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Recent advances in the chemistry of α,β-unsaturated trifluoromethylketones

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Abbreviations: Ac, acetyl; (*R*)-Binol, (*R*)-(+)-1,1′-bi-2-naphthol; COD, 1,5-cyclooctadiene; DABCO, 1,4-diazabicyclo[2.2.2]octane; Dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Dess–Martin reagent, 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxole-3-(1*H*)-one; DIP-Cl, (-)-*B*-chlorodiisopinocampheylborane; DME, dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMF-DMA, *N*,*N*-dimethylformamide dimethylacetal; DMSO, dimethylsulfoxide; fod, 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione; LDA, lithium diisopropylamide; LTMP, lithium 2,2,6,6-tetramethylpiperidide; MCPBA, *m*-chloroperbenzoic acid; MsCl, methanesulfonylchloride; PMB, 4-methoxybenzyl; PPA, polyphosphoric acid; PPTS, pyridinium *p*-toluenesulfonate; Py, pyridine; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic acid anhydride; Th, thienyl; THP, tetrahydropyranyl; $TMSCF_3$, trimethyl(trifluromethyl)silane; TMSCl, chlorotrimethylsilane; TMSCN, trimethylsilyl cyanide; *p*-Tol, *p*-tolyl (4-methylphenyl); Tos, 4-methylphenylsulfonyl; *p*-TsOH, *p*-toluenesulfonic acid.

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1. Introduction

The trifluoromethyl group, due to its unique stereoelectronic properties, is one of the most important substituents in organic chemistry. Because of the close Van-der-Waals radii (CF_3=1.35 Å, CH_3=1.29 Å), a compound containing a trifluoromethyl group is comparable with its methyl analog and this plays a very important role in drug–receptor interactions. The high electronegativity of the CF_3 group (3.5 on the Pauling scale) results in a quite different electron-density distribution and significantly changes the reactivity of the molecule. The influence of the trifluoromethyl group on the physiological activity is usually concerned with the increasing lipophilicity, which this substituent is bringing to the active molecules. The improvement of their transport characteristics in vivo and also the durability of the C–F bond compared with the C–H bond (116 and 100 kcal/mol, respectively), which allows the avoidance of undesirable metabolic transformations should be taken into consideration. In this respect, the introduction of trifluoromethyl groups into bioactive molecules, especially in the positions responsible for their physiological profile, becomes a very important direction in pharmaceutical studies that stimulates work directed to elaboration of synthetic methodology for various compounds containing trifluoromethyl groups.

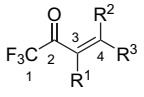
The existing methods for direct fluorination and trifluoromethylation of organic compounds do not always allow the introduction of a CF_3 group in the required position of the molecule. As a result, a more flexible synthetic approach based on the application of simple and available fluorine-containing compounds is a good supplement for direct fluorination methods and is nowadays gaining importance.

α,β-Unsaturated trifluoromethylketones are readily available compounds. Their application in synthesis broadens the arsenal of existing building blocks and demonstrates the perspective and potential of this approach for the introduction of trifluoromethyl groups into compounds from different alicyclic, carbo- and heterocyclic classes.

The literature up to 1999 have been highlighted previously by members of our scientific group in two reviews[1,2] describing the synthesis of α,β-unsaturated trifluoromethylketones and their application in organic synthesis. In the present review, the publications in this area over last seven years are discussed.

2. Methods for synthesis of α,β-unsaturated trifluoromethylketones

Analysis of the literature shows that several basic methods for the synthesis of α,β-unsaturated trifluoromethylketones were at the center of various investigations and these can be classified starting from the structure of the target compounds **1**.



1

— Creation of C^2–C^3 bonds (e.g., trifluoroacylation of alkenes).
— Creation of C^3=C^4 bonds (e.g., condensation of carbonyl compounds with 1,1,1-trifluoroacetone derivatives).
— Creation of C^4–R^3 or C^4–R^2 bonds (e.g., nucleophilic substitution at the β-carbon atom in α,β-unsaturated trifluoromethylketones containing a good leaving group in the β-position, reactions of amines with 1,3-dicarbonyl compounds, etc.).
— Creation of C^1–C^2 bonds (e.g., trifluoromethyl-organometallic reagent addition to acrylic acid esters).
— Creation of C^3–R^1 bonds (e.g., halogenation of α,β-unsaturated trifluoromethylketones at the α-position).

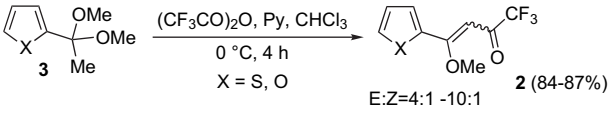
The approaches for the synthesis of α,β-unsaturated trifluoromethylketones are described in the sequence given above.

2.1. Creation of C^2–C^3 bonds

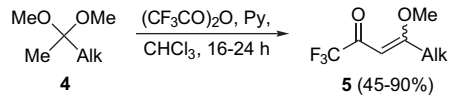
Activated alkenes and compounds from which they are generated in situ can be trifluoroacetylated using trifluoroacetic acid anhydride (TFAA). This method is widely used, due to its simplicity and adaptability for a wide range of substrates.

Nowadays, in spite of the fact that this method is well known, several groups still continue to investigate it.

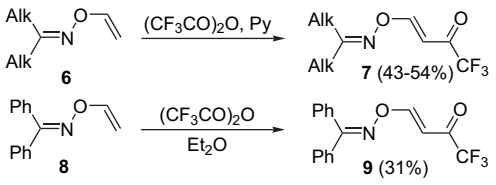
Trifluoroacetylation with TFAA in the presence of pyridine was applied for the synthesis of 1,1,1-trifluoro-4-(hetaryl)-but-3-en-2-ones **2**.[3] The starting materials were dimethyl acetals **3** of the corresponding ketones. The use of two equivalents of trifluoroacylating agent is needed. The first is consumed for generation of the enol ether, which is then trifluoroacetylated with the second equivalent of TFAA. The products were obtained as a mixture of *E*- and *Z*-isomers with *E*-isomer predominating.



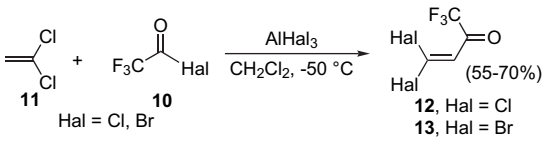
The same methodology—the trifluoroacylation of dimethyl acetals **4** of ketones—was used for the synthesis of 1,1,1-trifluoro-4-methoxy-4-alkyl-3-buten-2-ones **5**.[4] It should be mentioned that, in the case of substrates containing bulky alkyl substituents, a higher temperature of ~60 °C is needed, while, using non-bulky alkyl substituents, room temperature is sufficient. The geometrical isomerism (*E*/*Z*) for compounds **5** has not been determined. The compounds **5** are highly volatile at room temperature and, because of this property, the elemental analysis of **5** could not be performed.



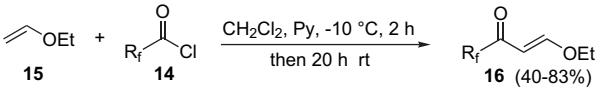
Ketone *O*-vinyl oximes, which have become accessible in recent times may also be regarded as *O*-substituted vinyl ethers. The goal of this work[5] was to obtain a deeper insight into specific features of the reaction of aliphatic and aromatic ketone *O*-vinyl oximes with TFAA. There are several examples of the trifluoroacylation of *O*-vinyl oximes **6** of various ketones forming the corresponding trifluoromethyl-ketones **7**. The reaction is stereoselective and only one more stable trans-isomer is formed. The trifluoroacylation of benzophenone *O*-vinyl oxime **8** was also investigated.[6] The reaction proceeds at room temperature for several hours and the target product **9** was isolated in low yield.



Besides TFAA, trifluoroacetyl chloride and bromide **10** (Hal=Cl or Br) have been used[7,8] for trifluoroacylation of 1,1-dichloroethene **11**. The low activity of the double bond in 1,1-dichloroethene **11** requires the use of a catalyst. Aluminum halides were used as the catalysts in this reaction. Noteworthy, using aluminum bromide with **10** (Hal=Cl or Br) the only product, 2,2-dibromovinyltrifluoromethyl-ketone **13**, is formed,[8] whereas $AlCl_3$ with **10** (Hal=Cl or Br) gives the corresponding dichloroketone **12**.

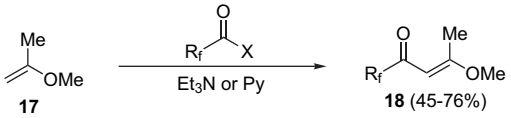


In order to prepare a number of β-alkoxyenones with various fluoro-containing substituents of different length and branching, as well as a different number of fluorine atoms, the reaction of polyfluorocarboxylic acid chlorides with ethyl vinyl ether instead of acid anhydrides was investigated.[9] Various acyl chlorides **14** were applied for the acylation of **15** in the presence of pyridine in methylene chloride. The corresponding β-ethoxyketones **16** containing various fluorinated substituents were obtained in good yields.



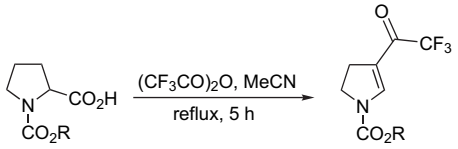
R_f = CF_3, CHF_2, C_2F_5, C_3F_7, $CH(CF_3)_2$

In addition, the acylation of 2-methoxypropane **17** with anhydrides or perfluoroacyl chlorides and fluorides in the presence of triethylamine or pyridine has been described.[10] Regardless of the carbon chain in the acylating agent, the target ketones **18** were obtained in high yields.



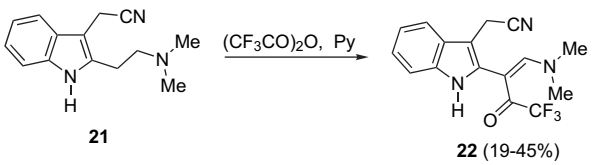
R_f = CF_3, C_2F_5, C_4F_9, C_8F_{17} ; X = Cl, F, $OCOR_f$

The behavior of several *N*-protected prolines **19** in the Dakin–West reaction was studied.[11] In the case of the application of TFAA as the acylating agent, instead of the target aminoketones the main products were the corresponding cyclic enaminoketones **20**, which were obtained in moderate yields.

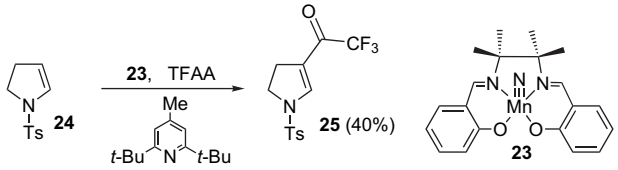


R = Me, Et, Bu, Ph, 9-fluorenyl, allyl, benzyl

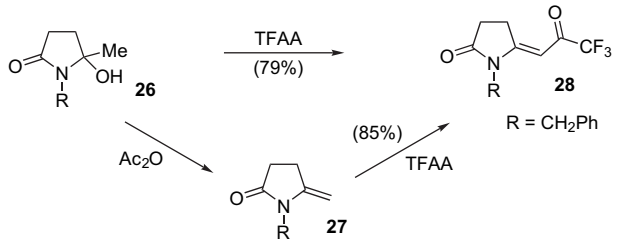
Furthermore, an example of CF_3-enaminoketone formation in the acylation of a tertiary amine has been described. Enaminoketone **22** was obtained in low yield in the reaction of the substituted *iso*-tryptamine **21** with TFAA in the presence of pyridine.[12] The reaction is not preparative, because of the low rate and the difficulty of isolation of the target product.



