfur nucleophiles by substitution of the trifloxy group to give **111** and **112**, presumably due to the good leaving group properties of triflate anion. Hydrolysis of **107** with aqueous acetonitrile also proceeds at C-3, whereas treatment of the triflates with the two-phase system $CHCl_3/H_2O$ led to the corresponding β-formylvinyl triflates **110** (Scheme 45).

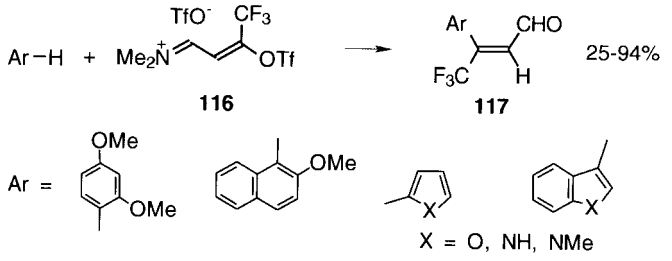
The salts **107** can undergo thermal β-elimination of triflic acid to furnish the propyniminium triflates **113**.[94,95] The latter systems are valuable precursors of substituted aminoallenes,[96] and 1- and 2-aminobutadienes (Scheme 46).[97]

Maas et al.[98] have investigated the application of triflic anhydride as an activation reagent in the vinylogous Vilsmeier–Haack reaction. It was considered that the scope of vinylformylation could be expanded if 3-trifloxypropeniminium triflates rather than the 3-chloropropeniminium salts were used. Unfortunately, it was found that the reaction with electron-rich aromatics proceeds more slowly and in lower yields when the dimethylaminoacrolein was activated with Tf_2O rather than with $POCl_3$. The apparently low efficiency of triflic anhydride in this case can be explained by the conversion of the initially formed triflate **107c** to the less electrophilic dication **114** (Scheme 47).

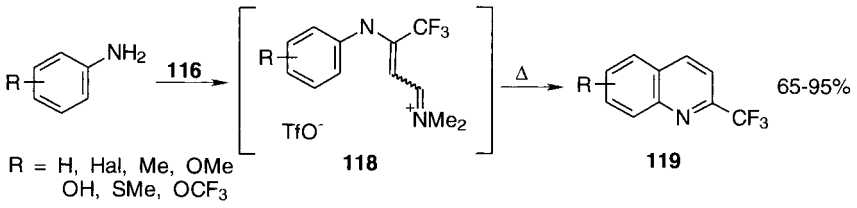
In contrast to **107c**, the substituted analogue **107a** can be



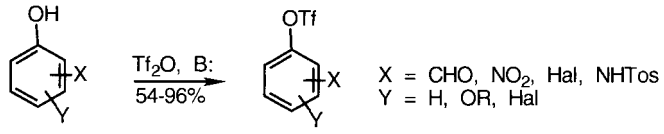
Scheme 48.



Scheme 49.



Scheme 50.

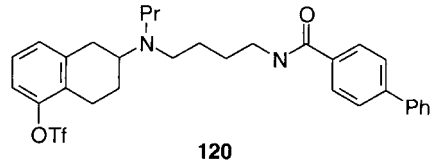


Scheme 51.

prepared cleanly, without any dication formation. The more electrophilic salt **107a** reacted with anisole and mesitylene to provide the expected 3-aryl-2-hexenals **115** (Scheme 48).[98]

In a similar manner, the reaction of the 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one-triflic anhydride complex **116** with various aromatics allowed the preparation of 3-CF_3 substituted cinnamaldehydes **117**. The reaction proceeds stereoselectively to give preferably aldehydes with an *E* configuration (Scheme 49).[99]

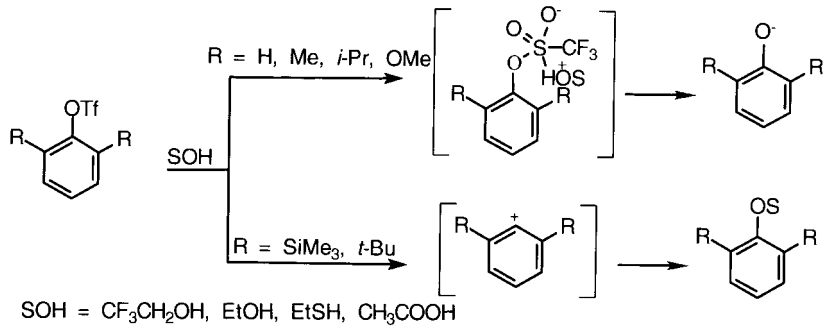
2-Trifluoromethylquinolines **119** were prepared in excellent yields by reaction of the iminium triflate **116** with different anilines.[100] Presumably, treatment of the trifloxypropeniminium salt with two equivalents of amine results in the replacement of the OTf group by the amino moiety and formation of the vinamidinium salt **118**. Subsequent intermolecular cyclisation led to the target quinolines (Scheme 50).



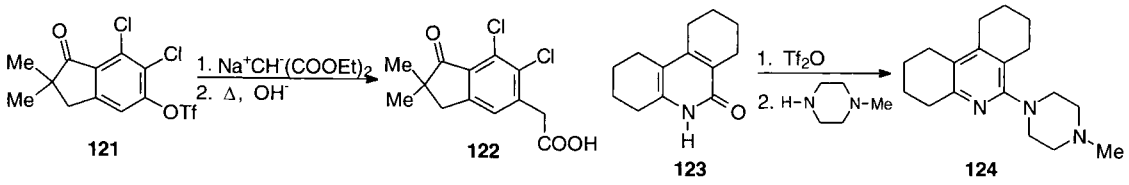
Scheme 52.

2.2. Synthesis of aryl triflates. Vinyl and aryl triflates in the cross-coupling reactions

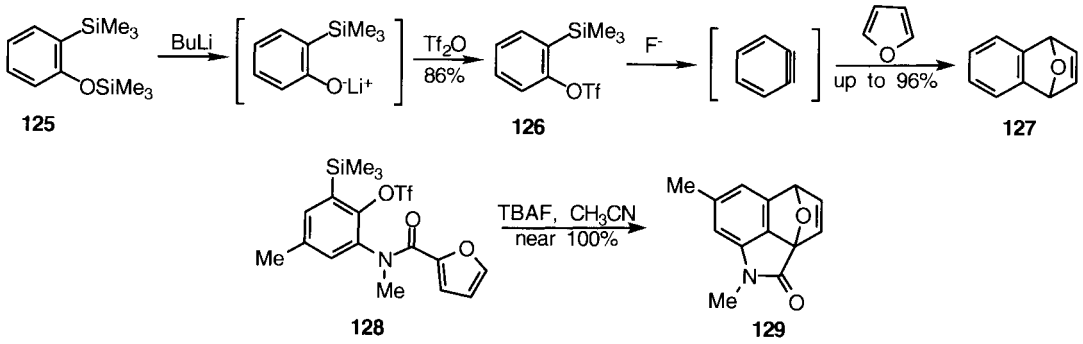
The most convenient procedure for the preparation of aryl triflates involves the treatment of phenols with triflic anhydride in the presence of a base such as a tertiary amine or sodium carbonate.[1] Aromatic *N*-heterocycles (pyridines,



Scheme 53.



Scheme 54.



Scheme 55.

indoles, quinolines, isoquinolines and carbazoles) bearing a hydroxy group could also be converted to the corresponding triflates by this method (Scheme 51).[2]

In some cases, triflate modification of an arene hydroxy group has resulted in the generation of a new pharmacologically active compound. Thus, tetraline derivatives **120**, which were evaluated as antagonists with a high affinity and selectivity for the dopamine D_3 receptor,[101] showed potential as an antipsychotic therapy which was free of the extra-pyramidal side effects (Scheme 52).

Aryltriflates appear to be extremely stable and unreactive compounds. Despite the high leaving group properties of the triflate anion, earlier investigations of the solvolytic reactivity of various aryl triflates revealed the absence of any aryl cations.[102] In highly polar non-nucleophilic solvents, no reaction occurred and the starting triflates were recovered quantitatively even after several days heating at 200°C, whereas in the presence of a nucleophile, nucleophilic attack upon sulfur and S–O bond cleavage were observed.[102] Sonoda et al.[103] have recently reported an example of the generation of aryl cations in the solvolysis of 2,6-disubstituted aryl triflates. The presence of bulky trimethylsilyl and/or *t*-butyl group(s) at *both ortho* positions is essential for the S_N1 solvolysis (Scheme 53).

Aryl triflates with strong electron-withdrawing substituents in the ring undergo nucleophilic displacement via an addition–elimination mechanism. For example, reaction of the triflate **121** with sodium malonate followed by decarboxylation furnishes the corresponding arylacetic acid **122**.[104] Primary and secondary amines react smoothly with nitro-substituted aryl triflates[105] or 2-pyridyl(quinolyl) triflates[106] to afford the corresponding aromatic amines **124** (Scheme 54).

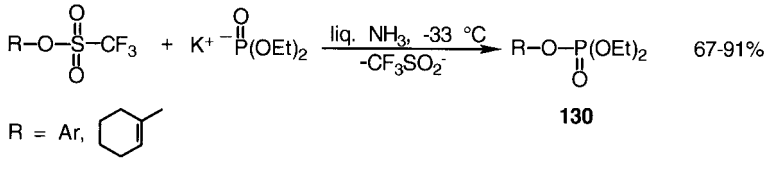
Fluoride-induced 1,2-elimination of *o*-trimethylsilylphenyl triflate **126**, which could be readily synthesized from the silane **125**, provided a convenient route to benzyne under mild conditions.[107] Detriflation from an aryl anion intermediate appeared to have occurred in preference to protonation even in the presence of alcohols. This fragmentation has some advantages over other methods of aryne generation,[107,108] and it could be applied to the preparation of the polycyclic oxindole-containing system **129** (Scheme 55).[108]

Interestingly, aryl triflates can act as oxidizing agents toward phosphites.[109] Their reaction with potassium diethylphosphite in liquid ammonia afforded the corresponding aryl diethylphosphate esters **130**, with concomitant loss of trifluoromethylsulfinate anion (Scheme 56).

Due to the high stability and consequent unreactivity of aryl triflates, their chemistry had attracted little attention until the discovery of the transition metal catalyzed cross-coupling reaction of aryl and vinyl triflates. In the last 15 years there have been numerous demonstrations of the utility of this reaction, which proceeds with high regioselectivity under mild conditions and can be used not only for carbon–carbon bond formation, but additionally for the preparation of vinylstannanes, unsaturated phosphonates and for the removal of the sulfonate group by hydrogenation. The corresponding vinyl and aryl halides show a similar spectrum of reactions, and the iodides and, in some cases, the bromides, are more reactive than the triflates. The main feature of unsaturated triflates is their convenient preparation from carbonyl compounds and phenols. The synthetic transformations of vinyl and aryl triflates have been extensively reviewed recently by Ritter.[2]

2.3. Reaction with alcohols. Synthesis of alkyl triflates

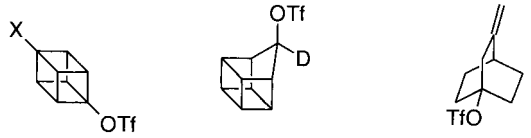
The past 30 years have witnessed a significant increase in the utilization of alkyl triflates as one of the most powerful groups of alkylating agents, capable of alkylating not only carbon but also oxygen, nitrogen and sulfur. The most widely used parent compound, methyl triflate, for example,



Scheme 56.

was found to be only 5 to 12 times less reactive than the unstable trimethyloxonium ion.[110] The literature on the applications of alkyl triflates in organic synthesis is too profuse to be covered in full and, therefore, only representative examples are highlighted in this section. The literature up to 1982 has been reviewed in detail by Stang and Hanack.[1]

Alkyl triflates may generally be prepared from the reaction of an alcohol with triflic anhydride in the presence of a base. Other methods such as the interaction of an alkyl halide with silver triflate or treatment of an appropriate diazonium compound with triflic acid are less convenient. Primarily, alkyl triflates have been used for the generation and investigation of highly energetic carbenium ions.[1] Some typical recent examples are shown below (Scheme 57).[111–113]



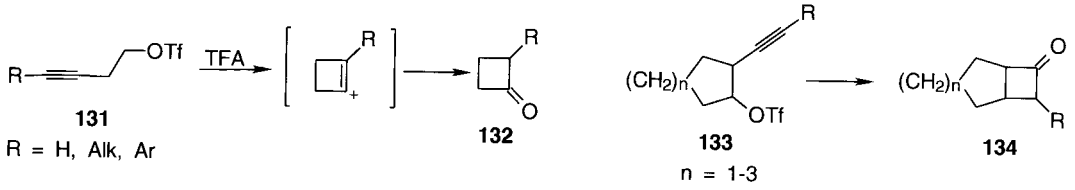
Scheme 57.

Interestingly, solvent effects and kinetic deuterium isotope effects show that, despite their high reactivity, primary (and presumably some secondary) alkyl triflates undergo an S_N2 process with little carbenium ion character[114] and, therefore, nucleophilic substitution of the triflate group in chiral triflates can proceed with clean inversion.

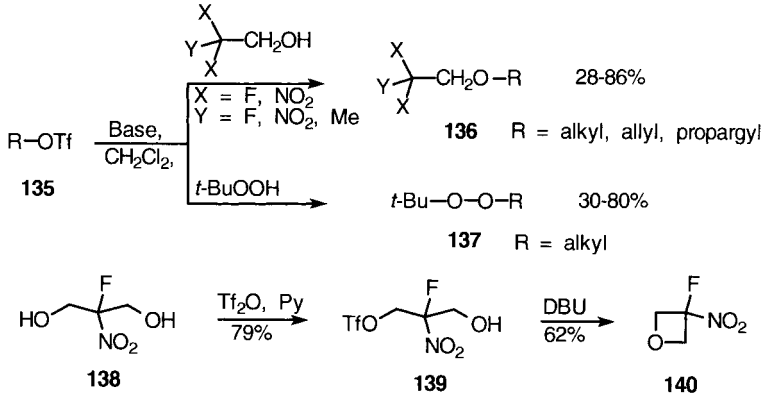
Solvolytic studies in the homopropargyl triflate series **131** resulted in elaboration of a simple and effective method of cyclobutanone **132** formation.[115] Fused cyclobutanones **134** are also accessible in good preparative yields through the triple bond participation in solvolysis of cyclic homopropargyl systems **133** (Scheme 58).[116]

Highly reactive alkyl triflates **135** were prepared and used to alkylate under mild conditions alcohols of low nucleophilicity[117] and alkyl hydroperoxides to prepare **136** and **137**.[118] An intramolecular version of this reaction in the case of the monotriflate of diol **138** gave 3-fluoro-3-nitrooxetane **140**, the first characterized oxetane with a nitro group on the ring (Scheme 59).[119]

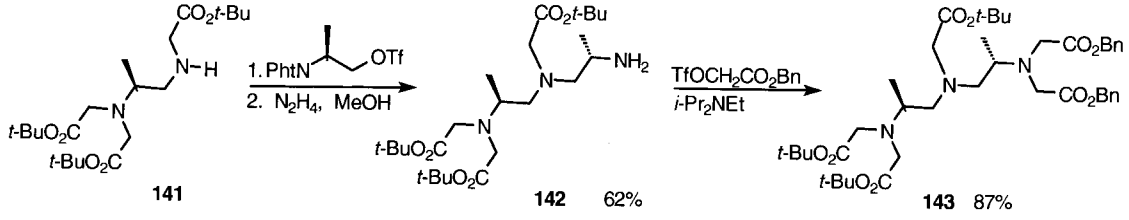
A series of α-carbonyl and α-cyano triflates was prepared either from alcohols and anhydride or from diazo precursors



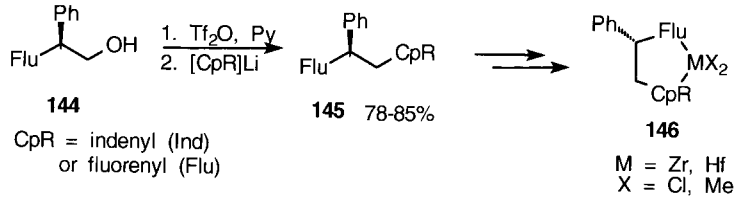
Scheme 58.



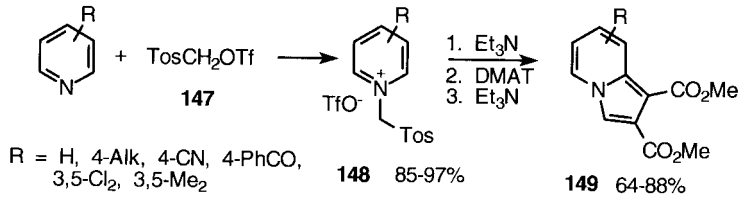
Scheme 59.



Scheme 60.



Scheme 61.



Scheme 62.

and triflic acid.[120] These reagents react smoothly with different S- and N-nucleophiles and thus provide easy access to a variety of stabilized ylids.[120] More recently, triflates derived from glycolic esters have been used for alkylation of sterically hindered disubstituted triazacyclononanes[121] and for the preparation of the diethylenetriaminepentaacetic acid (DPTA) analogue **143** (Scheme 60).[122]

Some carbanions may also undergo efficient alkylation by triflates. Rieger and co-workers[123] have applied the alkylation of fluorenyl- and indenyllithium to the synthesis of enantiomerically pure ethylene-bridged *ansa*-metallocene complexes **146** (Scheme 61).

Different indolizines **149** were synthesized via a sequence involving the alkylation of pyridines to form pyridinium salts **148** with tosylmethyl triflate **147** as a key step.[124] The latter could be conveniently prepared in 70% yield by esterification of the corresponding diol with triflic anhydride (Scheme 62).

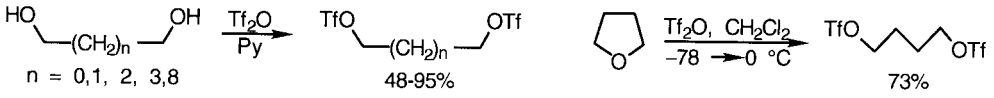
A series of bistriflates has been reported.[125,126] Although these have usually been synthesized from diols and triflic anhydride, the reaction with cyclic ethers may offer a better alternative.[117] Bistriflates are good linking agents; for example, the 1,4-bis(hydroxymethyl)cyclohexane-derived bistriflate **150** was used for the preparation of bicyclic and hydrocarbon bridged transition metal complexes **151** and **152** (Schemes 63 and 64).[127]

The bistriflate **154**, prepared in good yield from the weakly nucleophilic diol **153** and triflic anhydride,[128] represents one of the rare examples of a stable tertiary alkyl triflate (Scheme 65).

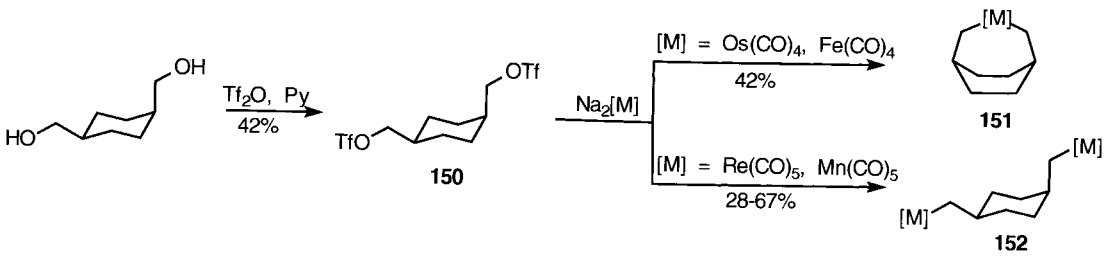
Elongation of the side chain in cyclic ethers to form **156** and **158** could be achieved by a coupling reaction of the primary alkyl triflates **155**, **157** with Grignard reagents using CuBr catalysis.[129] The corresponding bromides and tosylates failed to give the desired products (Scheme 66).

Johnson and co-workers[130] reported a synthesis of $\Delta^{6,7}$-taxols **161** and 7β,8β-methano(cyclopropyl)taxols **163**. They involve, as key steps, the DBU- or silica gel-induced elimination of triflic acid from the 7-O-triflates of either baccatin III **159** or of the taxol analogs (Scheme 67).

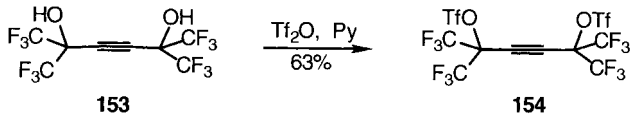
In the presence of Tf_2O, the allylic alcohols **164** undergo intramolecular [3+2] cycloaddition forming predominantly the *cis*-fused tricyclic compounds **165** (Scheme 68).[131]



Scheme 63.



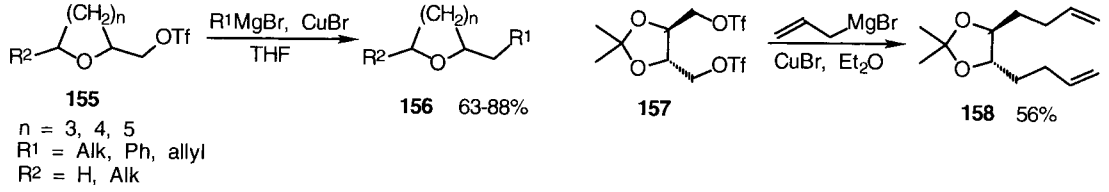
Scheme 64.



153 154

Scheme 65.

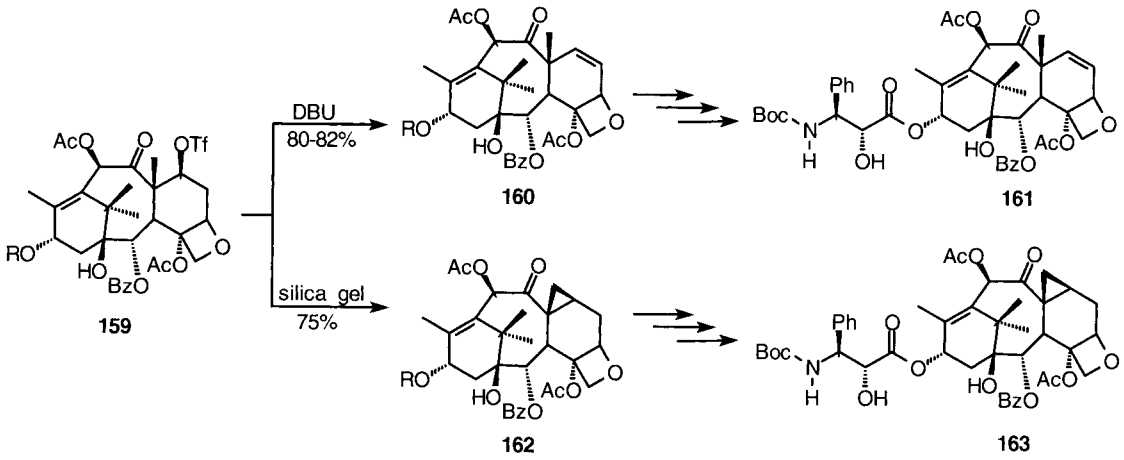
Effenberger et al.[132–134] originally found that, despite the highly cationic nature of alkyl triflates, nucleophilic displacement of the trifloxy group in chiral α-trifloxycarboxylic esters proceeds at low temperatures with clean inversion and excellent chemical and optical yields. This approach was shown to be much more effective than the



155 156 63-88% 157 158 56%

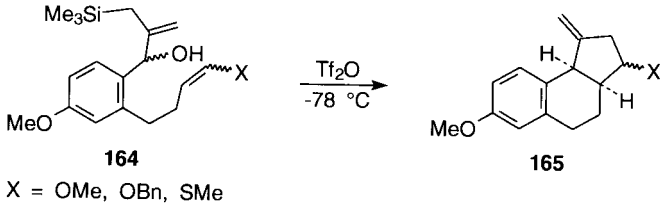
n = 3, 4, 5
R1 = Alk, Ph, allyl
R2 = H, Alk

Scheme 66.



159 160 161 162 163

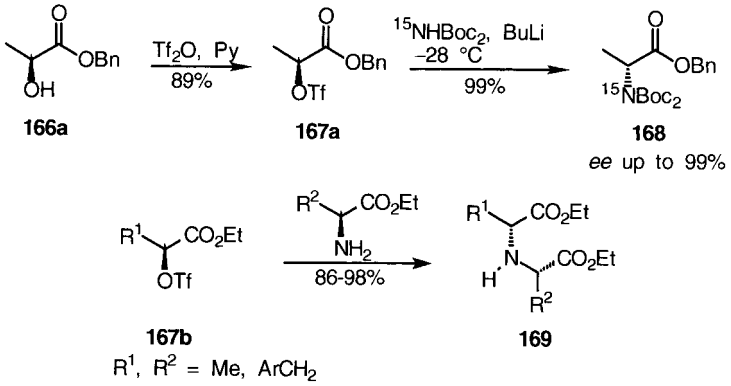
Scheme 67.



164 165

X = OMe, OBn, SMe

Scheme 68.



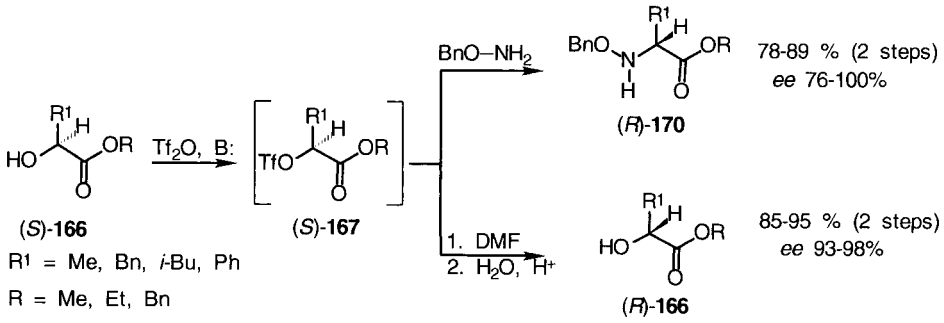
166a 167a 168

ee up to 99%

167b 169

R1, R2 = Me, ArCH2

Scheme 69.



Scheme 70.

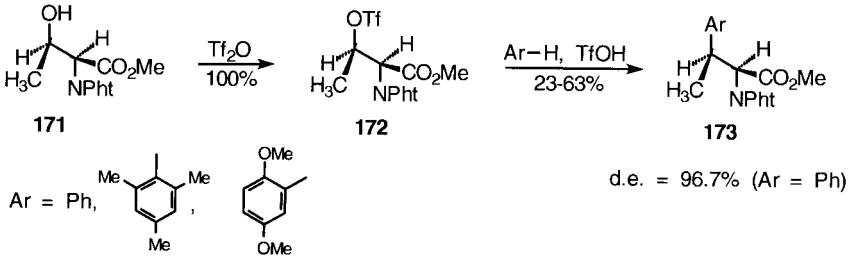
Mitsunobu reaction[135] and could be used for the direct synthesis of different *R*-α-amido acids,[132] ^{15}N-labelled protected amino acids (such as **168**)[135,136] as well as for the preparation of diastereomerically pure α,α'-imino dicarboxylic acids **169** (Scheme 69).[133]

Hydrolysis of triflates **167** derived from (*S*)-α-hydroxy esters offers an attractive route to enantiomerically pure unnatural (*R*)-isomers.[137] Both (*S*)- and (*R*)-O-benzyl-α-hydroxylamino acid esters **170** are available in high chemical and optical yields from α-hydroxy esters **166** via the corresponding triflates (Scheme 70).[137]

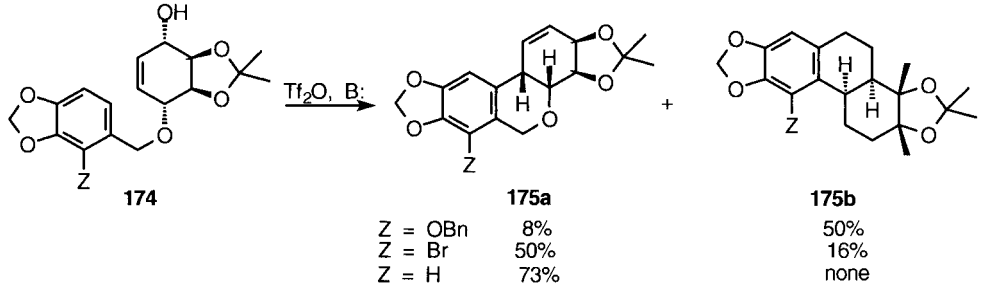
Secondary alkyl triflates may also be used for the alkylation of non-activated aromatic compounds.[138] In fact, the reaction proceeds rapidly at room temperature not only in the absence of a Lewis acid catalyst but in the presence of a non-nucleophilic base. Effenberger[139,140] has applied this methodology to the conversion of *N*-protected threonine **171** and allothreonine into the corresponding β-methyl phenylalanine derivatives **173**. It is interesting to note that reaction of the threonine derivative **172** with an aromatic nucleophile proceeds with almost complete retention of configuration, presumably due to the steric hindrance of rotation and shielding of the back side of the intermediate carbocation by the phthaloyl protecting group (Scheme 71).[140]

The intramolecular allylic version of this reaction has been exploited by Haseltine et al.[141] in an efficient route to the precursors for the anticancer agent (+)-pancratistatin. Triflation of the alcohols **174** induced intramolecular electrophilic *ortho* versus *ipso* alkylation of the piperonyl aromatic ring furnishing the pentacycles **175a** and **175b**. The regiochemistry of the attack could be controlled by the choice of arene substituent Z (Scheme 72).