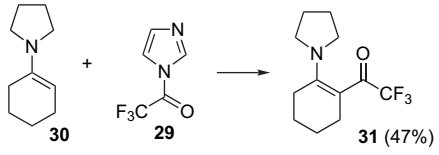
The application of TFAA and salen-manganese complex **23** in combination was described for the acylation of *N*-tosyl-2-pyrroline **24** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine.[13] The corresponding cyclic enaminoketone **25** was obtained in moderate yield.



On treatment with acetic anhydride, 5-hydroxypyrrolidin-2-one derivative **26** is converted into enamine **27**, while, under treatment with TFAA, the formation of the heterocyclic enaminoketone **28** is observed, probably due to the more electrophilic character of TFAA.[14,15]

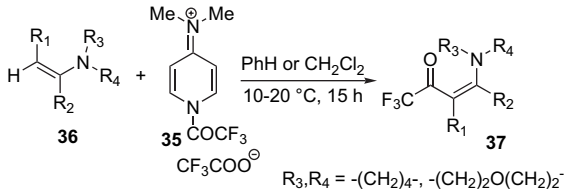


In addition to TFAA, trifluoroacetylimidazole **29** was used for the trifluoroacylation of cyclic enamines.[16] Enamine **30** obtained from cyclohexanone and pyrrolidine was trifluoroacetylated at room temperature to form the corresponding enaminoketone **31** in moderate yield.



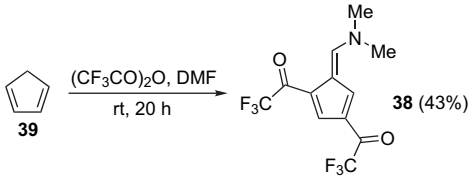
A similar approach was used for the synthesis of potato glycoalkaloid derivatives.[17] Enamine **33** generated in situ from *N*-oxide **32** was trifluoroacetylated with TFAA, forming enaminoketone **34** in moderate yield.

The complex **35** prepared from 4-dimethylaminopyridine and trifluoroacetic acid anhydride was used for the trifluoroacetylation of various enamines **36**.[18] The reaction was carried out in benzene or methylene chloride as the solvent at room temperature. The yields of the products **37** are rather high, but the procedure seems to have no advantages over other methods of trifluoroacylation in the presence of other amines such as pyridine.

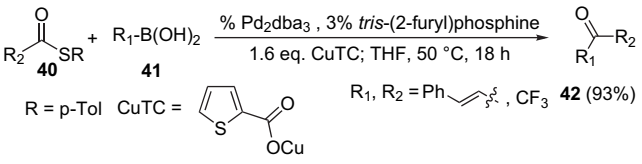


R_1,R_2 = -$(CH_2)_4$-, (80%); R_1 = Me, R_2 = Et, (60%);
R_1 = H, R_2 = *t*-Bu, (69%); R_1= H, R_2 = Ph, (70%);
R_1 = H, R_2 = 4-MeC_6H_4, (72%); R_1 = Me, R_2 = Ph, (75%)

The preparation of an unusual disubstituted CF_3 derivative of fulvene **38** has been described.[19] This compound was obtained by trifluoroacylation of cyclopentadiene **39** with TFAA at room temperature using dimethylformamide as the solvent.

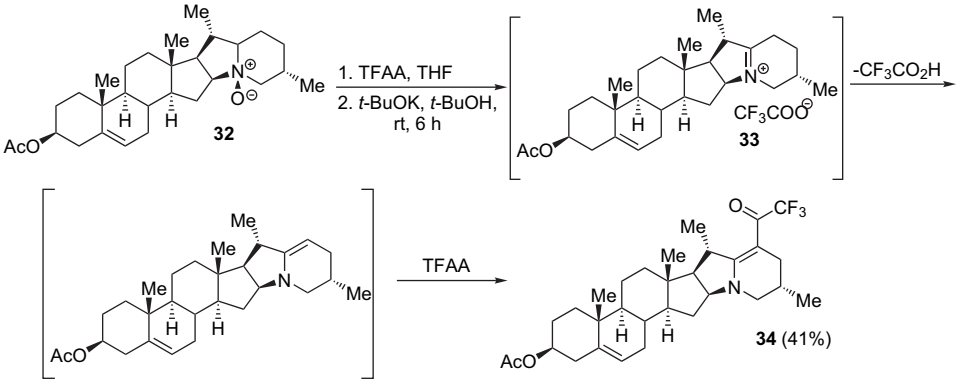


For the preparation of various ketones, the method based on cross-coupling reactions of thioesters **40** with the corresponding boronic acids **41** was used. The application of this method has been demonstrated for the synthesis of β-aryl-CF_3-enones, an example being ketone **42**.[20]

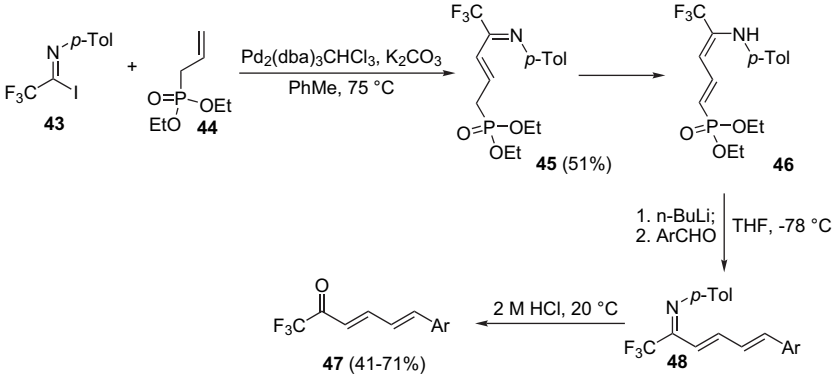


R_1, R_2 = 3-$NO_2C_6H_4$, CF_3; R_1, R_2 = 3-$NO_2C_6H_4$, CF_3; R_1, R_2 = Ph, 2-MeOC_6H_4;
R_1, R_2 = Ph, 3-MeOC_6H_4; R_1, R_2 = Ph, 2-Naph; R_1, R_2 = Ph, 4-HOC_6H_4;
R_1, R_2 = ClCH_2, 2-Naph; R_1, R_2 = 4-$NO_2C_6H_4$, 3,4-methylendioxyphenyl

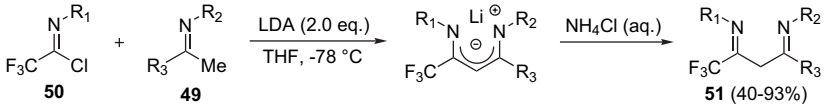
The method using cross-coupling of *N*-(4-methylphenyl)trifluoroacetimidoyl iodide **43** with diethyl allylphosphonate

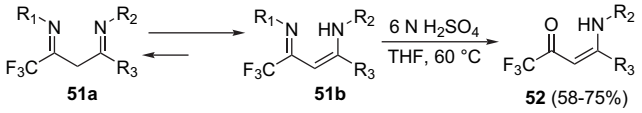


44 in the presence of a palladium catalyst forming *N*-(4-methylphenyl)imino-5,5,5-trifluoropent-2-enylphosphonate **45** was elaborated. Compound **45** readily undergoes migration of the double bonds, isomerizing into compound **46**. The structure of **46** was confirmed by ^{1}H NMR data. Additionally, the compound **46** can be used in the Horner–Emmons reaction with various aromatic aldehydes, generating the corresponding *E*,*E*-dienones **47** after acidic hydrolysis of the imine fragment in the imines **48**.[21]



The possibility for introduction of a trifluoroacetyl group to the carbonyl group in various imines of methylketones **49** by reaction of the corresponding lithium azaenolates with *N*-substituted trifluoroacetimidoyl chlorides **50** or trifluoroacetic acid esters was investigated.[22] In the first case, the products are diimines of diketones **51**. Using ^{1}H and ^{19}F spectroscopy, it was established that the compounds exist in the form of tautomer **51b** containing an enolized imino-fragment neighboring trifluoromethyl group, so that the formed double bond exists in the *Z*-configuration. Only hydrolysis of the imino-fragment neighboring trifluoromethyl group is observed under acidic treatment for compounds **51**. This leads to the formation of the β-enaminoketones **52**.

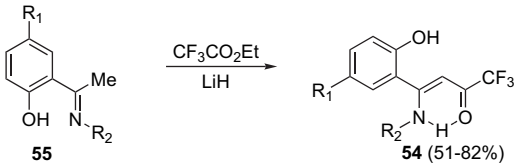




R^1 = *p*-MeOC$_6$H$_4$, (*R*)-(+)-PhCHMe; R^2, R^3 = Alk, Ar

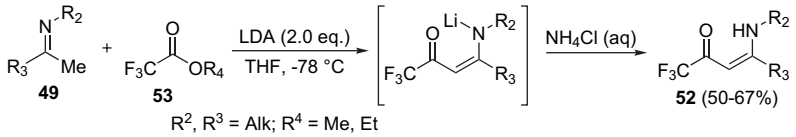
The second alternative approach for the synthesis of **52** consists of trifluoroacylation of imine azaenolates generated from **49** with methyl and ethyl trifluoroacetates **53**, which allows the enaminoketones to be obtained directly in one step.[22]

An analogous method was suggested for the preparation of enaminoketones **54** by acylation of imines **55** with ethyl trifluoroacetate. Imines **55** were prepared from substituted *o*-hydroxyacetophenones and various aliphatic amines.[23] The ketones obtained exist in the *Z*-form containing an intramolecular hydrogen bond.



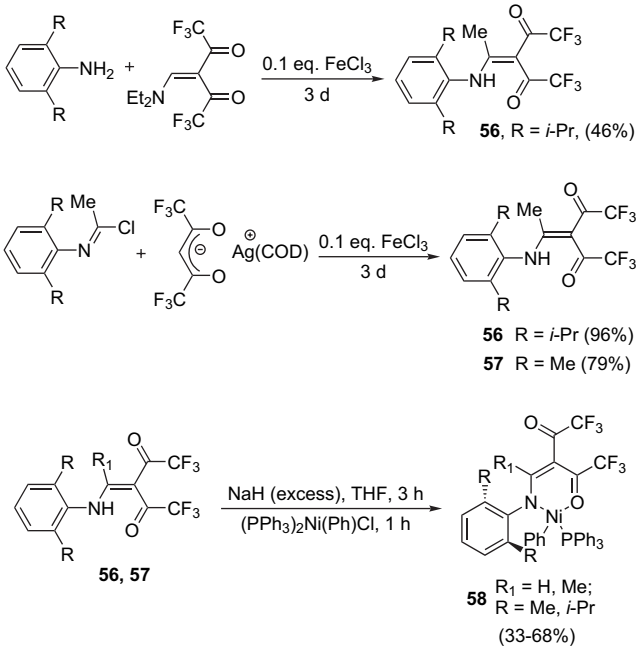
R_1 = Me, H; R_2 = CH_2Ph, *i*-Pr, $(CH_2)_2OH$

Some CF_3-enones were used for the preparation of effective catalysts for ethylene polymerization. The first neutral Ni(II) catalysts for ethylene polymerization were reported in the 1980s. These catalysts were primarily based on modifications of the SHOP (Shell higher olefin process) systems and incorporated anionic phosphino-enolate ligands. Such systems normally provided low-molecular-weight linear polyethylene at modest rates. Incorporation of bulky substituents or perfluoroalkyl groups in the backbone of the P,O chelates greatly accelerated the polymerization rates. Several CF_3-enaminoketones for subsequent preparation of such complexes with several fluorine-containing ligands were synthesized.[24] Ligand **56** was prepared by displacement of the Et_2N group in ((diethylamino)methylene)-1,1,1,5,5,5-hexafluoroacetylacetone (DAMFA) by 2,6-diisopropylaniline catalyzed by $FeCl_3$ as Lewis acid by analogy with the known chemistry of DAMFA. Following chromatographic purification, compound **56** was isolated in good yields and high purity. Alternatively, similar ketones can be prepared

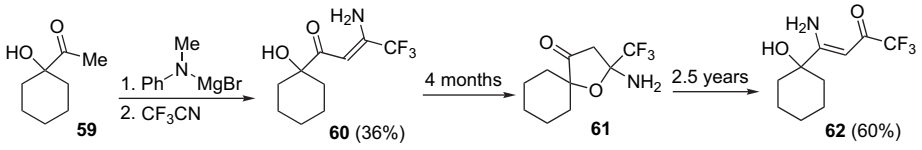


R^2, R^3 = Alk; R^4 = Me, Et

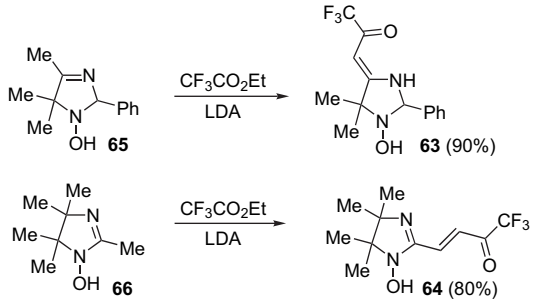
by acylation of silver salts with imidoyl chloride derived from sterically hindered anilines. The enamines **57** were readily deprotonated with an excess of sodium hydride in THF to yield the corresponding sodium salts. In situ reactions of these sodium salts with $(PPh_3)_2Ni(Ph)Cl$ at 25 °C generated the desired Ni(II) complexes **58**. These complexes are active for ethylene polymerization in the presence of an activator $(Ni(COD)_2$ or $B(C_6F_5)_3)$ to sequester PPh_3. Moderately branched polyethylenes generally in the range of 35–55 branches per 1000 carbons are produced, consistent with expectations based on the presence of *ortho*-disubstituted aryl groups on nitrogen.



An example of using trifluoroacetonitrile as acylating agent has also been described. The enolate generated from 1-acetylcyclohexanol **59** by treatment with a magnesium amide derivative was reacted with trifluoroacetonitrile to form the β-enaminoketone **60** by isomerization of intermediate compounds.[25] For a period of four months, this β-enaminoketone cyclizes into furan-3-one derivative **61** (yield is not given). After standing for 2.5 years, furan-3-one derivative **61** rearranges into enaminoketone **62**. All attempts to accelerate these reactions were unsuccessful.



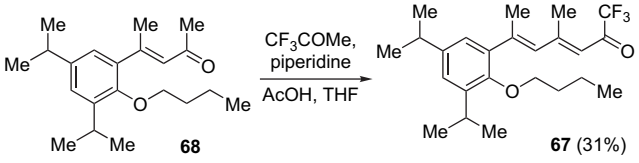
Using an analogous strategy, enaminoketones containing imidazole substituents **63** and **64** were obtained. Ethyl trifluoroacetate was used for acylation of the starting compounds **65** and **66** with lithium diisopropylamide (LDA) as the base.[26,27]



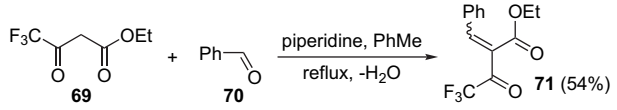
2.2. Creation of $C^3{=}C^4$ bonds

The traditional method for the creation of $C^3{=}C^4$ bond is the condensation of carbonyl compounds with 1,1,1-trifluoroacetone or its derivatives under the conditions of Knoevenagel reaction.

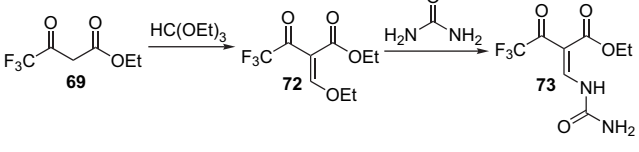
The synthesis of ketone **67** was described using condensation of substituted chalkone **68** with trifluoroacetone in the presence of piperidine as a base.[28] The low yields in such reactions are caused by the self-condensation of the trifluoroacetone.



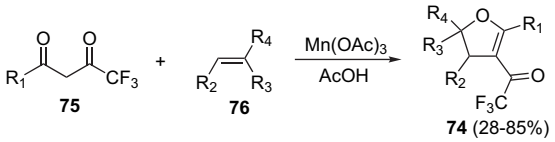
The reaction of ethyl trifluoroacetoacetate **69** with benzaldehyde **70** has been described.[29] The target product was formed by refluxing of the starting compounds in toluene in the presence of piperidine with azeotropic separation of water. The product **71** was obtained in moderate yield as a 1:1 mixture of *E*- and *Z*-isomers.



In a similar way, in the reaction of ethyl trifluoroacetoacetate **69** with triethyl orthoformate, derivative **72** is formed, which reacts with urea generating β-enamidoketone **73** containing an ethoxycarbonyl group in the α-position.[30] The yields for the obtained products are not given.

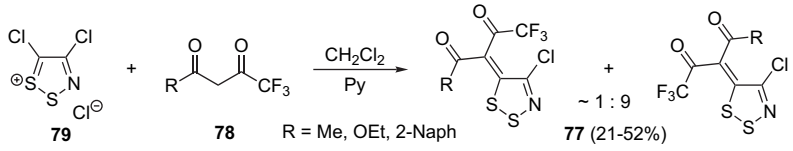


An original method for the synthesis of cyclic CF_3-enones **74** has been elaborated.[31] The radical cyclization reaction of fluorinated 1,3-dicarbonyl compounds **75** with alkenes **76** was induced by manganese(III) acetate. Ketones **74** were obtained in various yields.

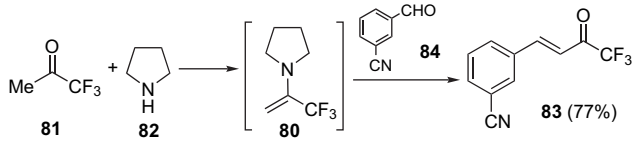


R_1 = 2-Thiophenyl, Ph, Me; R_2 = H, Me, Ph;
R_3 = H, Me, Ph, 4-MeC_6H_4; R_4 = Ph, 4-MeC_6H_4

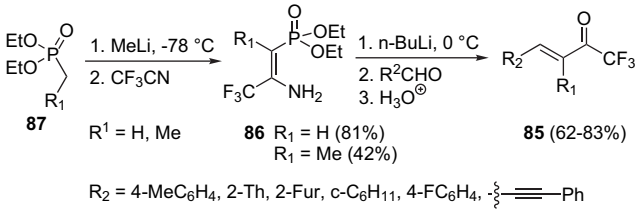
Several ketones **77** containing a β-dithiazolyl substituent have been obtained.[32] The starting compounds were fluorinated 1,3-dicarbonyl compounds **78** and 4,4-dichloro-1,2,3-thiazolium chloride (Appel salt) **79**. A mixture of *E*,*Z*-isomers of **77** was formed.



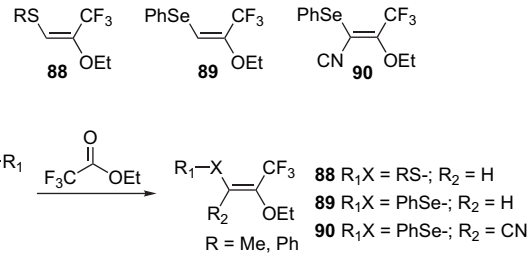
For a single example, the application of enamine **80**, generated in situ from 1,1,1-trifluoroacetone **81** and pyrrolidine **82**, for the synthesis of β-aryl-substituted CF_3-enone **83** by reaction with aromatic aldehyde **84** has been described.[33] The ketone **83** containing a 3-cyanophenyl substituent in the β-position was obtained in good yield. It should be noted that the method is suitable for the preparation of large amounts of ketone **83**.



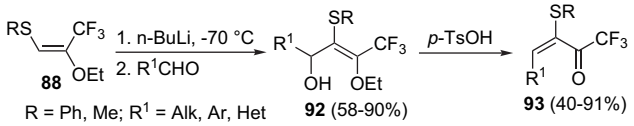
The synthesis of α,β-unsaturated trifluoromethylketones **85** using enaminophosphonates **86** in a Horner–Emmons reaction with various aldehydes has been described.[34,35] Compounds **85** can be prepared by condensation of diethyl alkylphosphonates **87** with trifluoroacetonitrile. Noteworthy is the fact that the trifluoromethyl group and the phosphorus atom in enamines **86** are located in the trans-position. In addition, all compounds **85** were obtained as their *E*-isomers.[34]



Several publications [36–38] are devoted to application of substituted ethyl(1-trifluoromethyl)vinyl ethers **88–90** in the synthesis of α,β-unsaturated trifluoromethylketones. The ethers **88–90** were obtained using a Wittig reaction of ethyl trifluoroacetate and ylide **91**.

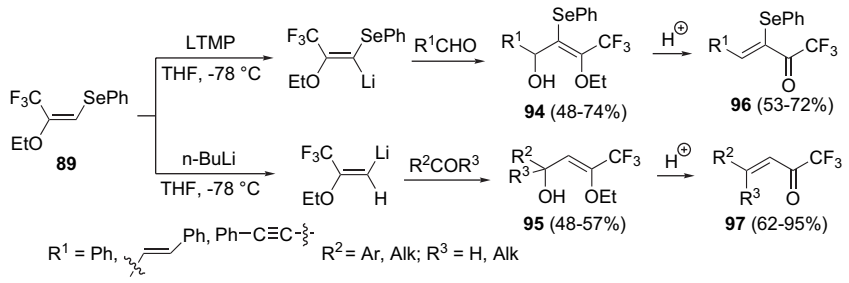


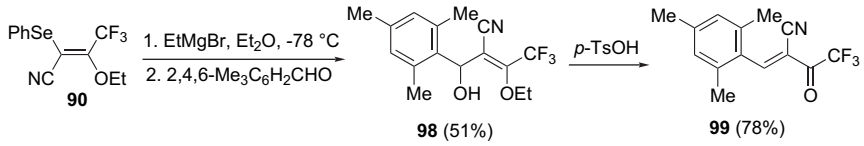
Compounds **88** obtained by the Wittig reaction of phenylthio- or methylthiophenylphosphorane and ethyl trifluoroacetate can be easily lithiated by treating the free vinyl position with *n*-BuLi. The subsequent reaction with various aldehydes leads to the corresponding allylic alcohols **92**. Under treatment with *p*-toluenesulfonic acid, compounds **92** are rearranged into the trifluoroketones **93**.[36] All ketones **93** were obtained as their *E*-isomers. This method clears the way to preparing α-alkyl(aryl)thio-α,β-unsaturated trifluoromethylketones **93**.



Compounds **89** were obtained by the condensation of bis-(phenylseleno)methane with ethyl trifluoroacetate with further elimination of the phenylselenyl group under treatment with methanesulfonyl chloride. The generation of the corresponding vinyllithium compounds is possible through two independent pathways—by lithiation of the unsubstituted vinyl position or by Se–Li exchange.[37] In both cases, the organometallic derivatives obtained are used in the reactions with various aldehydes, forming the respective allylic alcohols **94** or **95**. Subsequent acidic treatment leads to the α,β-unsaturated trifluoromethylketones **96** or **97**. In most cases, the reactions proceed stereoselectively. Compounds **96** are formed as the *Z*-isomers, excluding reaction with 3-phenylpropyn-2-al, in which case the *E*/*Z*-isomeric ratio in the α-phenylseleno-α,β-unsaturated trifluoromethylketone is 3:7. Compounds **97** are formed as the *E*-isomers.[37]

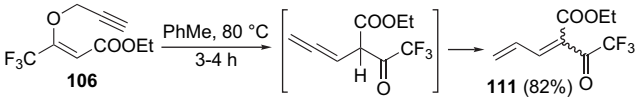
Vinyl selenide **90** was synthesized by condensation of phenylselenoacetonitrile with ethyl trifluoroacetate in the presence of methanesulfonyl chloride. Subsequent Mg–Se exchange using EtMgBr and treatment with 2,4,6-trimethylbenzaldehyde leads to the benzylic alcohol **98**, which can be transformed into the α-cyano-α,β-unsaturated trifluoromethylketone **99** by reaction with *p*-toluenesulfonic acid.[38] It is to be noted that using *n*-BuLi as the reagent for the Li–Se exchange causes a decrease in the yield of **98** to 17%. This synthetic sequence opens up the pathway to α-cyano-α,β-unsaturated trifluoromethylketones **99**.