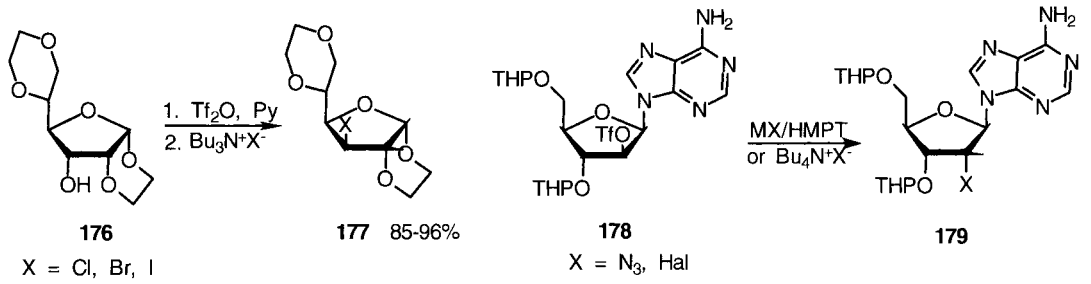
Triflic anhydride has also been widely used in sugar chemistry. Binkley et al.[142] have reported a sequence involving the conversion of partially protected carbohydrates **176** into triflate esters, followed by triflate displacement by halide or azide ions. This process is not accompanied by rearrangement or elimination and works well for both primary and secondary hydroxyl groups. Analogously, a simple synthesis of substituted adenosines **179** was achieved by activation of the hydroxy group with the triflate moiety



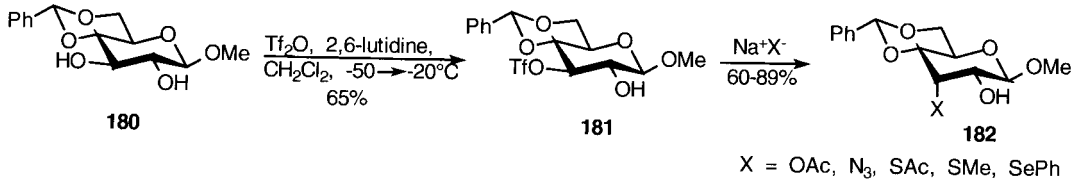
Scheme 71.



Scheme 72.



Scheme 73.



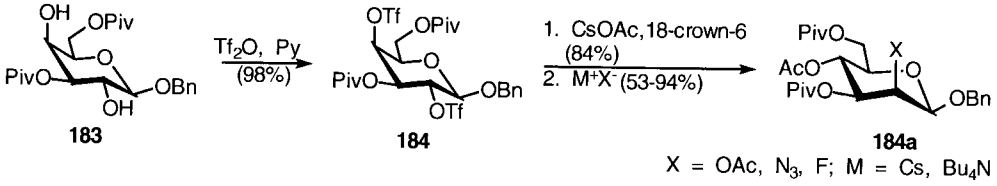
Scheme 74.

via formation of the triflate **178**.[143] 3-Deoxy sugars have been synthesized via the reduction of corresponding triflates with sodium in liquid ammonia (Scheme 73).[144]

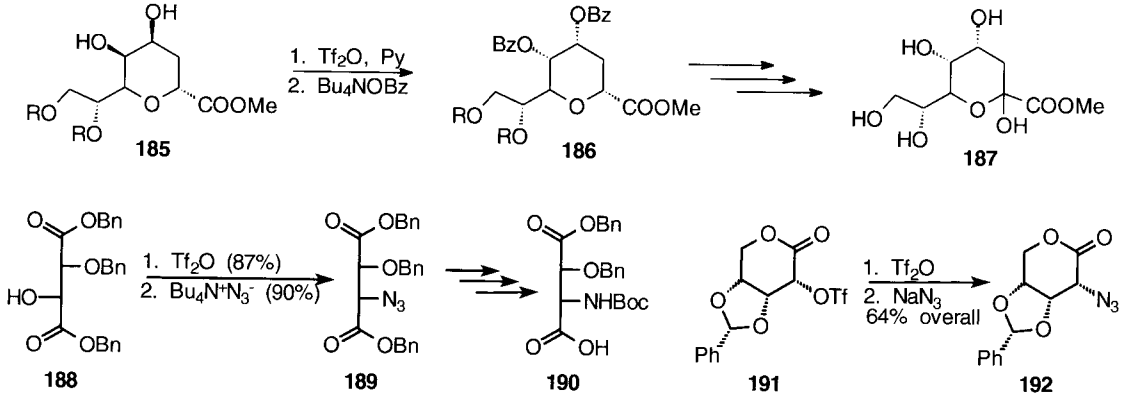
Some carbohydrate diols and triols can be selectively monotriflated;[145,146] by using Tf_2O and 2,6-lutidine, for example, the glucopyranoside **180** was selectively triflated at the C-3 hydroxyl to give **181** in 65% yield.[146] The S_N2 displacement of triflate from **181** represents an efficient way to introduce heteroatoms on to the pyranoside ring system (Scheme 74).[146]

A convenient and practical construction of the β-D-mannosidic and 2-heterosubstituted β-D-mannosidic units from the readily available 3,6-diprotected galactopyranoside **183** could be achieved via a stepwise inversion of the corresponding 2,4-bistriflate **184** to give **184a** (Scheme 75).[147]

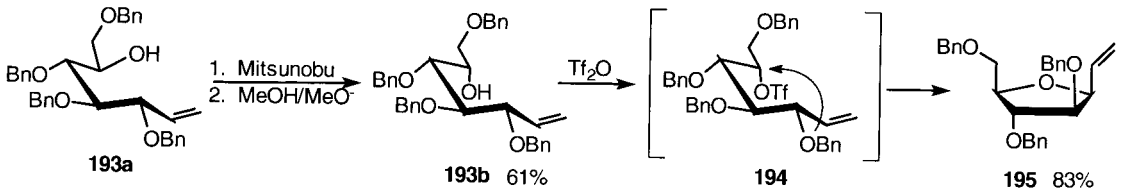
Auge[148] and, more recently, Burke[149] have used the stereospecific nucleophilic substitution of the triflate group in the total synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO, **187**) from **185**, a key component of the outer membrane lipopolysaccharide (LPS) of all Gram-negative bacteria. The desired double inversion was performed by treatment of the in situ formed bistriflate with tetrabutylammonium benzoate. Similarly, the azide **189** could be prepared by stereoselective S_N2 substitution of the triflate group in **188** with tetrabutylammonium azide.[150] In contrast,



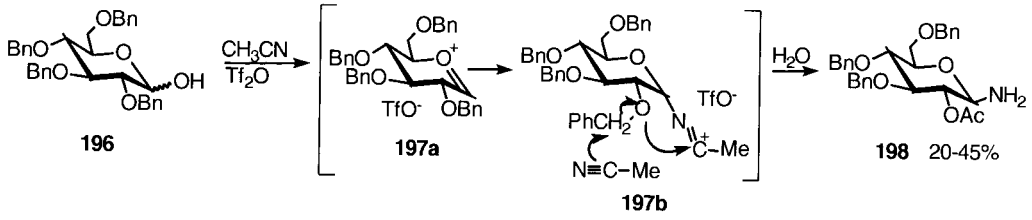
Scheme 75.



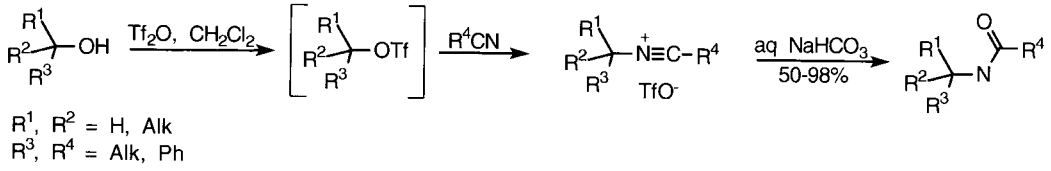
Scheme 76.



Scheme 77.



Scheme 78.



Scheme 79.

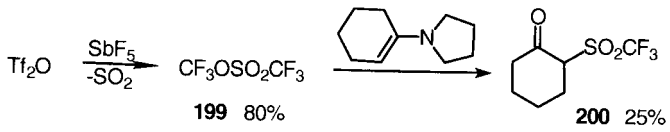
the displacement of triflate in **191** by sodium azide proceeds with overall retention of configuration to form **192**, possibly by equilibration of the product epimeric azides (Scheme 76).[151]

Triflates derived from hept-1-enitols **193** were extremely unstable and underwent spontaneous internal displacement, with clean inversion, by the favourably-placed benzyloxy group.[152] Concomitant dealkylation furnished the substituted furanosides **195** via intermediate **194** (Scheme 77).

Treatment of the glucopyranose **196** with Tf_2O in acetonitrile resulted in formation of the glucosylamine **198** in moderate yield.[153] This reaction proceeds through a glucosyloxocarbanion intermediate **197a** which is trapped by the nitrile (Scheme 78).

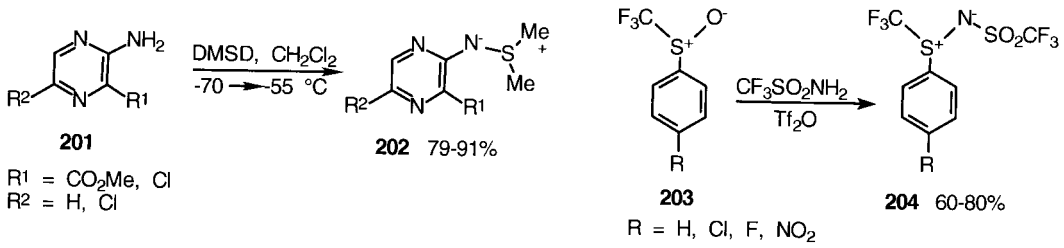
The reaction of nitriles with in situ-formed alkyl triflates was indicated as an improved modification of the Ritter reaction.[154] In contrast to the normal Ritter reaction the best yields of amides were obtained starting from primary and secondary alcohols (Scheme 79).

On treating triflic anhydride with a strong Lewis acid catalyst quickly decomposed into SO_2 and trifluoromethyl triflate (TMFT, **199**).[155,156] The latter could be considered as an alkyl triflate and possible CF_3^+ equivalent. It was found, however, that TMFT does not react with different nucleophiles as a trifluoromethylating agent, but it gives products that result from an initial attack of the nucleophile at sulfur.[156,157] The utility of TMFT as a triflating reagent is severely limited owing to its rapid breakdown into COF_2 and CF_3SO_3F in the presence of a nucleophile (Scheme 80).[156]

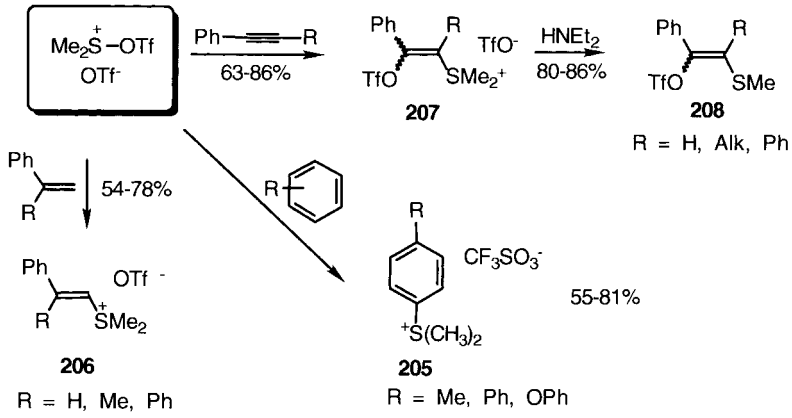


Scheme 80.

Scheme 81.



Scheme 82.



Scheme 83.