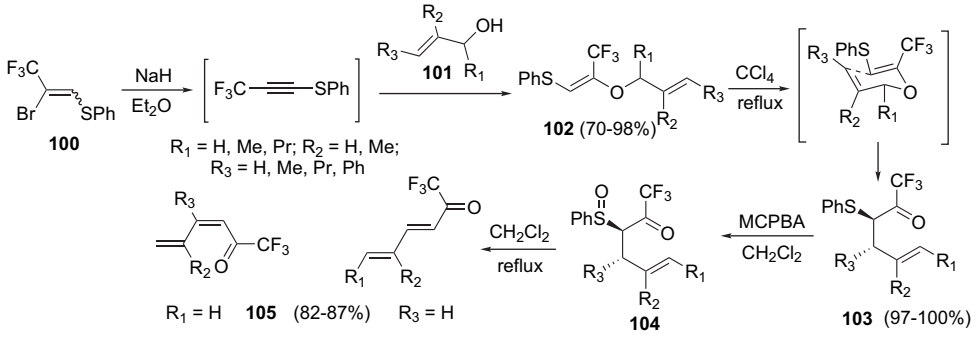


The Claisen rearrangement can also be used for the synthesis of α,β-unsaturated trifluoromethylketones. A method for the preparation of CF_3-dienones based on the application of this rearrangement has been elaborated.[39] 1-Phenylsulfanyl-2-bromo-3,3,3-trifluoropropene **100** served as the starting material. Its reaction with sodium hydride leads to in situ formation of the CF_3-acetylene, which reacted with various allylic alcohols **101** to form the vinyl ethers **102**. The vinyl ethers were rearranged by heating in carbon tetrachloride solution to generate the γ,δ-unsaturated ketones **103**. The target dienone **105** was formed by oxidation of phenylsulfanyl group in **103** with *m*-chloroperbenzoic acid and elimination of the sulfinic acid from the sulfoxide **104**. The stereochemistry of the obtained compound is explained by a more favorable chair-like conformation of transition state in the Claisen reaction and also by *syn*-elimination of sulfinic acid from the sulfoxide **104**.

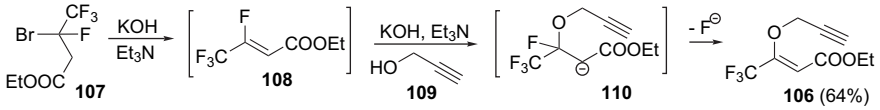
through the intermediate ester **108** and Michael addition of propargylic alcohol **109** with further elimination of fluoride anion from intermediate **110**. Vinyl propargyl ether **106**, in turn, by heating in toluene at 80 °C for 3–4 h undergoes Claisen rearrangement with further double-bond migration leading to **111** (*Z*/*E* ratio 2/1).[40]

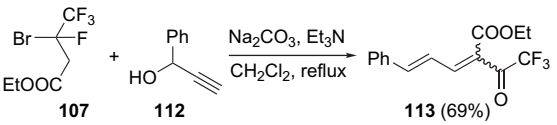


In the case of propargyl alcohol **112** bearing a phenyl substituent near to the hydroxyl group, the intermediate



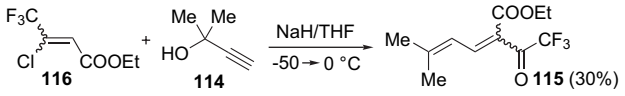
The Claisen reaction was also studied for various fluoroalkyl-containing vinyl propargyl ethers. Compound **106** was prepared by subsequent dehalogenation of ester **107** vinyl propargyl ether has not been isolated—in the reaction conditions, it rearranges directly into the dienone (*Z*/*E*-ratio 1.2/1).





107 **112** **113** (69%)

An attempt to carry out analogous transformations for 1,1-dimethylpropargyl alcohol **114** failed. In this case, preparation of dienone **115** using the reaction of acrylate **116** with alcohol **114** in tetrahydrofuran in the presence of sodium hydride was described. The ratio of *Z*/*E* isomers was 1/1 and only the *E*-isomer was isolated by chromatography.



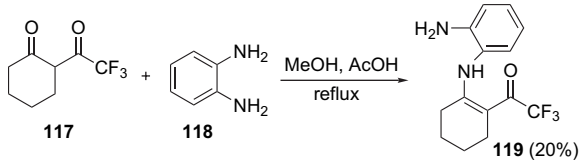
116 **114** **115** (30%)

2.3. Creation of C^4–R^3 or C^4–R^2 bonds

α,β-Unsaturated trifluoromethylketones having a heteroatom (e.g., alkoxy or dialkylamino) in the β-position can take part in reactions with nucleophiles by an 'addition–elimination' mechanism with the further formation of new α,β-unsaturated trifluoromethylketones.

In addition, 1,3-dicarbonyl compounds containing a trifluoroacetyl fragment react easily with primary and secondary amines. The reaction proceeds as an addition on the carbonyl atom with further water elimination and preservation of the trifluoroacetyl group. The products of this reaction are β-enaminoketones containing a trifluoroacetyl group. A large number of reports are devoted to investigations of this reaction.

In one example, the reaction of cyclic 1,3-diketone **117** containing a CF_3 group with *o*-phenylenediamine **118** was studied.[41] The reaction proceeds rapidly under reflux in methanol solution in the presence of acetic acid. The corresponding enaminoketones **119** were prepared in low yields.

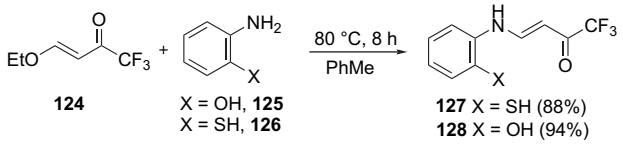


117 **118** **119** (20%)

The analogous reaction of 1,3-diketones **75** with substituted *o*-phenylenediamine **120** is described.[42] Noteworthy is the fact that the nucleophilic attack of the more nucleophilic NH_2 group is not directed onto the trifluoroacetyl group. The β-enaminoketones **121** were obtained in good yields.

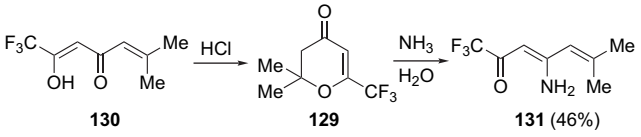
Under reaction of *o*-phenylenediamine **118** with triketones **122** containing two fluorinated alkyl groups, the formation of the corresponding 1,5-benzodiazepines **123** is observed.[43] The reaction proceeds in good yields during 10–15 min of methanol reflux. Equilibrium of the two tautomeric forms for the obtained products **123** is observed.

The reactions of CF_3-enone **124** with 2-aminothiophenol **126** and 2-aminophenol **125** were investigated. The reactions were carried out in toluene and the ketone **124** reacted easily to give **127** or **128** in high yield.[44]



124 X = OH, **125** X = SH, **126** **127** X = SH (88%) **128** X = OH (94%)

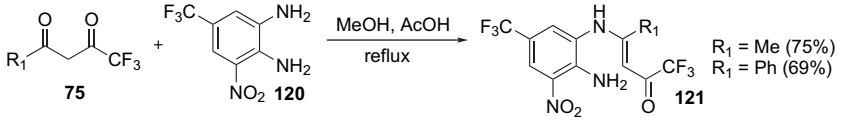
The reaction of dihydropyran-4-one **129** with ammonia proceeds by an analogous route. Dihydropyran-4-one **129** was obtained by treatment of 1,3-dicarbonyl compound **130** with aqueous hydrogen chloride.[45] Reaction of **129** with ammonia was complete in 2 days at room temperature, but the yield of enaminoketone **131** was not very high.



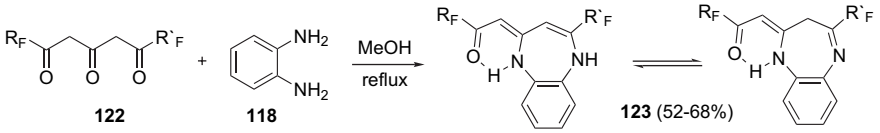
130 **129** **131** (46%)

Similarly, this reaction proceeds with the hydroxy-pyranone **132**. CF_3-enaminoketones **133** were obtained in good yields by treatment of **132** with aqueous ammonia.[46] Applying benzylamine instead of ammonia leads to acidic splitting of the 1,3-dicarbonyl compound with loss of the trifluoroacetyl group instead of enaminoketone **133** formation. The products of the reaction in this case were hydroxyketone **133a** and *N*-trifluoroacetylbenzylamine **133b**.

Ketones **134** containing an aziridine fragment in the β-position were prepared by the reaction of *cis*-1,2-diphenylaziridine **135** with CF_3-enone **136** containing a chlorine atom in the β-position. The reaction proceeds with the formation of a mixture of *E*,*Z*-isomers of ketone **134**.[47]

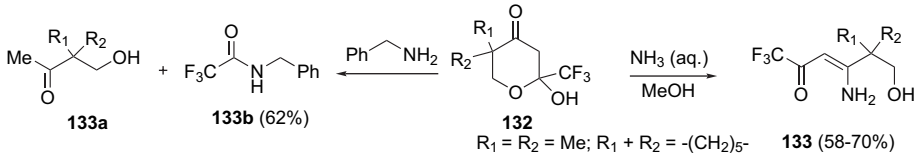


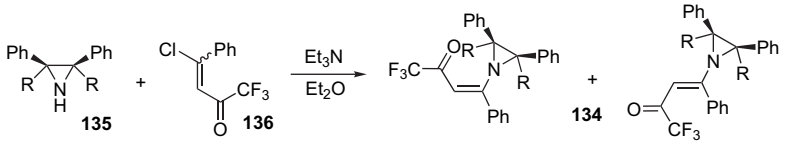
75 **120** **121**



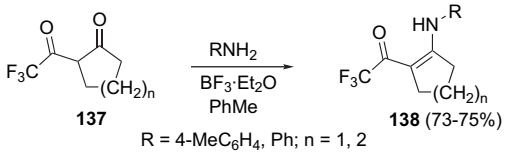
122 **118** **123** (52-68%)

RF/R`F = CF_2H/CF_2H; CF_2H/CF_3; CF_3/CF_2H; CF_3/CF_3; C_2F_4H/CF_3; C_3F_7/CF_3; C_6F_{13}/CF_3; C_2F_4H/C_2F_4H; C_4F_9/C_4F_9; C_4F_9/C_2F_4H

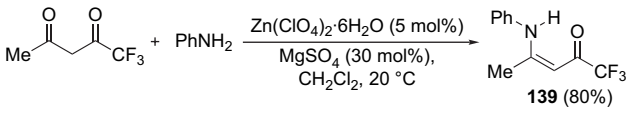




A $BF_3 \cdot Et_2O$ complex was used to accelerate the reaction of 1,3-diketones **137** with aromatic amines and to increase the yields.[48] Catalytic amounts of this complex essentially accelerate the reaction and increase the yields of the target enaminoketones **138**.