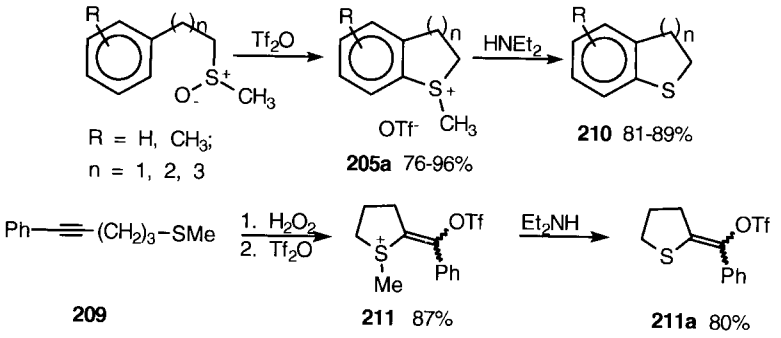
2.4. Reaction of triflic anhydride with nonmetal oxides

2.4.1. Synthesis and chemistry of trifloxysulfonium(selenonium) triflates. Early studies by Hendrickson and Schwartzman[158] established that triflic anhydride adds to dimethylsulfoxide to form the relatively unstable, air- and water-sensitive dimethyl(trifloxy)sulfonium triflate (dimethylsulfide ditriflate, DMSD). This carries the best leaving group at the sulfonium center and thus could be used for the facile oxidation of alcohols to carbonyl compounds (Scheme 81).[158]

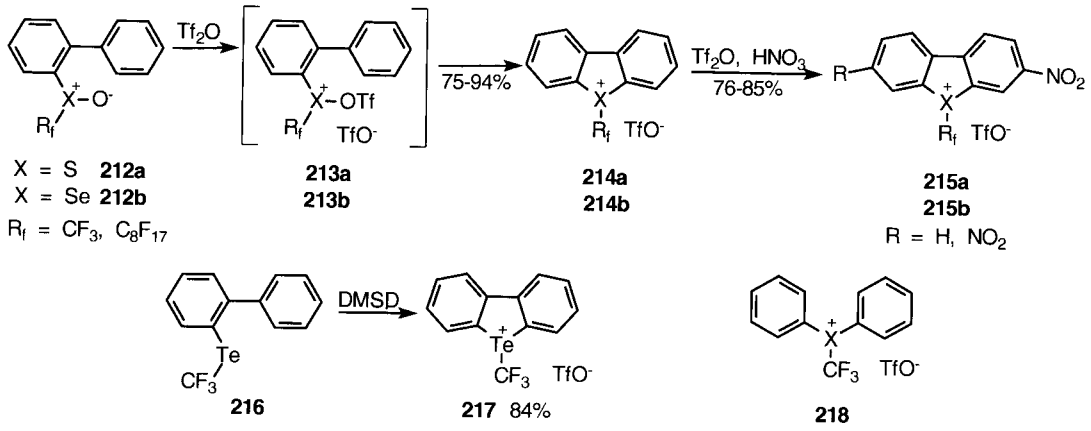
Trifloxysulfonium triflates are generally superior to other existing reagents for the synthesis of sulfimines **202** from amines with a low nucleophilicity **201**.[159] Thus, different amino heterocycles[159,160] **201** and even the weakly nucleophilic triflamide[161] could be converted into corresponding sulfimines **202** and **204** by treatment with sulfoxides (DMSO or **203**) in the presence of triflic anhydride (Scheme 82).

Recently, the authors have shown that DMSD can act as a highly reactive S-electrophile towards nonactivated arenes,[162] alkenes[163] and alkynes.[164] In these reactions, DMSD behaves as an S^{2+} synthon giving rise to the corresponding sulfonium salts **205–207**. It is of interest to note that the reaction with alkynes proceeds as a conjugate addition of an electrophile (dimethylsulfonium moiety) and a nucleophile (triflate group), and thus opens up a convenient route to vinyl triflates having a strong electron-withdrawing group at the β-position (Scheme 83).[164]

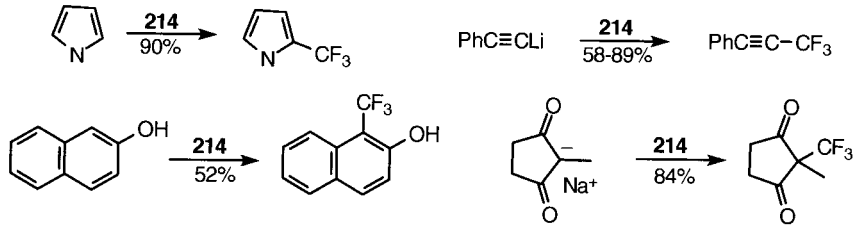
An intramolecular version of these reactions which proceeds via formation of the corresponding sulfonium



Scheme 84.



Scheme 85.



Scheme 86.

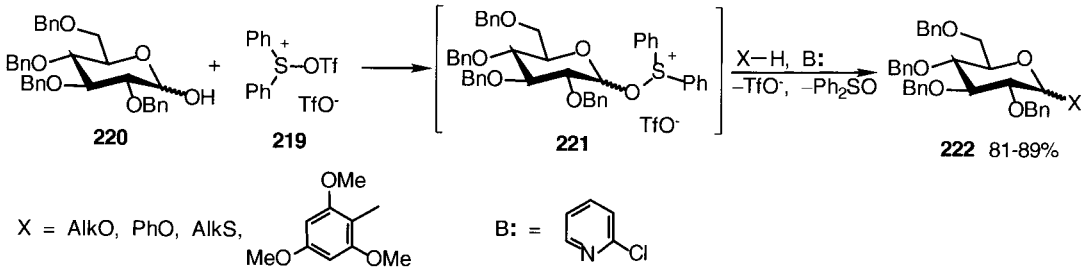
salts **205a** and **211**, after demethylation, gives different fused sulfur heterocycles **210**[162] and thiophene derivatives **211a**[164] has also been described (Scheme 84).

The most impressive application of trifloxysulfonium triflates is undoubtedly Umemoto's synthesis of electrophilic trifluoromethylating agents, the S-trifluoromethyl dibenzoheterocyclic salts **214a**.[165] These salts, as well as their selenium analogues **214b**, could be successfully prepared in high yields by treatment of the corresponding chalcogen oxides with Tf_2O. The tellurophenium triflate **217** was synthesized in an original way, by oxidation of the telluride **216** with DMSD.[166] The highly reactive nitronium triflate, prepared in situ from 94% nitric acid and a slight excess of triflic anhydride, could be used for the direct nitration of **214a–b** (Scheme 85).[165,166]

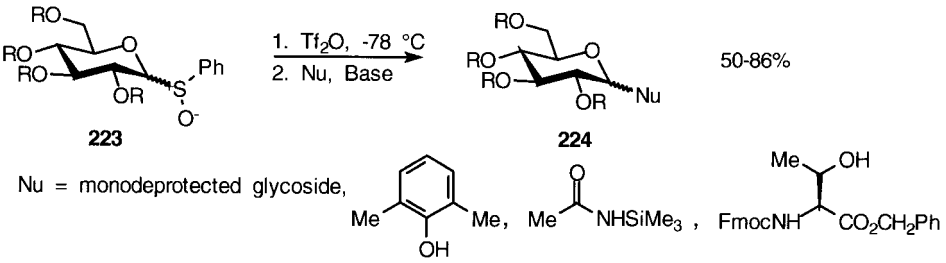
Extensive studies of the reactivity of trifluoromethyl onium salts revealed the heterocyclic salts to be highly reactive compared to their nonheterocyclic analogues **218**. The trifluoromethylation power of the heterocyclic salts depends on the heteroatom (S>Se>Te) and on the ring substituents (dinitro substitution being especially effective) so that the reagents can be considered as 'power-variable electrophilic trifluoromethylating agents'.[166] Some representative examples of trifluoromethylation are given in Scheme 86.

The diphenylsulfoxide-triflic anhydride complex (**219**) appears to be the reagent of choice for the construction of a wide variety of glucoconjugates directly from 1-hydroxy-glycosyl donors **220**.[167] A proposed mechanism for this transformation involves the in situ generation of the oxo-sulfonium triflate **221**, which can expel Ph_2SO to form the reactive oxocarbenium ion. This oxocarbenium ion reacts with different nucleophiles to yield the corresponding O-, S- and C-substituted glycosides **222** (Scheme 87).

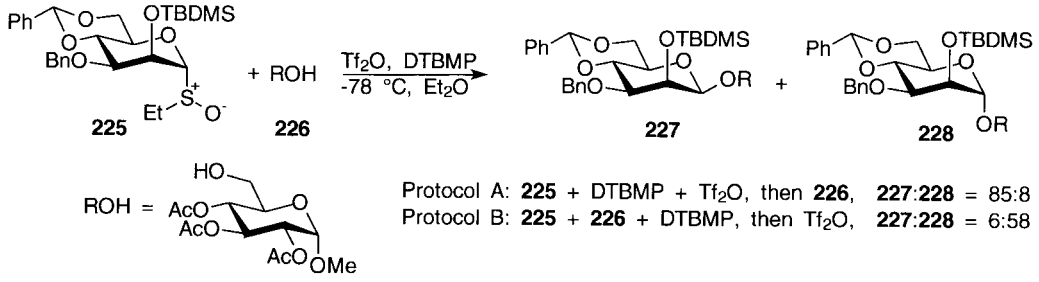
The activation of anomeric sulfoxides with Tf_2O has featured prominently in the field of oligosaccharide synthesis since its introduction by Kahne.[168] This method has



Scheme 87.



Scheme 88.

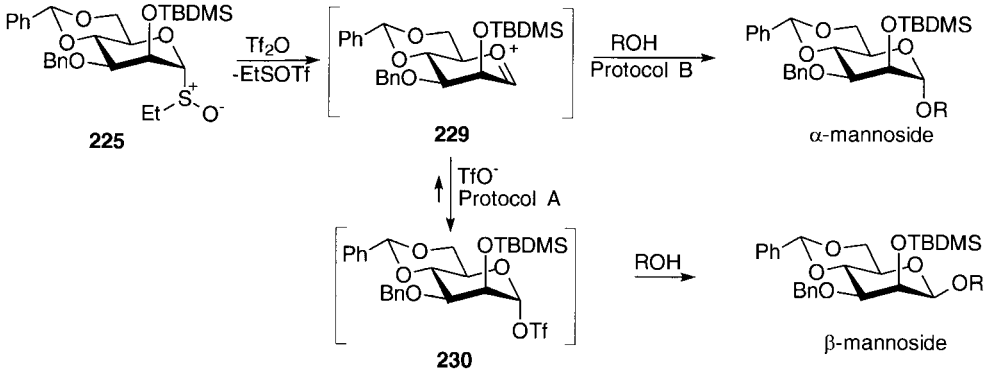


Scheme 89.

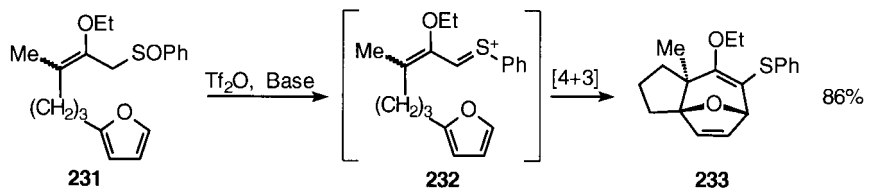
been successfully applied to an impressive variety of glycosyl acceptors including acetamide, hindered phenols,[168] hydroxylated amino acids[169] and a broad selection of carbohydrates.[168,170] Solid phase oligosaccharide synthesis could also be accomplished through the use of glycosyl sulfoxides and triflic anhydride (Scheme 88).[171]

Crich[172] has clearly demonstrated that triflic anhydride can be advantageously utilized for the activation of mannosyl sulfoxides **225** and synthesis of β-mannopyranosides **227**. The β:α selectivity strongly depends upon the order of addition of the reagents: premixing the donor **225**, acceptor **226** and base before addition of Tf_2O provided mainly the α-anomer **228** (protocol B), whereas prior activation of the sulfoxide with Tf_2O led to reversal of the stereoselectivity (protocol A).[173] With secondary acceptors, a greater β:α ratio could be achieved by reducing the steric bulk of the *O*-2 protecting group (Bn instead of TBDMS) and by using a less ionizing solvent (CH_2Cl_2 instead of Et_2O).[174] This selectivity is in stark contrast to the analogous glucopyranoside series, which affords the α-glycosides with excellent selectivity under the protocol A (Scheme 89).[175]

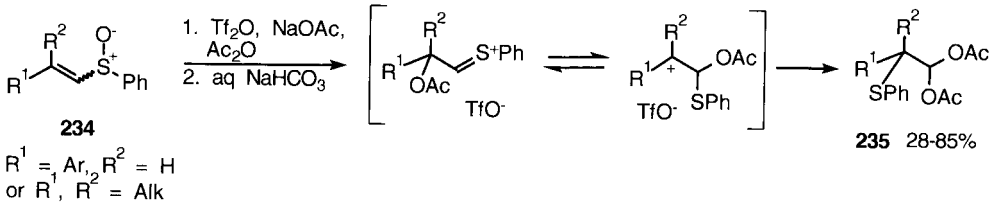
Presumably, in the absence of other nucleophiles (protocol



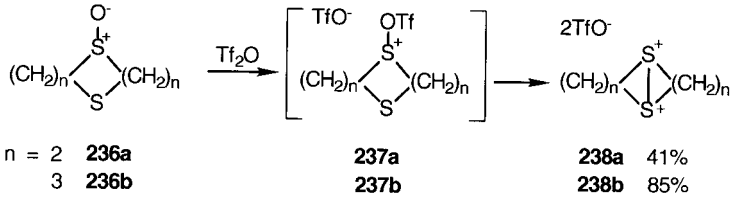
Scheme 90.



Scheme 91.



Scheme 92.



Scheme 93.

A), the reaction path involves the formation of the reactive glycosyl triflate **230**, which on addition of the acceptor underwent an S_N2-like reaction to give the β-mannoside.[174] The formation of an α-triflate was unequivocally demonstrated by a combination of ^1H, ^{13}C and ^{19}F NMR spectroscopy as well as by preparation of an authentic sample (Scheme 90).[176]

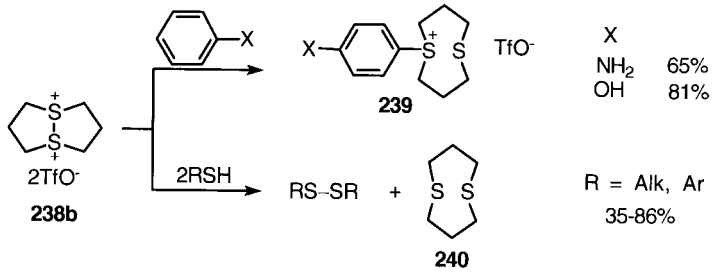
An attractive method for the construction of fused seven-membered carbocyclic systems, based on the triflic anhydride-induced Pummerer rearrangement of alkoxyallylic sulfoxides **231** and subsequent intramolecular [4+3] cycloaddition of intermediate **232** to **233**, has been reported.[177] In the case of furan, the stereoselectivity of cycloaddidion is high, whereas less nucleophilic dienes give a mixture of stereoisomers (Scheme 91).

Treatment of vinylic sulfoxides **234** with triflic anhydride-sodium acetate gave tandem additive Pummerer rearrangement reactions[178] leading to 2-(phenylsulfenyl) acylals **235**—convenient precursors to 2-(phenylsulfenyl) aldehydes and alcohols. When carried out on chiral substrates, the above sequence furnishes optically enriched acylals, albeit with a low enantiomeric excess (10.5–23% *ee*) (Scheme 92).

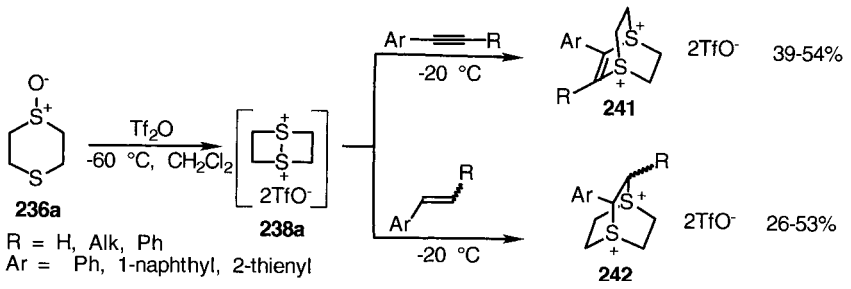
There have been several imaginative uses of triflic anhydride for the preparation of various dications. Furukawa and collaborators[179] have shown that reaction of the sulfoxides **236** with Tf_2O afforded via intermediate **237** the disulfide dications **238** as crystalline salt. The X-ray crystal structure of **238b** has been determined and this unequivocally confirmed the existence of the S^+–S^+ bond.[180] The triflate counterion is essential for the crystallisation, since attempts to obtain stable crystals with different anions such as SO_4^{2-} and BF_4^- failed (Scheme 93).[180]

The reaction of **238b** with different nucleophiles and bases has been described.[181] The dication **238b** was indicated to act as an S-electrophile toward electron-rich aromatics to give good yields of the corresponding sulfonium salts **239**.[181,182] Unlike the other aromatics, thiophenol does not normally produce the *p*-substituted sulfonium salt from **238b**; its reducing ability results in the formation of diphenyldisulfide, together with **240**.[182] This transformation was extended succesfully to a wide variety of aliphatic and aromatic thiols.[183] Surprisingly, the dication **238b** upon treatment with different organometallic reagents, including metal alkoxides, also underwent reduction.[181,184] In contrast to normal sulfonium salts, no hydrogen abstraction and ylide formation were detected (Scheme 94).[184]

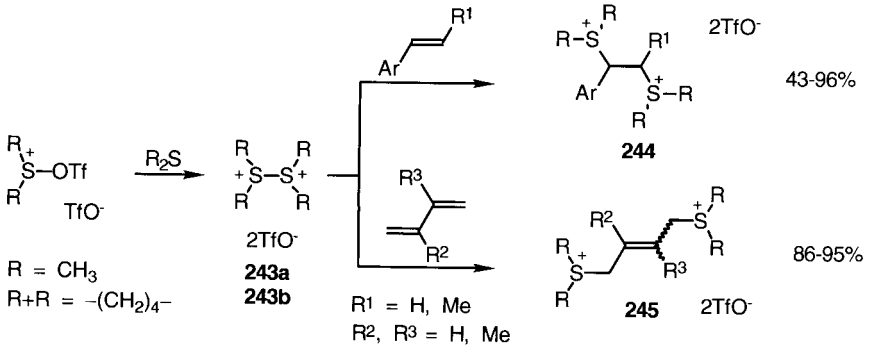
The strained dication **238a** can add to activated multiple bonds leading to the formation of different products **241** and **242** with a dithioniabicyclo[2.2.2]octane skeleton.[185] In the case of 1,2-disubstituted arylalkenes the reaction proceeds stereoselectively with retention of the relative arrangement of substituents at the double bond of the



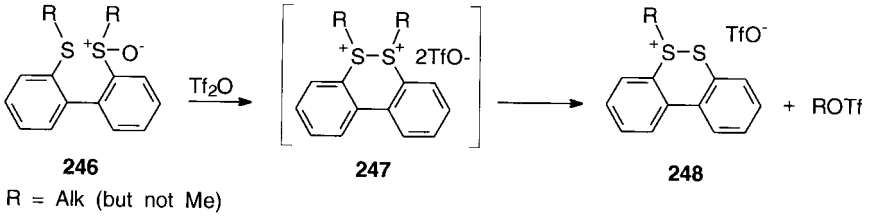
Scheme 94.



Scheme 95.



Scheme 96.



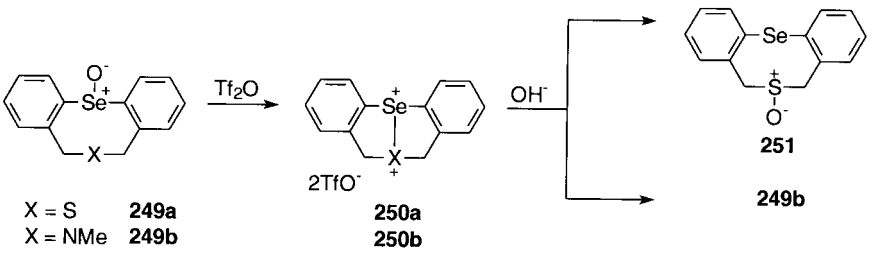
Scheme 97.

original alkene. The less electrophilic ditriflate **238b** turned out to be unreactive towards alkenes and alkynes (Scheme 95).[185]

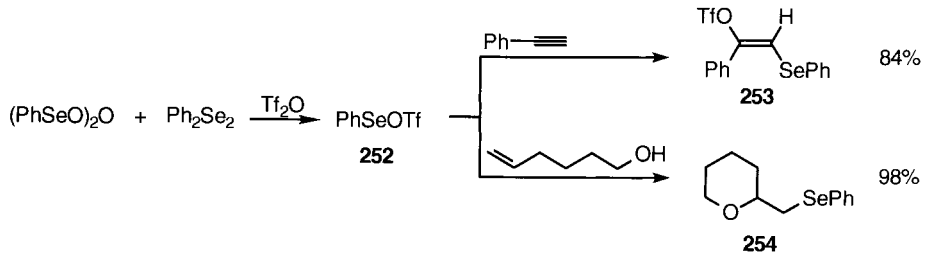
A similar behaviour in the reaction with alkenes was observed for the acyclic dication **243a** arising from the reaction of DMSD and dimethylsulfide.[186] The reaction results in formation of the 1,2-addition products **244**. The reaction of **243a** and its analog **243b** with dienes yielded relatively unstable 1,4-disulfonium salts **245** (Scheme 96).

Monooxides of 2,2′-bis(alkylthio)biphenyl[187] and alkyl 2-(methylthiomethyl)phenyl sulfoxides[188] **246** can undergo facile dealkylation (but not demethylation) on treatment with triflic anhydride to furnish the corresponding thiasulfonium salts **248** and alkyl triflates. The reaction proceeds via initial formation of the corresponding dithiadications **247** (Scheme 97).

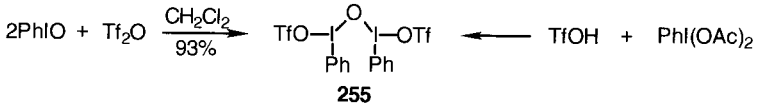
There are close similarities between the reactions of triflic anhydride with organosulfur reagents and those of their



Scheme 98.



Scheme 99.



Scheme 100.

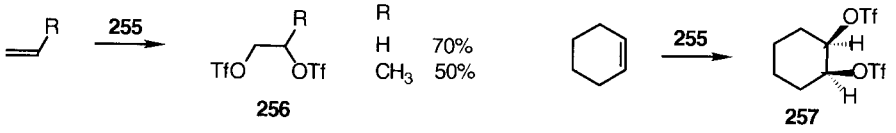
organoselenium counterparts, although the latter are rather less developed. Furukawa has described[189,190] the synthesis of the Se^{+}–S^{+} and Se^{+}–N^{+} dications **250a** and **250b** from the corresponding selenoxides **249a,b** and triflic anhydride. Interestingly, hydrolysis of **250a** gave an almost quantitative yield of the sulfoxide **251** and none of the selenoxide was obtained, whereas hydrolysis of **250b** yielded the starting selenoxide **249b** as the sole product (Scheme 98).

The reaction of benzeneseleninic anhydride and diphenyl diselenide in the presence of triflic anhydride represents an inexpensive alternative for the synthesis of phenylselenyltriflate **252**, which is usually prepared from the corresponding halide and silver triflate.[191] The triflate **252** is commonly used for the introduction of a phenylseleno moiety into organic molecules; for example, its reactions with phenylacetylene and 5-hexen-1-ol give high yields of vinyl triflate **253** and tetrahydropyran **254**, respectively (Scheme 99).[191]

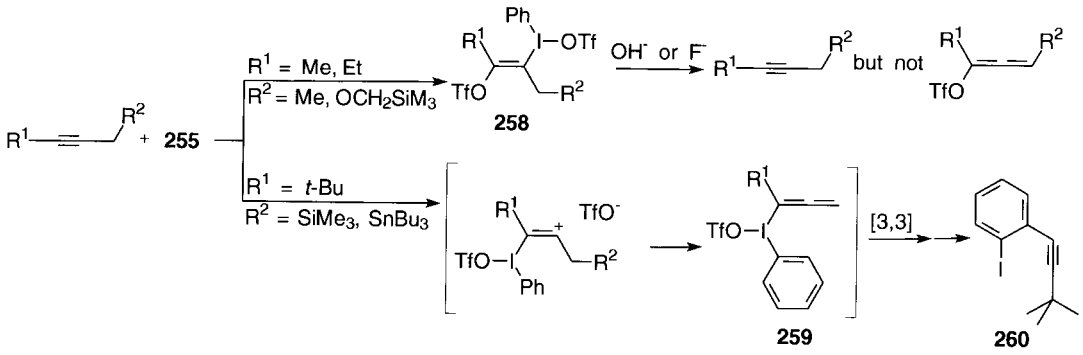
2.4.2. Application of triflic anhydride in hypervalent iodine chemistry. Much attention has been paid recently to the utilization of triflic anhydride in hypervalent iodine chemistry. Norton[192] was the first to apply Tf_2O to the convenient preparation of μ-oxobis[(trifloxy)(phenyl)-iodine)] (**255**), known as Zefirov's reagent (Scheme 100).[193]

255 Has been used primarily for the selective functionalization of multiple bonds. Thus, the reaction of **255** with alkenes provides the vicinal ditriflates **256** or **257** in good yields and excellent stereoselectivity (>99% *syn* addition for cyclohexene).[192,193] Dienes undergo selective 1,4-addition; for example, butadiene upon treatment with **255** gives an 89:11 mixture of the 1,4:1,2 bistriflates in 55% yield (Scheme 101).[192]

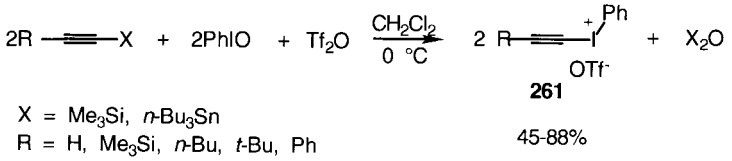
In contrast, reaction of **255** with alkynes proceeds as *anti*-addition affording the vinyliodonium triflates **258**.[194] Attempts to deprotonate **258** to an allenyl triflate resulted



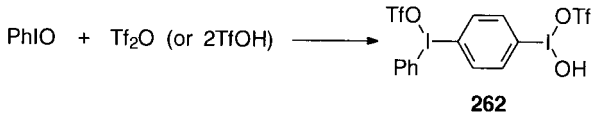
Scheme 101.



Scheme 102.



Scheme 103.



Scheme 104.

in the regeneration of the starting alkyne. Surprisingly, the addition of Zefirov's reagent to propargylsilanes and propargylstannanes gave the allenyl iodinane **259** which underwent [3,3] sigmatropic rearrangement to give the propargyliodoarene **260** (Scheme 102).[194]

The interaction of the in situ-formed bis-triflate **255** with a sila- or tin-acetylene has attracted attention as a versatile procedure for the preparation of a wide variety of stable alkynyl(phenyl)iodonium salts **261**.[195] This simple methodology could also be applied to the synthesis of the parent ethynyl triflate **261a** (R=H) (Scheme 103).[196]

Alkynyliodonium salts (primarily the readily available and the most stable iodonium triflates), bearing the most powerful PhI leaving group, have been extensively used as an electrophilic acetylene equivalent. The chemistry of this iodonium species has been recently reviewed.[3]

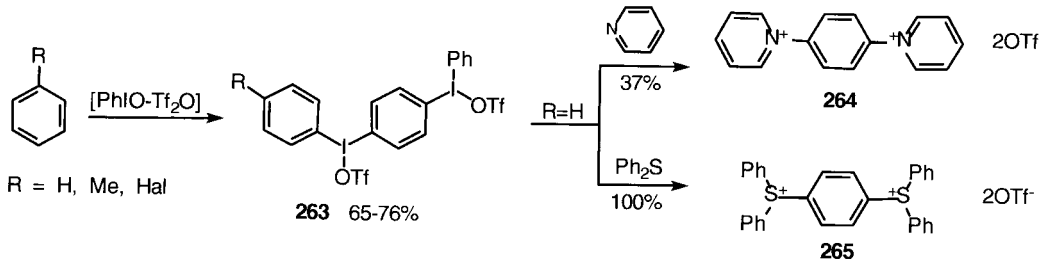
Treatment of Zefirov's reagent with Tf_2O resulted in the generation of the reactive phenyl iodonium triflate, $PhI(OTf)_2$.[197] The same reagent would be expected to be formed from the combination of equimolecular quantities of PhIO and Tf_2O; however, more recent work[198,199] has indicated that this reaction, as well as the interaction of iodosobenzene with two molar equivalents of TfOH, affords the bisiodine derivative **262** (Scheme 104).