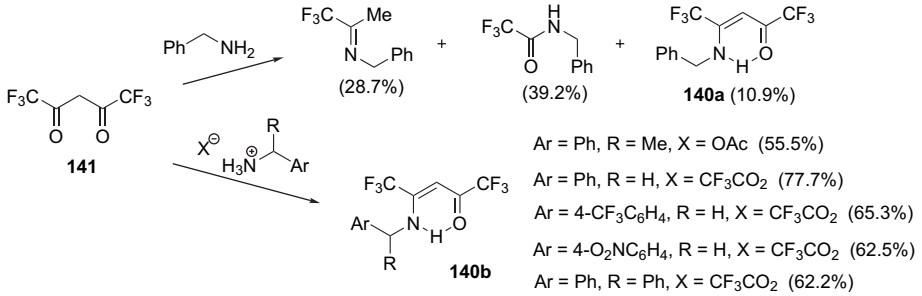
In addition, zinc perchlorate hexahydrate was found to be an effective catalyst for this reaction.[49] This catalyst was very active for the transformation of 1,1,1-trifluoroacetylacetone into the enone **139** in the reaction with aniline.

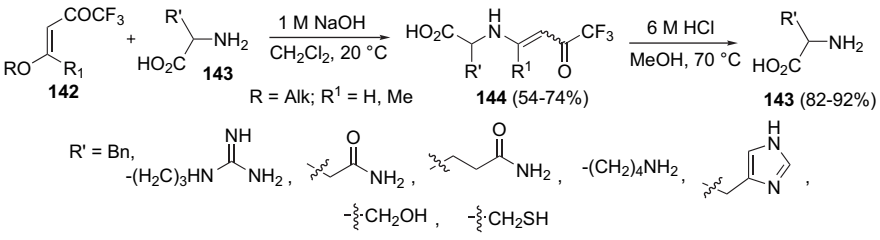


The preparation of the target enamine **140a** by the reaction between diketone **141** and benzylamine using water-separation conditions failed.[50] The yield of the expected enamine **140a** in this reaction was only about 11%. Less nucleophilic trifluoroacetates of amines were used in an attempt to improve the yield of **140a**. The reaction between diketone **141** and benzylamine trifluoroacetate proceeded at a good rate. The important feature of this reaction was the absence of unwanted by-products. To demonstrate the practicality of the developed reaction conditions using benzylamine trifluoroacetate as a reagent, the reaction was performed on a relatively large scale (20 g) with successful reproducibility in the yield of the enamine **140b**.

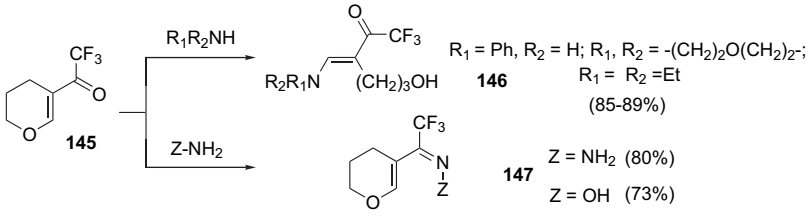
The enones **142** can be used as selective protecting groups for the α-amino group of α-aminoacids **143** containing additional functional groups in the side chain (arginine, asparagine, etc.). The protection is provided by formation of the enaminoketone **144**. An exception is lysine, in which case both amino groups react equally.[51] The cleavage of this protective group is performed by treatment with hydrogen chloride in methanol.

The reactions of 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran **145** with various nucleophiles have been studied.[52] This ketone reacts readily with many nucleophiles such as amines

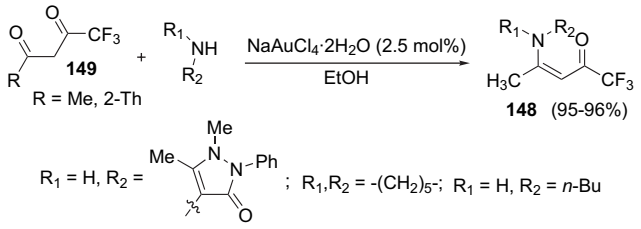




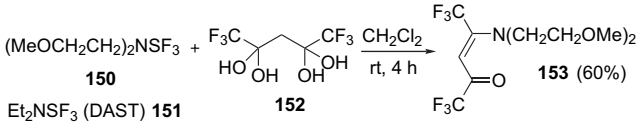
and Grignard reagents to give the ring-opened products **146**. Hydrazine and hydroxylamine attack the carbonyl carbon of compound **145** to form hydrazone or oxime **147**.



In recent years, environmentally benign synthetic methods have received considerable attention and new procedures for the synthesis of enaminones have been reported. The results of a gold(III)-catalyzed synthesis of β-enaminones **148** from 1,3-dicarbonyl compounds **149** have been reported.[53] This procedure is quite general for a wide range of amines such as aliphatic, cyclic and aromatic amines using the commercially available catalyst $NaAuCl_4 \cdot 2H_2O$.

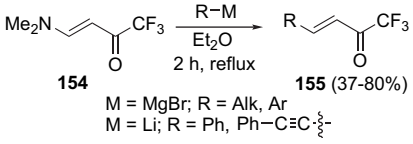


Deoxofluor **150** appears in some cases to be a more effective fluorinating reagent than DAST **151** and is easier to handle than sulfur tetrafluoride. A new route to polyfluoro ethers from alkyl, aryl, and mixed glyoxal hydrates and other hydrates using Deoxofluor has been reported.[54] The reaction of Deoxofluor with hexafluoroacetylacetone dihydrate **152** led to the formation of the β-enaminoketone **153** in good yield, without the formation of either a cyclic or an acyclic ether. No vicinal difluoroamine formation was observed in the reaction, indicating that the condensation proceeds more rapidly, producing the β-enaminoketone as the main product.

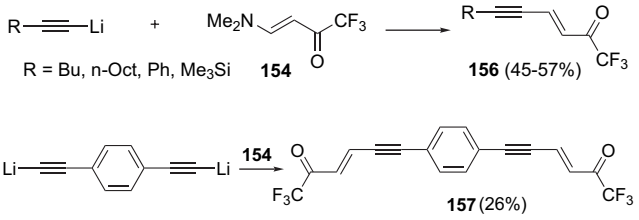


This work[55] continues with an investigation of the application of CF_3-enaminones for the synthesis of β-alkyl(aryl)-enones. The reaction of various Grignard and organolithium reagents with enone **154** was investigated. The reaction proceeds stereoselectively, leading to the formation of only the trans-isomer of CF_3-enone **155**. It was shown that the use of organolithium reagents has no advantages over Grignard reagents. Application of latter in several cases is more justified. It was shown that the application of Grignard reagents modified with cerium(III) salts does not lead to any improvements, in comparison to the non-modified reagents.

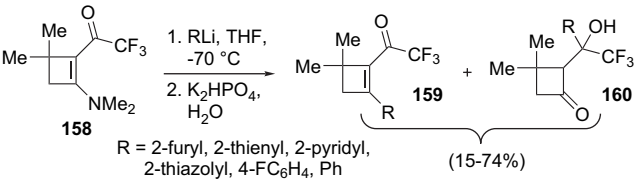
Additionally, enone **154** was used for the preparation of conjugated trifluoromethylenones **156** containing an acetylenic fragment.[56] The reaction of enone **154** with various lithium



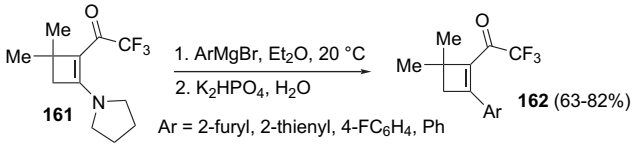
derivatives of terminal acetylenes leads to the formation of the target products in moderate yields. Diketones **157** were obtained in moderate yields using the dilithium derivatives of di-acetylenes.



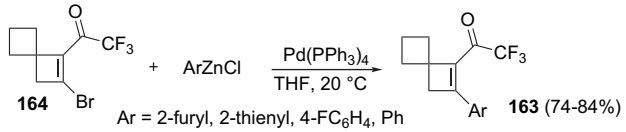
The same reaction of organolithium derivatives with enaminoketones **158** was applied to the synthesis of cyclobutene ketones **159** containing various substituents in the β-position.[57] The formation of the corresponding hydroxyketones **160** as by-products was observed.



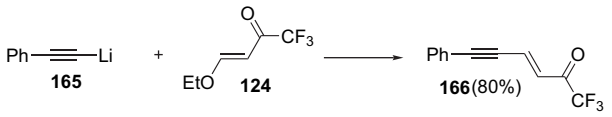
The problem of the formation of by-products—the corresponding keto-alcohols **160**—was solved using the reaction of enaminoketones **161** with Grignard reagents. In this case, the reaction proceeds regioselectively to form the target CF_3-enones **162** in high yields.[58]



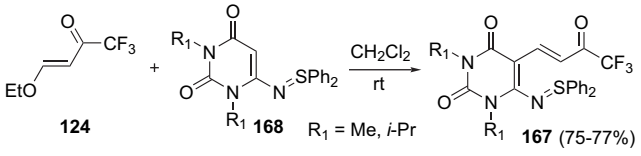
A cross-coupling reaction for the synthesis of bicyclic cyclobutene ketones **163** containing various substituents in the β-position has been reported.[59] The reaction of arylzinc derivatives with the corresponding bromide **164** in the presence of $(Ph_3P)_4Pd$ catalyst was used.



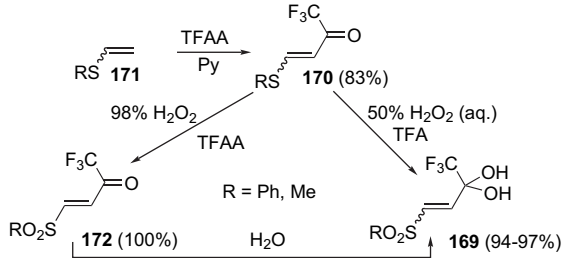
The greater effectiveness of β-alkoxy-CF_3-enone **124** in the reaction of the lithium derivative of phenylacetylene **165** was demonstrated for preparing the trifluoromethyl enone **166** containing an acetylenic fragment.[60]



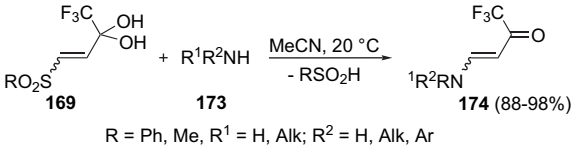
The reaction of ethoxyketone **124** was used for the preparation of β-uracil-substituted CF_3-enone **167** containing a sulfimine group.[61] The reaction with imine **168** was performed in methylene chloride at room temperature.



A number of reports[62,63] are devoted to the application of 4-sulfonyl-1,1,1-trifluorobut-3-en-2,2-diols **169** for the synthesis of various β-amino- and β-thio-α,β-unsaturated trifluoromethylketones. Compounds **167** can be prepared in yields close to quantitative by oxidizing β-thiosubstituted enones **170** prepared by trifluoroacylation of the corresponding vinyl sulfides **171**.[64] The oxidation was carried out using 50% H_2O_2 aqueous solution in the presence of trifluoroacetic acid or utilizing 98% H_2O_2 in the presence of trifluoroacetic acid anhydride. Subsequent hydration of the 4-sulfonyl-1,1,1-trifluorobut-3-en-2-ones **172** formed in the reaction proceeded in quantitative yields.[63] In the case of compound **172** with R=Ph, the *E*/*Z*-isomeric ratio is 7/2, and with R=Me, only the *E*-isomer is formed.