The complex PhIO–Tf_2O exhibits an enhanced reactivity towards different aromatic compounds including non-activated derivatives to give rise to the corresponding (*p*-phenylene)bis(aryliodonium) ditriflates **263**.[198,200] These have two good leaving groups on a single aromatic ring and may thus be used as precursors to 1,4-disubstituted benzene derivative **264**, **265** (Scheme 105).

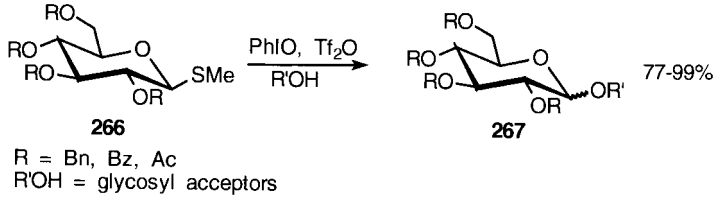
In the same manner as diphenylsulfide ditriflate (**219**),[167] the complex PhIO–Tf_2O may be used as an efficient promoter for the glycosidation reaction.[201] Both 'armed' (R=Bn) and 'disarmed' (R=Ac or Bz) thioglycosides **266** in the presence of **262** react smoothly with different acceptors to form the corresponding disaccharides **267** in high yields. In the case of disarmed donors, excellent β-selectivity was observed (Scheme 106).[201]

2.4.3. Reaction with nitrogen and chlorine oxides. Chlorine(I)[202] and nitrogen(V)[203] oxides or nitric acid[165,166,204] react with triflic anhydride to give highly effective electrophilic reagents, chlorine and nitronium triflates. These were shown to effect chlorination and nitration of deactivated aromatics under mild conditions in high yields. Triflic acid, which is liberated in the course of chlorination, is reconverted to the anhydride by phosphorus oxychloride, which was used as the solvent; thus, 20–30% of Tf_2O are sufficient for optimum yields (Scheme 107).

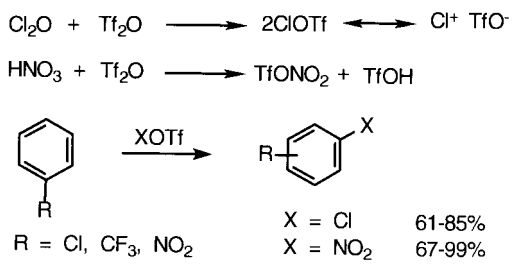
The generation of nitronium triflate in aprotic conditions



Scheme 105.



Scheme 106.



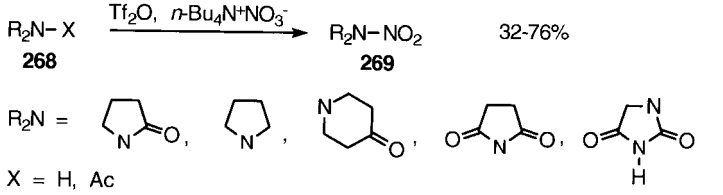
Scheme 107.

could be achieved using tetrabutylammonium nitrate and Tf_2O in CH_2Cl_2.[205] Subsequent addition of cyclic secondary amines or amides **268** gave the corresponding N-nitro products **269** in moderate to good yields (Scheme 108).[205]

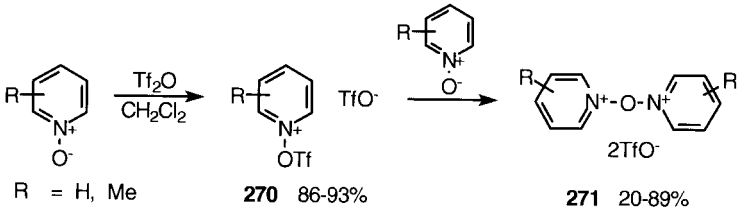
2.4.4. Reaction with amine oxides. Pyridine and related N-oxides have been reported[206] to react with triflic anhydride in a similar manner to phosphine oxides, ureas and pyridones to give rise to the dication ether salts **271**. The initially-formed very hygroscopic monocations **270** can also be isolated in excellent yields (Scheme 109).

N-Trifloxycarbamates such as **272** which are readily available from the thallium salt of the N-hydroxycarbamate and triflic anhydride can be used as a reactive aminating reagent for sulfides.[207] Some advantages have been outlined for this procedure for the synthesis of sulfimines **273** over previously known method namely (i) the yields are high; (ii) the actual scope is wide and (iii) a large excess of sulfide is not required (Scheme 110).

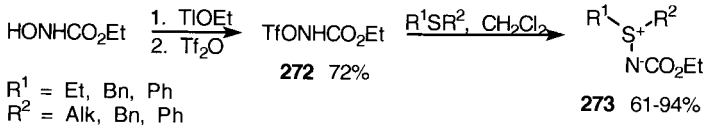
2.4.5. Reaction of triflic anhydride with other pnictogen oxides. Triphenylphosphine oxide[208,209] **274a** as well as HMPA[210] **274b** react exothermically with triflic anhydride in CH_2Cl_2 to give white precipitates of the corresponding diphosphonium salts **275a**,**b**.[210] A similar behaviour was observed for triphenylarsine oxide **274c**, whereas the reaction of triphenylstibine oxide or triphenylbismuth trifluoroacetate with Tf_2O furnished the stable hygroscopic *gem*-bistriflates **276** and **277** (Scheme 111).[211]



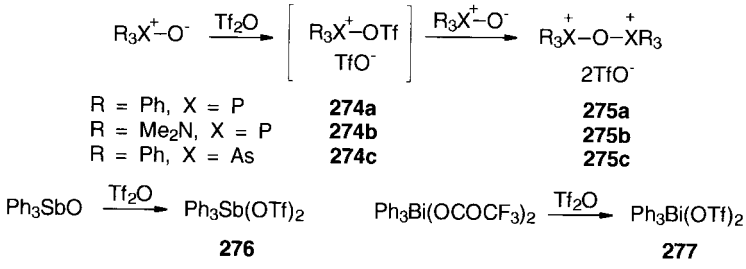
Scheme 108.



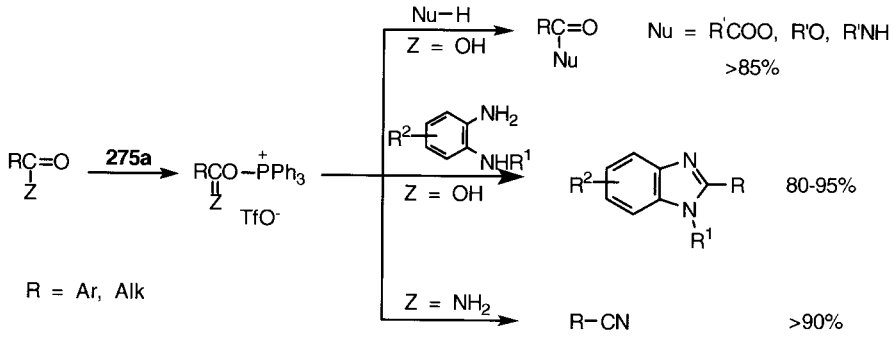
Scheme 109.



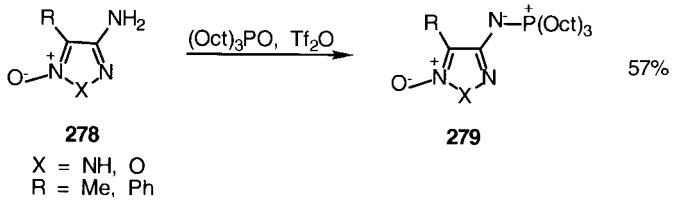
Scheme 110.



Scheme 111.



Scheme 112.

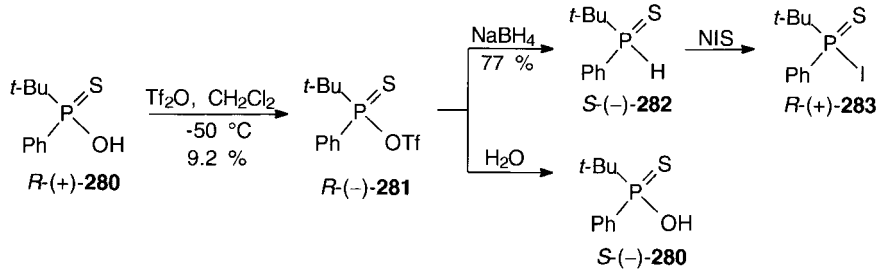


Scheme 113.

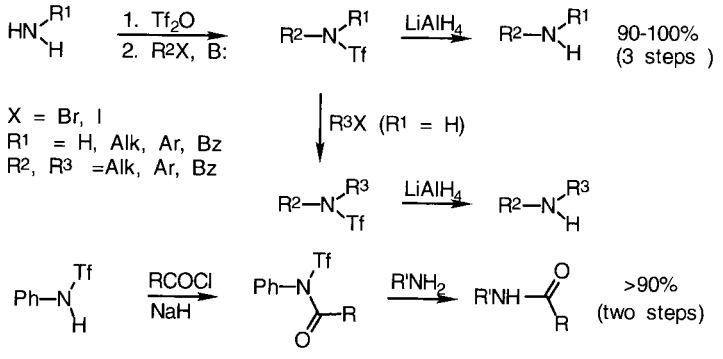
The dication **275a** was shown to be a powerful dehydrating agent and also a promising reagent for the conversion of carboxylic acids to anhydrides,[212] esters, amides,[208,212] benzimidazoles[212,213] and cyclic aryl ketones.[212] In an analogous manner to the carboxylic acids, primary amides and oximes can be activated by this reagent at oxygen to produce nitriles in excellent yields and under mild conditions (Scheme 112).[213]

Both dications **275a**,**b** were conveniently converted into phosphinimines[214] (the yields were respectively 82 and 90%) by reaction with ammonia followed by hydrolysis. Conversion of aminofuroxanes **278** into the corresponding phosphinimino derivatives **279** was achieved by trioctylphosphine ditriflate, generated in situ from trioctylphosphine oxide and triflic anhydride (Scheme 113).[215]

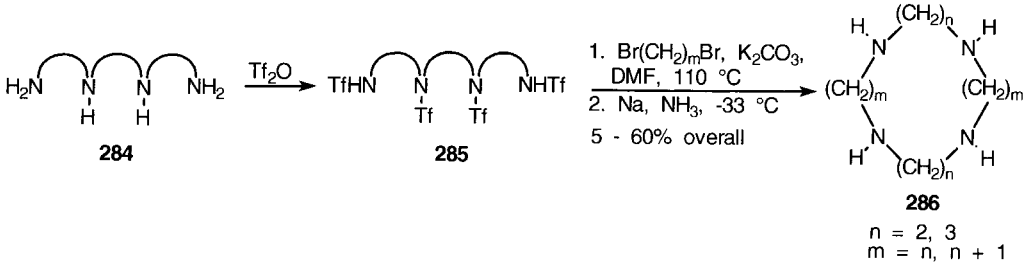
The optically pure mixed anhydride **281**, prepared in low yield by triflation of the chiral phosphinothionic acid **280**, on treatment with sodium borohydride was converted into **282** with inversion of configuration; standard functional group manipulation was used to transform **282** into the



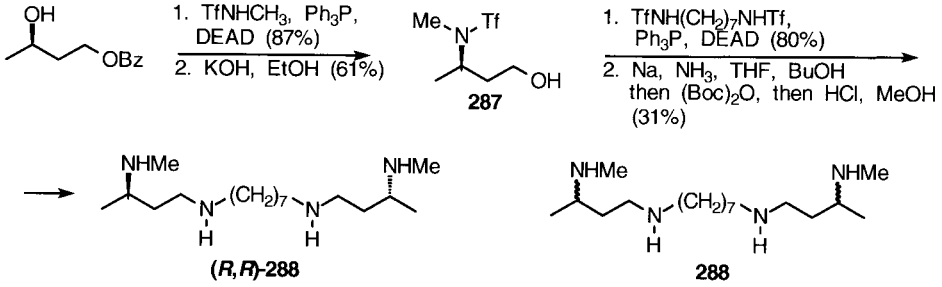
Scheme 114.



Scheme 115.



Scheme 116.



Scheme 117.

optically pure phosphinodithioate *t*-BuPhP(S)SMe, the phosphinothioic iodide **283** and thioselenophosphinic acid *t*-BuPhP(Se)SH.[216] Hydrolysis of the triflate **281** also proceeds with full inversion of configuration at the phosphorus atom (Scheme 114).[216]

3. Reaction with Amines. Triflamides: Synthesis and Synthetic Applications

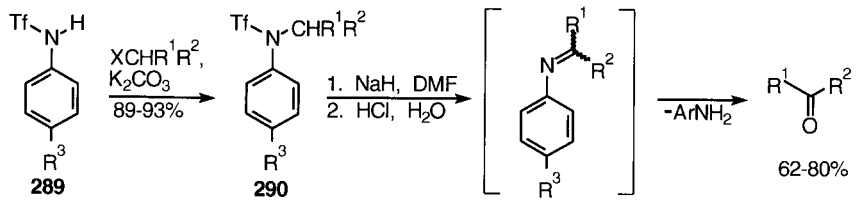
Due to the electron-withdrawing and relatively good leaving group properties of the CF_3SO_2 group, triflamide reagents have useful applications in organic chemistry. Primarily they can be applied to amine synthesis and the synthesis of vinyl triflates from enolates, which occur under mild conditions and in many cases are superior to other reagents.

Triflamides are usually prepared from the corresponding amines by treatment with triflic anhydride in the presence of a base.[217,218] Alternatively, the mild, selective triflating reagents *N*-phenyltriflimide[219] and *N*-trifylimidazolide[220] may be used for transferring the trifyl group to the amines. Interestingly, *N*-phenyltriflimide does not react with secondary aromatic amines and thus provides a useful analytical discrimination for these compounds.[219]

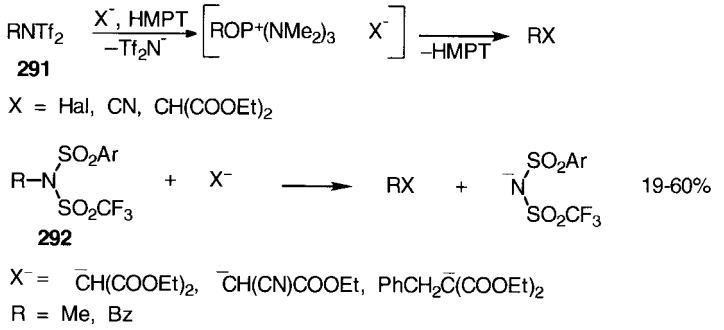
The readily formed triflamide anions (for example, for $CF_3SO_2NH_2$, pK_a=5.8)[219] undergo smooth alkylation[218] and acylation.[219] *N*-Alkylation and subsequent removal of the trifyl group by reduction allowed an almost quantitative sequence for the protection and alkylation of amines.[221] The stable crystalline *N*-acyltriflamides acylating agents are less reactive than the acid chlorides but react cleanly in high yields with moderately basic nucleophiles (Scheme 115).[219]

The deprotection of triflamides can also be performed under mild conditions using sodium in liquid ammonia.[222] This procedure has been employed in the facile two-step synthesis of tetraaza macrocycles **286** from **284** using triflamides as the protecting group (Scheme 116).[223]

Triflamides, for example **287**, show promise as acidic components in the Mitsunobu reaction. Edwards and co-workers[222] have demonstrated that this reaction proceeds with full inversion of configuration and provides a convenient synthetic route to the (*R*,*R*)- and (*S*,*S*)-enantiomers



Scheme 118.



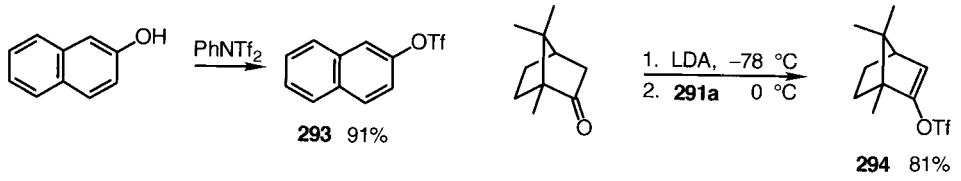
Scheme 119.

of the antitumor polyamine **288**, starting from the readily available (*S*)- and (*R*)-1,3-butanediols. The use of the corresponding *N*-alkyltosylamides is unsatisfactory for the synthesis of chiral polyamines (Scheme 117).

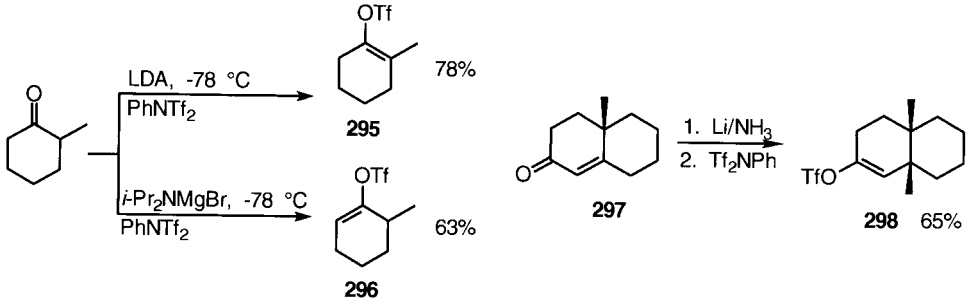
Due to the relatively good leaving group properties of the trifloromethanesulfinic group,[218] *N*-aryltriflamides **289** were applied to the mild oxidation of α-haloketones and alkyl halides.[224] In the case of inactivated alkyl halides, trifluoromethanesulfinic acid could be eliminated under mild conditions when *N*-(4-acetoxyphenyl)triflamide was used as the oxidizing reagent (Scheme 118).

S_N2 displacement of the triflimides **291**[225,226] and the mixed sulfonimides **292**[227,228] from saturated carbon represents a rare example of a nitrogen leaving group, made possible by the strong electron-withdrawing properties of the trifyl group. Trifyl activation of amines was succesfully used for the alkylation of simple carbon and sulfur nucleophiles and introduction of a chiral methyl group (Scheme 119).[228]

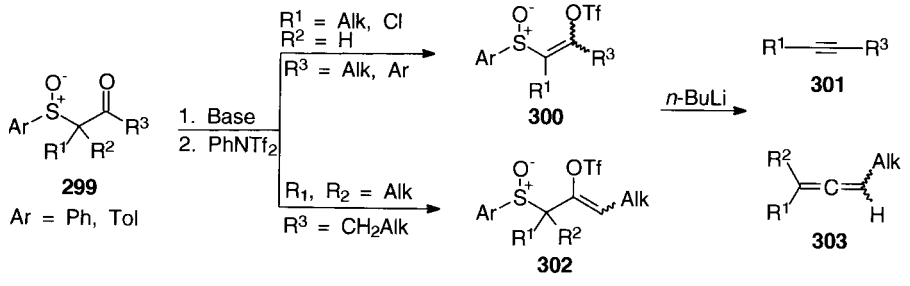
Stable, crystalline *N*-phenyltriflimide (**291a**) has been extensively used as the selective triflating agent in reactions with phenols[219] (to form aryl triflates **293**) and enolates.[229] Thus, camphor could be converted to the corresponding



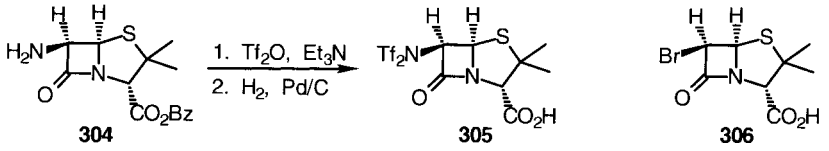
Scheme 120.



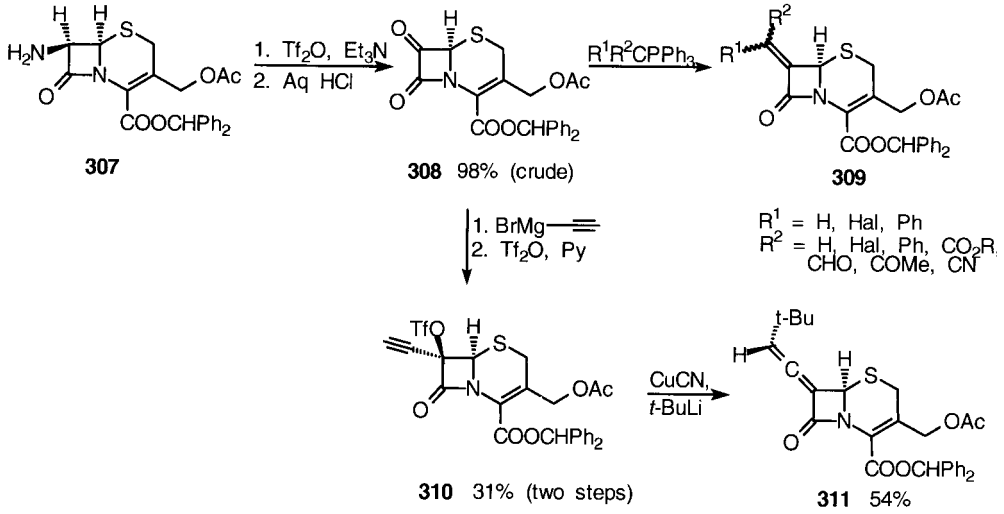
Scheme 121.



Scheme 122.



Scheme 123.



Scheme 124.

vinyl triflate **294** in 81% yield[229] by deprotonation with LDA followed by trapping with **291a**, whereas treatment of camphor with triflic anhydride yielded only different rearrangement products (Scheme 120).[43]

N-Phenyltriflimide has been applied to the regioselective synthesis of 'kinetic' cycloalkenyl triflates **295** or **296** from unsymmetrical cycloalkanones[230] as well as to the synthesis of regio-defined triflates **298** via the 1,4-addition of hydride to conjugated cycloalkenones **297**.[229] The synthesis of vinyl triflates from *N*-phenyltriflimide has been previously reviewed (Scheme 121).[2]

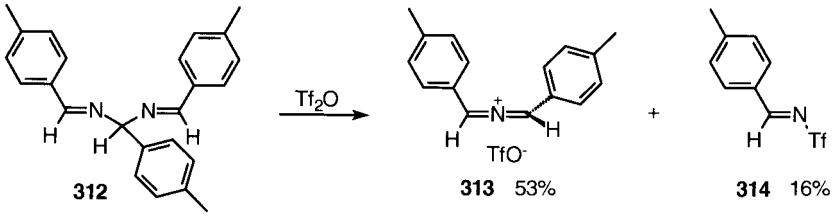
N-Phenyltriflimide reacts cleanly with ketones bearing a sulfoxide group at the α-position **299**.[231] Ligand exchange reactions of the resulting vinyl triflates **300** or **302** with *n*-BuLi offers an attractive route to disubstituted acetylenes **301** and trisubstituted allenes **303** (Scheme 122).

Recently, Comins et al.[232,233] have developed more reactive triflating agents, the *N*-pyridyltriflimides, and have employed these compounds in the total synthesis of (−)-porantheridine[234] and some dendrobatid alkaloids.[235]

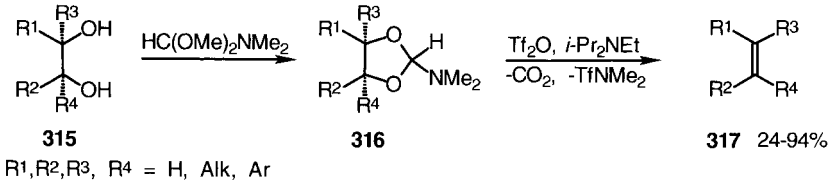
Treatment of the benzyl ester of 6-β-aminopenicillanic acid (**304**) with two equivalents of triflic anhydride followed by hydrogenolysis yielded the β-lactamase-inhibitor **305**,[236] which behaved biochemically as the 6-bromo analog **306**[236] due to the known tendency of the bistriflamido group to function as a leaving group in S_N2 type displacement reactions (Scheme 123).[218]

Bistriflates derived from 6-aminopenicillanic or 7-aminocephalosporanic esters can undergo base-catalysed β-elimination of trifluoromethanesulfinic acid to yield the corresponding imines.[237] Mild acid hydrolysis of these compounds effected their oxidative transformation to provide the 6-oxo and 7-oxo derivatives. A series of 7-alkylidenecephalosporins **309**[238] and 7-vinylidenecephalosporins **311**[239] prepared from the diketone **308** was biologically evaluated as β-lactamase inhibitors[239] and human leukocyte elastase inhibitors (Scheme 124).[238]

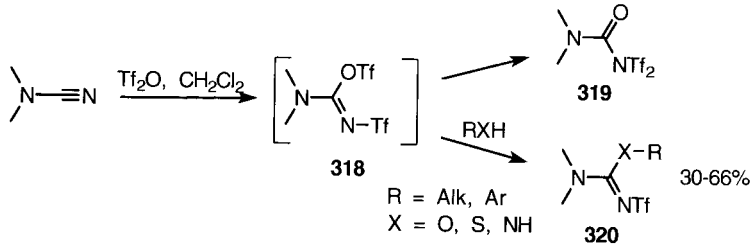
Triflic anhydride was used for the preparation[240] of the highly reactive 2-azaallenium salt **313**, which required a nonnucleophilic counterion for its isolation and could thus not be isolated as the chloride or iodide.[240] This reaction



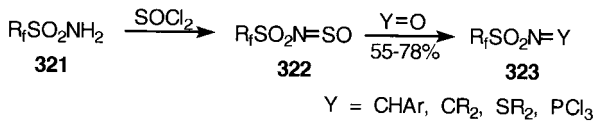
Scheme 125.



Scheme 126.



Scheme 127.



Scheme 128.

presumably proceeds via the initial electrophilic attack of the anhydride on one of the two nitrogen atoms of **312** followed by fast fragmentation of the adduct so formed into **313** and **314** (Scheme 125).

Stereospecific deoxygenation of 1,2-diols **315** to olefins **317** may be achieved cleanly under very mild conditions by treatment of the corresponding dimethylaminodioxolanes **316** with triflic anhydride (Scheme 126).[241]

A series of 2-substituted 3-trifluoromethylsulfonyl-isoureas, -thioisoureas and guanidines **320** was prepared[242] by the reaction of dimethylcyanamide with triflic anhydride followed by treatment with different O-, S- and N-nucleophiles. The reaction proceeds via the formation of a hygroscopic and reactive 2,3-bis(trifyl) isourea **318** (Scheme 127).

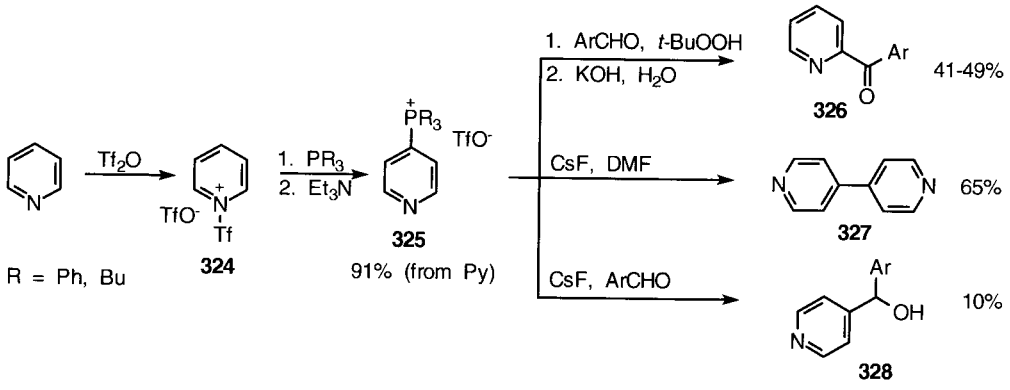
The parent triflamide **321** reacted with thionyl chloride to afford the corresponding sulfonamide **322**. The latter contains the strongly electron-withdrawing $CF_3SO_2N{=}$ group[243,244] and can be easily converted to the corresponding aldimines,[244,245] sulfimides and phosphimides **323** (Scheme 128).[245]

Although pyridine is one of the most common bases used for the preparation of triflate esters,[1] its interaction with Tf_2O giving the salt **324** is sometimes the major pathway,[1,246] and the actual sulfonylation is often accomplished by **324** rather then the anhydride itself. The pyridinium salt **324** as well as the analogous salts of pyrazine, benzothiazole and quinoline, however, can act as an electrophile towards trialkyl- or triarylphosphines yielding the corresponding phosphonium salts **325**.[247,248] These have been shown to act as precursors for 2-acylpyridines **326**, 4,4′-bipyridines **327** and pyridylcarbinols **328** (Scheme 129).[248]

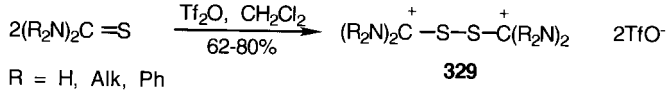
4. Oxidative Properties of Triflic Anhydride

4.1. Reaction with sulfides and thiols

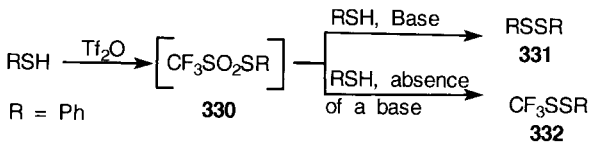
Maas and Stang[249] were the first to show that in the reaction



Scheme 129.