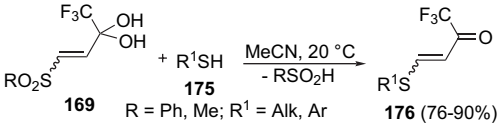


The reaction of **169** with various amines **173** or their aqueous solutions leads to the formation of corresponding enaminoketones **174** in high yields.[61] When one of the substituents (R^1 or R^2) is a hydrogen atom, the formation of the *Z*-isomer of **174** is observed (except when R^2=3-Py). If the formation of an intramolecular hydrogen bond N–H···O is impossible, the formation of the *E*-isomer is observed.[61] The reaction is completed in the presence of only 1 equiv of amine, in spite of the evolution of sulfinic acid. This can be explained by the high reactivity of **169**.[61]



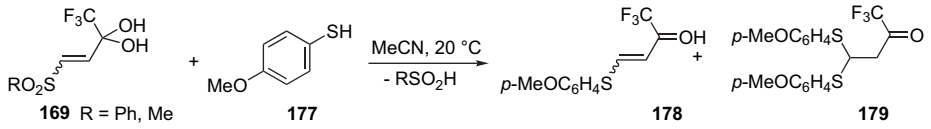
In the same work, the influence on the *Z*/*E*-isomer ratio in **174** (R^1=H, R^2=Ar) of substituents in the benzene ring was investigated. The presence of electron-donating substituents stabilizes the *Z*-isomer more favorably, because of intramolecular hydrogen bond N–H···O; the opposite situation is observed when an electronegative group is presented. Additionally, in nonpolar solvents (e.g., chloroform) the equilibrium is completely turned to the *Z*-isomer.[61] The configuration of the double C=C bonds in compounds **174** was established using ^{1}H NMR spectroscopy.

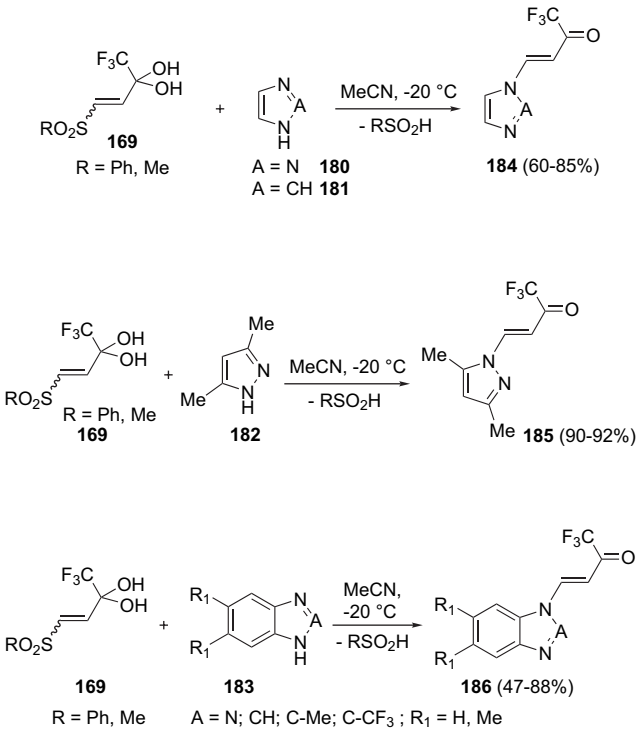
The reaction of **169** with various thiols **175** demonstrates a new pathway to β-sulfanylenones **176**.[63] The reaction proceeds in mild conditions in high yields. In most cases, the *E*-isomer is formed predominantly in this reaction. The yield of the product is not influenced by the nature of R substituent, except in the case of *p*-nitrothiophenol, where only the *Z*-isomer has been isolated.[63] The opposite correlation is observed for more nucleophilic *p*-methoxythiophenol **177**: in addition to the normal product **178**, the double-addition product **179** was isolated; using a twofold excess of *p*-methoxythiophenol **177** allows the product **179** to be obtained in high yield.[63]



In addition, the diol form of ketones **169** was used for the preparation of CF_3-enones containing heterocyclic substituent in the β-position. This transformation was achieved using the reaction of **167** with triazole **180**, imidazole **181**, 3,5-dimethylpyrazole **182** and their benzoderivatives **183**.[65] CF_3-enones **184**–**186** containing heterocyclic substituents were obtained in high yields.

The same workers[66] have reported the application of a new electrophilic reagent **187**, obtained by the oxidation





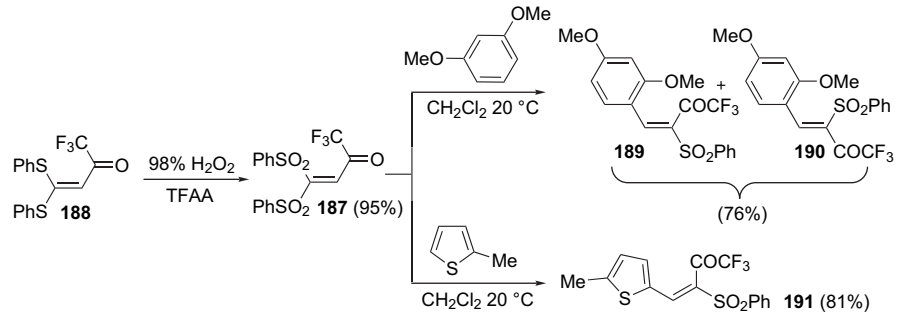
of ketene dithioacetal **188**. This reagent was applied for the synthesis of various α-phenylsulfonyl-α,β-unsaturated trifluoromethylketones. In one example, the reaction with 1,3-dimethoxybenzene leads to mixture of isomers **189** and **190** in a 7/1 ratio. The reaction of **187** with 2-methylthiophene proceeds 100% stereoselectively and only the *E*-isomer of ketone **191** is formed.[66]

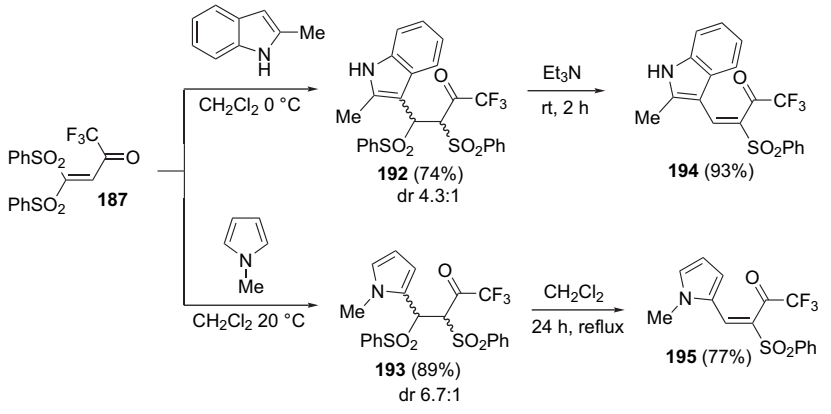
The reaction of **187** with more nucleophilic substrates proceeds without elimination of sulfinic acid and leads to the formation of adducts **192** and **193** (a mixture of diastereomers is formed). Elimination of sulfinic acid can be easily provoked by reflux of a methylene chloride solution for compound **193**, and using triethylamine as the base in the case of compound **192**.[66] Ketones **194** and **195** were obtained in high yields.

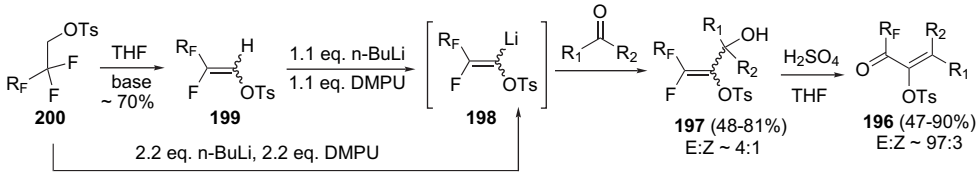
A method for the preparation of α,β-unsaturated ketones **196** containing an –OTs leaving group in the α-position to the carbonyl group has been described.[67] These compounds are formed under treatment of vinyl tosylate **197** with sulfuric acid in tetrahydrofuran. The allyllic alcohols **197** were prepared from lithium derivative **198** and carbonyl compounds. The intermediate lithium derivative **198** can be synthesized with isolation of fluoroalkene **199** and also by direct metallation of **200** with 2 equiv of *n*-BuLi. The target ketones **196** were obtained in good yields and high stereoselectivity.

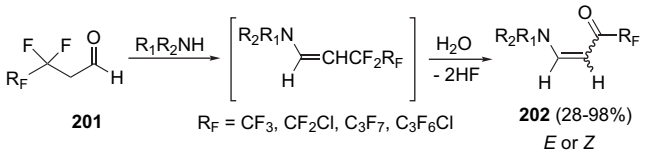
Polyfluorinated aldehydes **201** were used as starting compounds for the synthesis of β-enaminoketones **202**.[68] The target *N*-substituted β-enaminoketones **202** are formed in good yields by reflux of an acetonitrile solution of the polyfluorinated aldehydes with various amines in the presence of water.

The synthesis of β-selenoenones **203** using the reaction of methoxyenones **204** with methyl- and phenylselenol in the

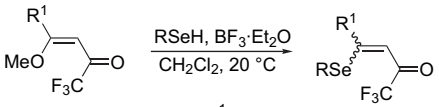




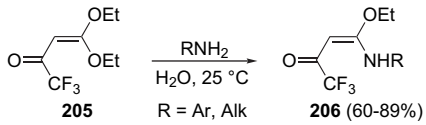




presence of 1 equiv of the BF_3–diethyl ether complex has been described.[69]



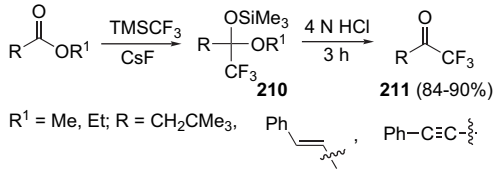
The substitution of one alkoxy group in enone **205** was used for the synthesis of *O*,*N*-acetals-aminals of trifluoroacetylketene **206**. The reaction was carried out in an aqueous medium. The method is characterized as being simple and effective and the yields of the products are rather high.[70]



Introduction of a cyano group in the β-position of α,β-unsaturated trifluoromethylketones can essentially broaden their synthetic potential as building blocks. The influence of a broad range of solvents and catalysts on the reaction of CF_3-enone **124** with TMSCN was investigated.[71] Depending on the solvent and the catalyst applied, individual products **207** and **208** or their mixtures can be obtained. β-Cyanoenone **209** was also prepared by treatment of **207** with concentrated sulfuric acid.[72] Compound **207** in this case was synthesized by the addition of trimethylsilyl cyanide to enone **124** in the presence of a catalytic amount of iodine.[73]

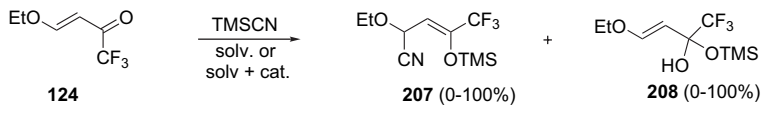
2.4. Creation of C^1–C^2 bonds

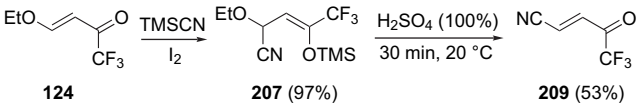
Acrylic acid esters can be converted into α,β-unsaturated trifluoromethylketones by addition of the Ruppert reagent ($TMSCF_3$) to the carbonyl group of esters. Cesium fluoride was suggested as the catalyst for the addition of $TMSCF_3$ to the carbonyl group of various esters.[74] The intermediate acetals **210** can be hydrolyzed in acidic conditions and various ketones **211** can be obtained including enones.