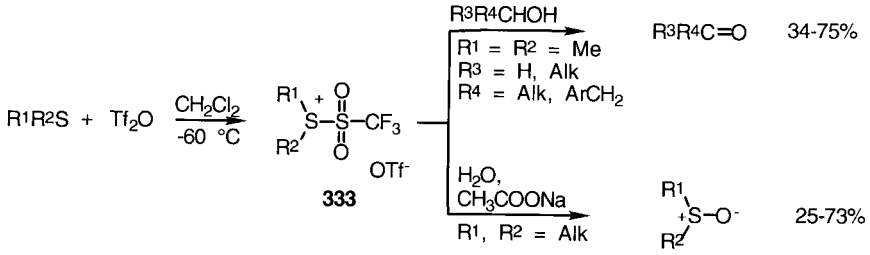
Scheme 130.



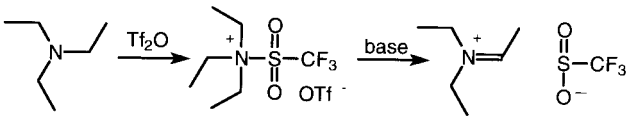
Scheme 131.

nonvolatile product (25%) along with diphenyl disulfide (Scheme 131).

The reaction of dimethylsulfide with triflic anhydride gave the sulfonium salt **333**.[251] The latter was used for the mild oxidation of primary and secondary alcohols to the carbonyl compounds. Treatment of the sulfonium salts **333** with



Scheme 132.



Scheme 133.

with sulfur-containing organic compounds, triflic anhydride can act as an oxidizing agent. Thus, its reaction with thioureas and trithiocarbonates results in stable dicationic disulfide salts **329** (Scheme 130).

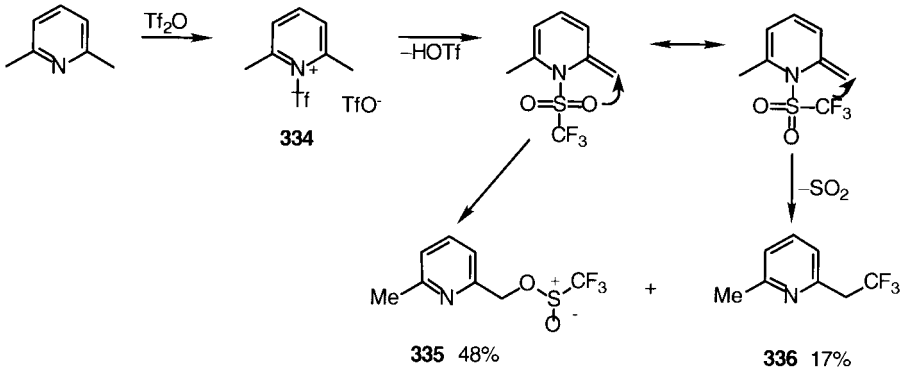
Thiols and sulfides are also readily oxidized by triflic anhydride. A recent paper[250] reports that thiophenol, triflic anhydride and pyridine failed to give the desired phenyl trifluoromethanethiosulfonate (**330**); only diphenyl disulfide **331** was obtained in excellent yield along with pyridinium triflate and triflinate. In the absence of any base, phenyl trifluoromethyl disulfide (**332**) was found to be the major

aqueous sodium acetate furnished the corresponding sulfoxides in acceptable yields (Scheme 132).[251]

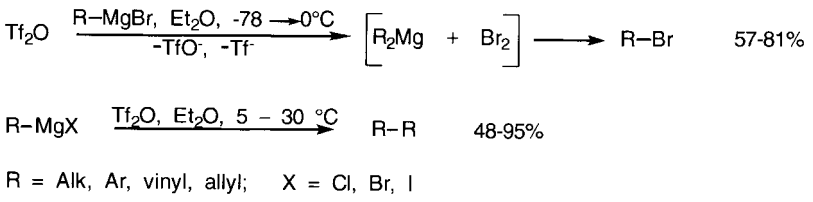
4.2. Oxidation of nitrogen-containing compounds

The most convenient and widely used method for preparation of triflate esters is the reaction of the appropriate alkohol with triflic anhydride in the presence of inexpensive tertiary amines such as pyridines or triethylamine. On standard treatment of sterically congested alcohols and phenols with triflic anhydride, however, unwanted trifluoromethanesulfinyl esters were obtained in up to 89% yields.[252] Presumably the amines (triethylamine and to a lesser extent Hünig's base) act as $S^{VI} \rightarrow S^{IV}$ reducing agents (Scheme 133).

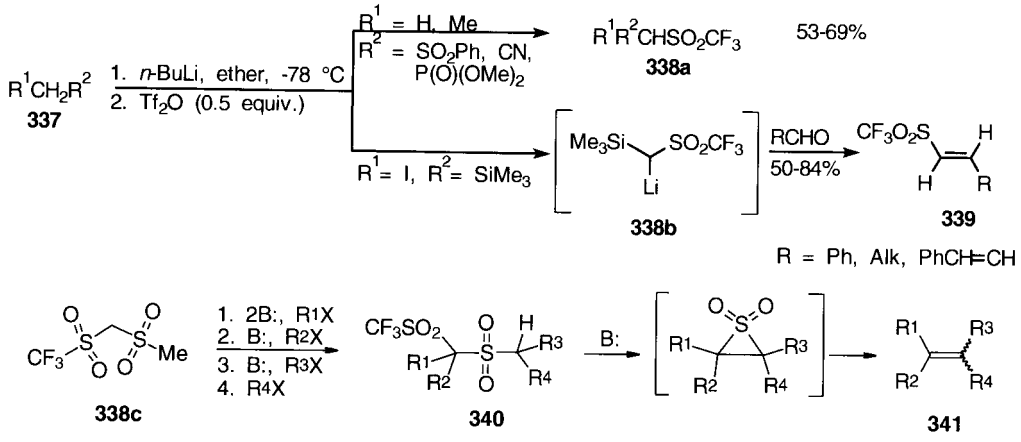
Lutidine and collidine also reacted with triflic anhydride to give pyridinium salt **334** which is transformed to the S^{IV}-containing products **335** and **336** (Scheme 134).[246]



Scheme 134.



Scheme 135.



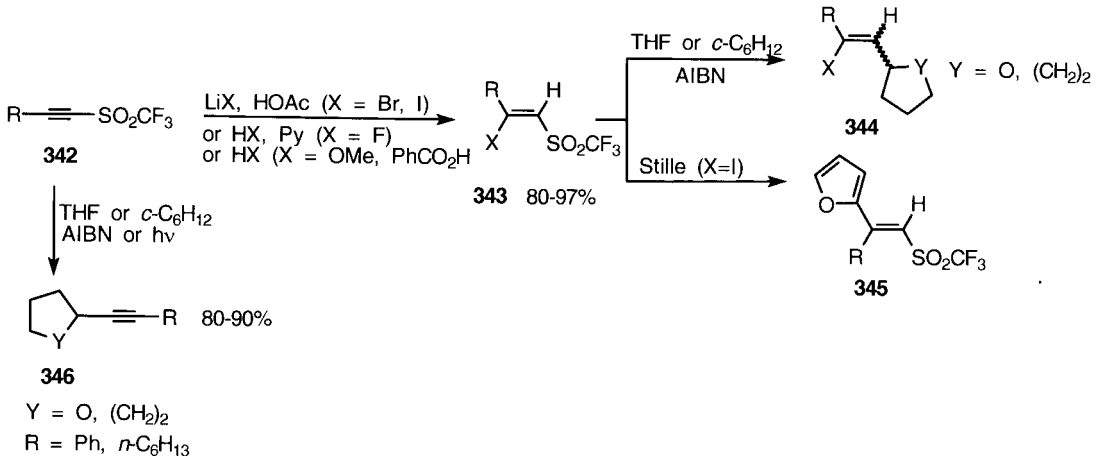
Scheme 136.

The simplest preparation of triflinate salts, which can be used for the synthesis of triflones,[218] is the reduction of trifyl azide by azide ion.[253,254] The triflinate salt, which is formed as a 1:1 mixture with triflate, need not be isolated in a pure form and reacts cleanly due to the extremely low nucleophilicity of the triflate anion.

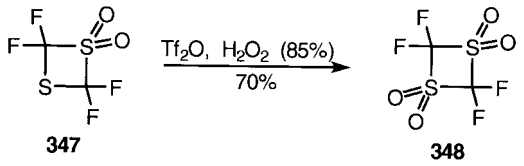
Triflic anhydride has been shown to promote the decomposition of aryldiazomethanes to *cis*-stilbenes.[255] This reaction presumably proceeds via a single electron transfer from the diazo compound to the anhydride and thus also demonstrates the oxidative properties of $(CF_3SO_2)_2O$.

4.3. Oxidation of organometallic compounds. Synthesis of triflones

Triflic anhydride can act as an oxidizing reagent towards various organometallic compounds. Creary[256] found that dropwise addition of different alkyl- and arylmagnesium bromides and iodides to a solution of Tf_2O at $-78°C$ produced the corresponding alkyl(aryl) halides. Presumably elemental bromine which arises from the reaction of magnesium bromide and triflic anhydride works as an electrophilic brominating agent.[256] Simple reversal of the order of addition of the reactants results in the smooth homocoupling reaction of Grignard reagents (Scheme 135).[257]



Scheme 137.



Scheme 138.

Triflic anhydride can be used as an electrophilic source of trifyl in the preparation of triflones, although this method is not completely general.[218] Primary (but not secondary or tertiary) alkylmagnesium chlorides[256,258] as well as sodium[259] or lithium[260] salts of the alkynes gave good yields of the corresponding triflones whereas both primary and secondary alkyllithium reagents yield considerable amounts of the ditriflated products.[261] Vinyl triflones are not available by this method.[218]

Functionalized methyl triflones **338a–c**, which can be prepared from the metalated compounds **337** and triflic anhydride,[262] have been used for the synthesis of tetrasubstituted alkenes[263] **341** and *E*-vinyl and dienyl triflones **339** (Scheme 136).[262]

Fuchs et al.[264,265] have demonstrated that acetylenic triflones **342** can be stereospecifically converted to (Z)-β-halovinyl triflones **343** via the addition of hydrogen halide. Both **342** and **343** react with THF and cyclohexane to undergo trifluoromethyl radical-mediated C–H functionalization reactions to afford β-halosubstituted olefins **344**[265] and disubstituted acetylenes **346**,[266,267] respectively. Alternatively, Stille coupling of iodovinyl triflones with different organostannanes provides trisubstituted vinyl triflones **345** (Scheme 137).[264]

5. Miscellaneous Reactions

Sundermeyer and co-workers,[268] faced with the difficult task of oxidizing 2,2,4,4-tetrafluorodithietane **347** into the corresponding disulfone **348**, found that simple addition of triflic anhydride to 85% hydrogen peroxide furnished the oxidizing agent trifluoromethanepersulfonic acid, which is superior to trifluoroperacetic acid or other related reagents and is suitable for efficient conversion of the monosulfone **347** into **348** (Scheme 138).

An alternative practical method for the preparation of trimethylsilyl triflate involves the reaction of triflic anhydride with hexamethyldisiloxane; the relative inertness of the latter compound allows the use of TMSOTf as an in situ-generated reagent.[269] Similarly, triflic anhydride-induced decomposition of alkyl trimethylsilyl ethers gives high yields of the corresponding alkyl triflates, which can be isolated after a rapid work-up or used for further reactions without isolation (Scheme 139).[270]

The mild silylating reagent *N,N*-bis(trimethylsilyl)triflamide (**349**) could be synthesized in 85% yield via the reaction of triflic anhydride with hexamethyldisilazane in the presence of a base.[271] NMR spectroscopy revealed two tautomeric forms, resulting from a 1,3-trimethylsilyl shift in solutions of **349** (Scheme 140).

6. Conclusions

Trifluoromethanesulfonic (triflic) anhydride plays a very important role in modern organic synthesis. Due to the unique properties of triflic anhydride it often has no alternative to provide the selectivity and efficiency of a transformation. More than 1000 publications concerning its chemistry have been published, but the chemistry of triflic anhydride is still in progress.

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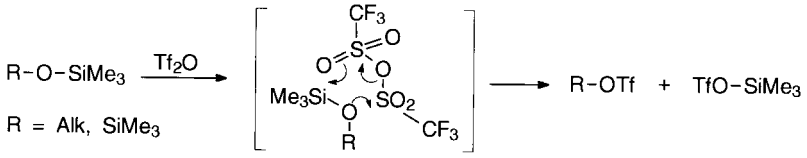
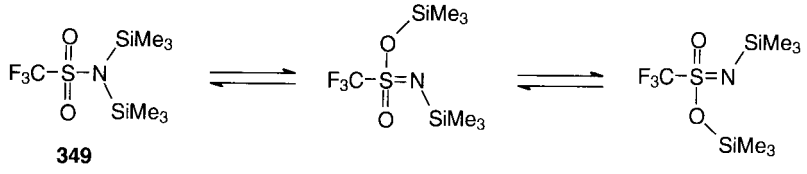


Scheme 139.



Scheme 140.

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