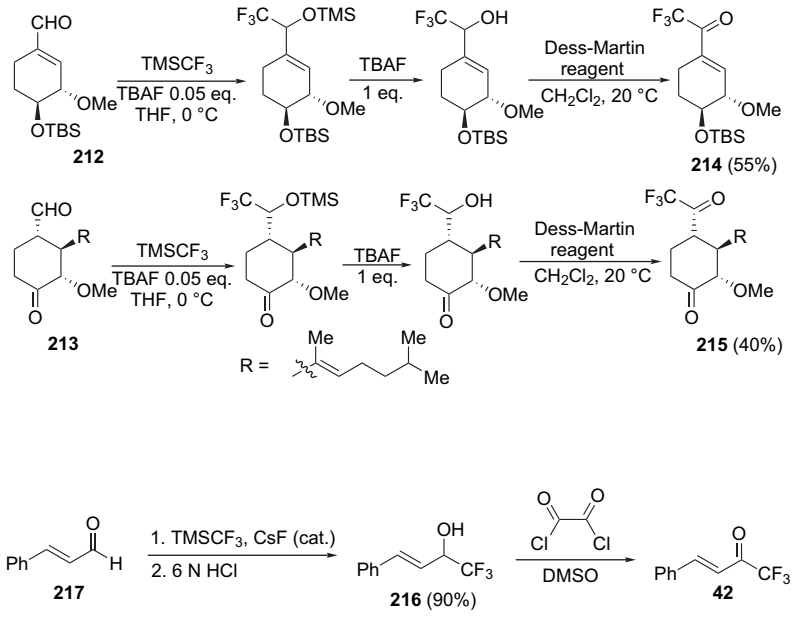
A similar methodology was carried out for cyclohexenyl- and 4-oxocyclohexenyl-carbaldehydes **212** and **213** followed by Dess–Martin oxidation. The corresponding CF_3-enones **214** and **215** were prepared in moderate yields. Noteworthy is the preservation of stereochemistry of the substituents in ketone **215**.[75]

An analogous method was applied[76] for the transformation of allylic alcohol **216** into the target ketone **42**. In this case, Swern oxidation was used. The addition of $TMSCF_3$ to **217** gives the allylic alcohol **216** in near-quantitative yield, but the yield of target CF_3-enone **42** was not given.

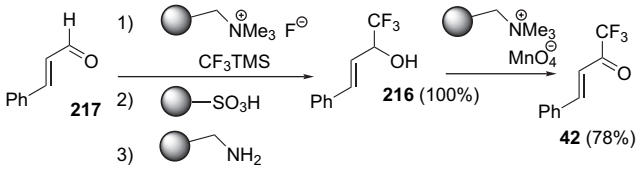




It has been shown that a variety of aldehydes react smoothly with trimethyl(trifluoromethyl)silane in the presence of fluoride ions supported on an Amberlyst A-27 resin.[77] The reaction work up involved quenching with Amberlyst A-15 (an



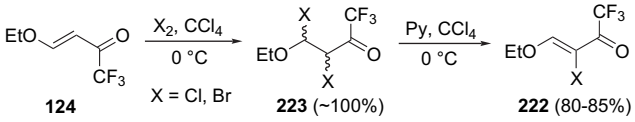
acidic ion-exchange resin) followed by sequestering any unreacted aldehyde starting material using an aminomethylated (AM-polystyrene) resin. The trifluoromethyl carbinols were obtained in good yields and purity after filtration and evaporation in vacuo. In this work, various solid-supported oxidizing agents were investigated, with the best results being obtained using permanganate supported on Amberlyst A-27. The reactions were conducted in refluxing methylene chloride in the presence of 4 Å molecular sieves to act as dehydrating agent. The corresponding trifluoromethylketones were separated in good yields and purity.



Systematic studies on intramolecular Pauson–Khand reactions of various fluorine-containing enynes were described.[78] The CF_3-containing alkynone **218** was synthesized by formylation of acetylene **219**, followed by reaction of aldehyde **220** obtained with $TMSCF_3$ and furnished the trifluoromethyl alcohol **221**. Oxidation of alcohol **221** with Dess–Martin periodinane produced the trifluoromethylketone **218**. All attempts at the direct synthesis of ketone **218** from acetylene **219** by metallation with BuLi followed by treatment with TFAA or CF_3CO_2Et failed. Surprisingly, no desired products were obtained from the prepared trifluoromethylketone **218** in Pauson–Khand reaction conditions.

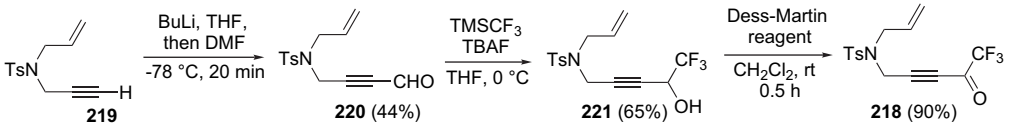
2.5. Creation of C^3–R^1 bonds

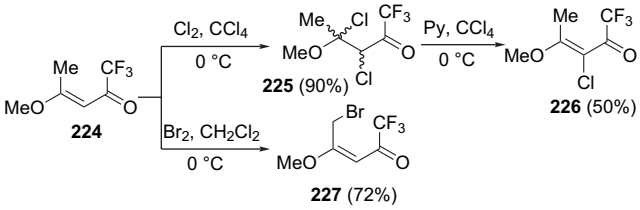
A new method for the preparation of α-chloro(bromo)-α,β-unsaturated trifluoromethylketones **222** has been described.[79] The approach is based on the addition of the appropriate halogen to the double bond of enone **124** followed by dehydrohalogenation of the intermediate dihaloketone **223**. The analogous introduction of iodine was not possible, but the application of iodine chloride allowed a solution to problem.[80] The corresponding product **222** with X=I can be prepared according to this procedure with a yield of 75%. In this case, the intermediate product analogous to **223** is unstable.

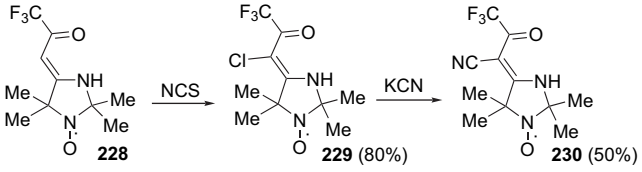


Halogenation of ketone **224** proceeds in two directions.[79] In the case of chlorination, the addition product **225** is formed, which can be transformed into **226** with base. Through brominating **224** with molecular bromine, the allylic bromination of the methyl group takes place forming the compound **227**.

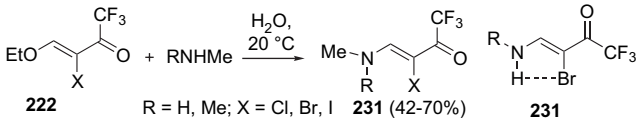
The chlorination reaction was performed for CF_3-enone **228** containing a β-imidazolyl substituent, which is present as the stable nitroxyl radical. *N*-Chlorosuccinimide was used as the chlorinating reagent.[81] The α-chloroketone **229** obtained was successfully converted into the corresponding α-cyanoketone **230** by treating with potassium cyanide.



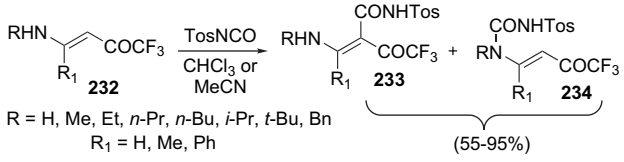




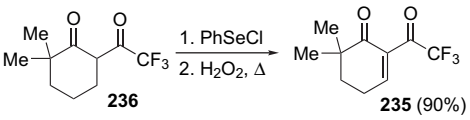
Compounds **222** similar to their non-halogenated analog **124** react with methyl- and dimethylamine forming the corresponding α-halogeno-β-amino-α,β-unsaturated trifluoromethylketones **231**, but the yields are lower in this case.[79,80,82] It is remarkable that, for compound **231** with R=H, the *Z*-isomer is more stable compared with the *E*-isomer, which would be favorable for intramolecular hydrogen bond N–H···O formation. This phenomenon is obviously provoked by steric hindrance caused as a result of a trifluoromethyl group and halogen atom interaction in molecule **231**.[79,80] Later, by analyzing NMR and IR spectroscopy data and quantum-chemical calculation results, it was established that only the *EZE*-form of **231** is realized for α-bromo-β-alkylamino-α,β-unsaturated trifluoromethylketones out of the eight forms possible (diastereomers and rotamers).[83] The stability of this form is uncharacteristic for α-unsubstituted aminoketones. Two reasons for the unexpected stability are the energy factor, which favors the formation of the ap,sp.-conformer and the additional gain in energy through the possibility of weak intramolecular hydrogen bond N–H···Br formation.[83]



The reaction of CF_3-enaminoketones **232** with tosyl isocyanate was investigated.[84,85] The reaction leads to mixture of the adducts **233** and **234**. The ratio of the products depends on the substituent in the enaminoketone and mostly does not depend on the polarity of the solvent used.

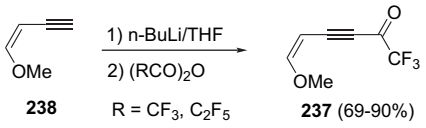


The standard method for the preparation of α,β-unsaturated ketones from aliphatic ketones is treatment with phenylselenyl chloride followed by oxidation with hydrogen peroxide and elimination of PhSeOH. This method was used for the preparation of cyclic CF_3-enone **235** with 1,3-diketone **236** as the starting compound.[86] The target ketone **235** was obtained in high yield.

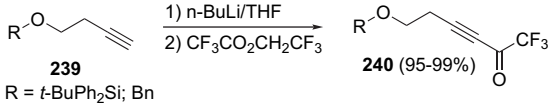


3. Synthesis of acetylenic CF_3-ketones

The range of methods for the preparation of acetylenic CF_3-ketones is much narrow than that for the preparation of CF_3-enones. There are only several universal methods for the preparation of acetylenic CF_3-ketones. One of the classical methods is the trifluoroacylation reaction of anions generated from terminal alkynes under treatment with strong bases. This approach was used for the synthesis of conjugated acetylenic ketones **237** containing perfluorinated groups. Acetylenides generated from vinylacetylene **238** under treatment with *n*-BuLi were acylated with anhydrides of the corresponding acids.[87]

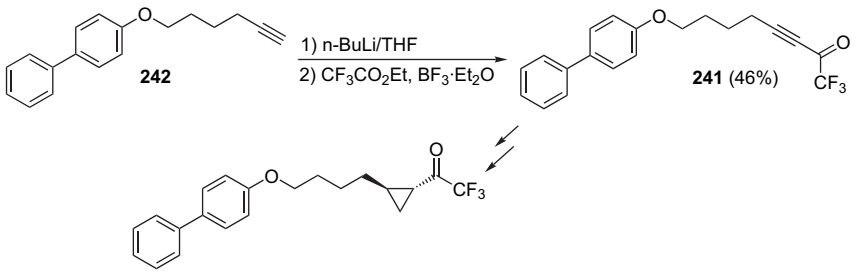


Trifluoroethyl trifluoroacetate can also be used for the acylation of carbanions generated from acetylenes **239**.[88] The target ketones **240** were obtained in yields close to quantitative. The application of TFAA, ethyl trifluoroacetate and ethyl trifluorothioacetate caused a severe decrease in the yields of **240**.

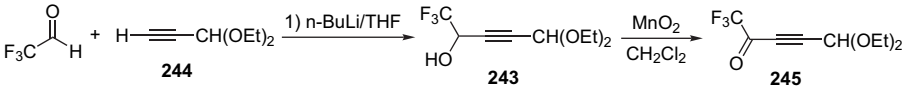


An analogous reaction was used for the synthesis of trifluoroacetylacetylene **241**.[89] Lithium acetylenide generated from acetylene **242** was treated with ethyl trifluoroacetate in the presence of $BF_3 \cdot Et_2O$. The target ketone **241** was obtained in moderate yield and was used for further transformations in the synthesis of physiologically active compounds (histone-deacetylase inhibitors).

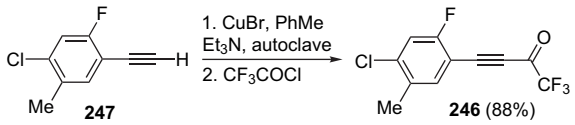
A second convenient method for the synthesis of acetylenic ketones containing a CF_3 group is the sequence for the preparation of secondary propargylic alcohol **243** starting with acetylene **244** and fluoral with further oxidation of **243** into ketone **245** using active manganese dioxide.[90] The



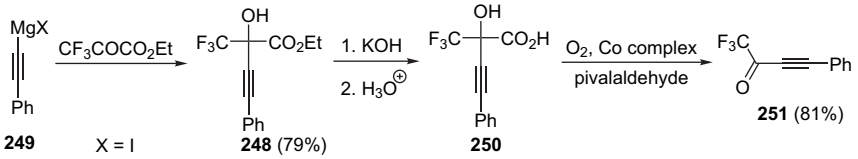
ketone **245** containing a CF_3 group was obtained in high yield, the value of which was not given in the article.

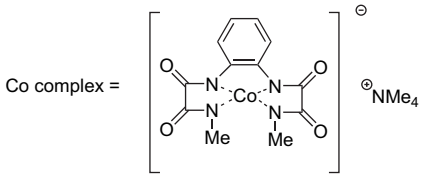


The synthesis of acetylenic CF_3-ketone **246** having an aryl substituent has been demonstrated.[91] The reaction of copper(I) acetylenide with trifluoroacetyl chloride was used. The acetylenide was prepared from the corresponding acetylene **247** and copper(I) bromide in an autoclave in the presence of triethylamine in toluene solution. The target acetylenic ketone **246** was isolated in good yield.



An interesting method for the synthesis of acetylenic CF_3-ketones has been elaborated.[92] Esters of α-hydroxycarboxylic acids **248** containing a CF_3 group in the α-position served as the starting compounds. These compounds are obtained in good yields in the reaction of Grignard reagents **249** with ethyl trifluoropyruvate. Further hydrolysis of the esters leads to the carboxylic acids **250**, which are oxidized with atmospheric oxygen in the presence of the tetramethylammonium salt of an *o*-phenylene-bis-*N*-methyloxamidate Co(III) complex and pivalic aldehyde into the target trifluoromethylketones including acetylenic **251**.

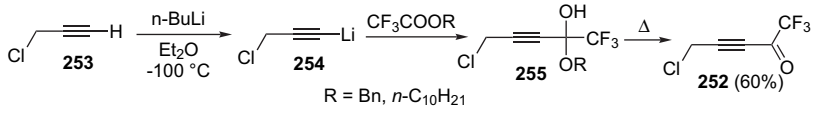


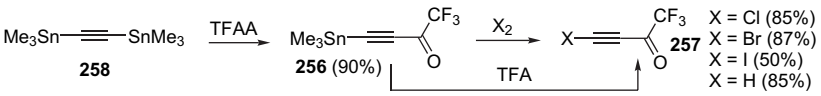


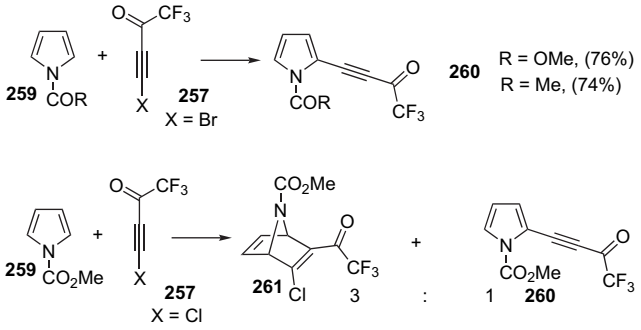
Earlier, an unknown chloromethyltrifluoroacetylacetylene **252** was prepared[93] using the following sequence: metallation of propargyl chloride **253** with *n*-BuLi, acylation of the lithium derivative **254** with benzyl or decyl trifluoroacetate and subsequent thermal decomposition of the acetal obtained **255** with formation of the target product.

Electrophilic substitution of a trimethylstannyl group under treatment with molecular halogens of trimethylstannyl trifluoroacetylacetylene **256** was used for the preparation of halogen derivatives of trifluoroacetylacetylenes **257**. These acetylenes **256** can be prepared using the reaction of bistrimethylstannylacetylene **258** and trifluoroacetic acid anhydride.[94] An analogous approach for the synthesis of the parent trifluoroacetylacetylene **257** (X=H) was proposed.[95] The method is based on the reaction of trimethylstannyl trifluoroacetylacetylene **256** with trifluoroacetic acid. The target acetylene **257** (X=H) was obtained in high yield.

The reaction of acetylene **257** (X=Br) with *N*-substituted pyrroles **259** was used for the preparation of the ketone **260** containing a 2-pyrrolyl substituent in the β-position.[96] In the case of the ketone **257** (X=Cl), the formation of the corresponding ketone **260** and the [2+4] addition product **261** was observed.





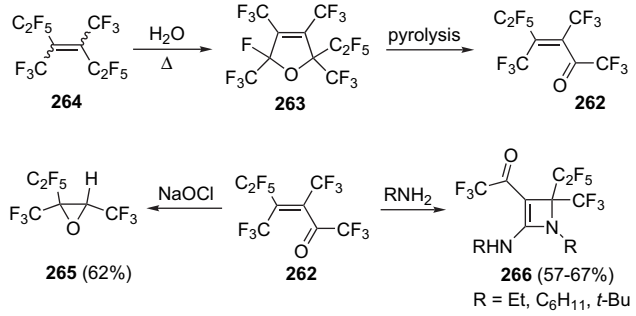


4. Application of α,β-unsaturated trifluoromethylketones in synthesis

The most outstanding area of application of α,β-unsaturated trifluoromethylketones is the synthesis of heterocyclic compounds, mainly due to their extensive synthetic utility, resulting in a large amount of work devoted to this problem. Heterocyclic compounds containing a trifluoromethyl group are attractive targets for medicinal chemistry and the elaboration of new effective methods for their synthesis is therefore an urgent and important task.

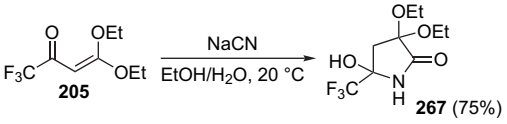
4.1. Heterocyclizations based on α,β-unsaturated trifluoromethylketone applications

4.1.1. Synthesis of three- and four-membered heterocycles. Numerous reactions of the perfluorinated CF_3-enone **262** have been studied.[97] This ketone is formed by pyrolysis of oxolene **263**, which in turn is prepared by high-temperature hydrolysis of **264** (tetrafluoroethene tetramer). The yields for this sequence are not given. The fluorinated derivatives of oxirane **265** and azetine **266** were obtained in the reaction of **262** with sodium hypochlorite and primary amines, respectively. The heterocyclic compounds were obtained in good yields.



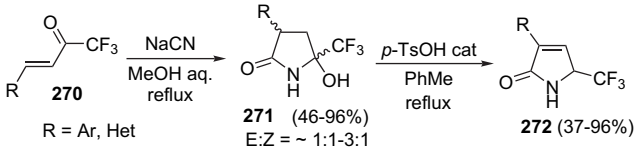
4.1.2. Synthesis of five-membered heterocycles.

4.1.2.1. Synthesis of pyrrole derivatives. Various heterocycles using diethoxyenone **205** were synthesized.[98] The reactions with several binucleophiles and sodium cyanide are described for the synthesis of the corresponding pyrrolidone **267**. The reaction proceeds in good yield under reflux of the reagents in aqueous ethanol.

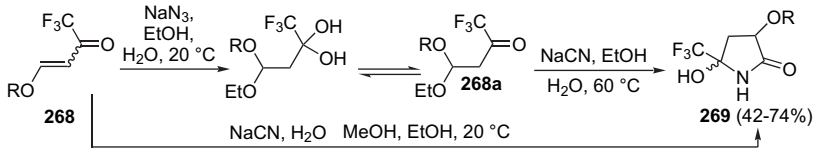


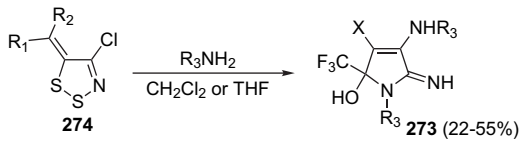
It was shown[99] that the reaction of several enones **268** with sodium cyanide gave the corresponding pyrrolidones **269** as a mixture of diastereomers. The product stereochemistry is rather complicated and was fully investigated using a combination of chromatography/mass-spectrometry and NMR spectroscopy methods.[99] This method seems to be more rational than that proposed earlier.[100] The latter method includes an additional stage of preparing the ketone monoacetal **268a**, which exists in equilibrium with its hydrate. The individual diastereomers of compounds **269** were not isolated.

The same reaction was investigated for ketones **270** having no alkoxysubstituents in the β-position.[101] The reaction was carried out in a refluxing aqueous methanol or ethanol solution of the CF_3-enone and sodium cyanide. The corresponding hydroxyderivatives of the pyrrolidin-2-ones **271** were obtained in good yields as a mixture of diastereomers, which were separated by column chromatography. Additionally, the dehydration reaction of the obtained products was carried out. This reaction proceeds with migration of the double bond and leads to 3-pyrroline-2-one **272** formation.



The pyrrole trifluoromethyl derivatives **273** were obtained using the reaction of ketones **274** with primary amines.[102] The starting heterocyclic ketones **274** were prepared from the Appel salt **79**.[32]



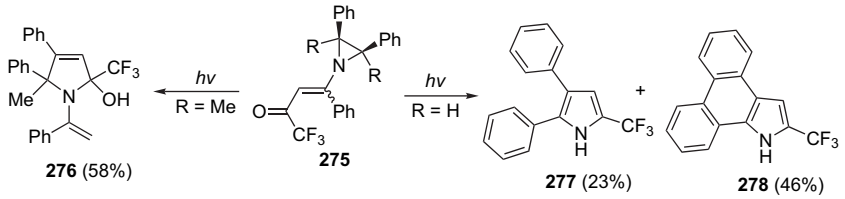


R_1 = CO_2Et, R_2 = $COCF_3$; R_1 = $COCF_3$, R_2 = CO_2Et;
R_1 = $COCF_3$, R_2 = COPh; R_1 = H, R_2 = $COCF_3$
R_3 = *i*-Pr, n-C_5H_{11}, Me, Et; X = CO_2Et, COPh

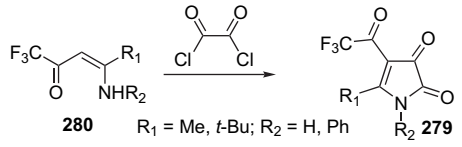
Using photolytic rearrangement of aziridine-substituted enaminoketones **275**, CF_3-pyrrole derivatives were obtained.[103] Depending on the substituents in the starting ketone **275**, the dihydropyrrole **276** or a mixture of diphenylpyrrole **277** and dibenzoindole **278** was formed.

β-amino CF_3-enones **281** and **282** with trimethylphosphine. The target β-alkoxy and β-amino pyrroles **284** and **283** containing a CF_3 group were obtained in good yields. β-Amino-CF_3-enones **282** were prepared from β-alkoxyenones **281** by the reaction with secondary amines.

The viability of a reaction sequence based on the reaction of an α-amino acid **285** with the alkoxy enone **124** followed by a cyclization was established with three aminoacids with isolation of the intermediate β-dialkylamino unsaturated ketones **286**.[106] Reaction of the proline **286a** with trifluoroacetic anhydride gave the fluorinated pyrrole **287** in 70% yield. In contrast, under similar conditions, *N*-benzylglycine **285c** gave the fluorinated pyrrolecarboxylic acid **288c** in 41% yield. An obvious simplification of this pyrrole synthe-



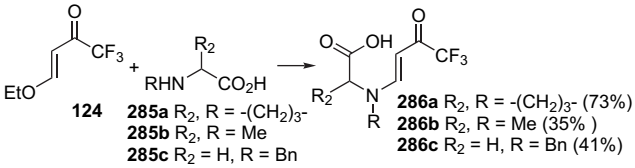
The widely used reaction of acylation of enaminoketones **280** with oxalyl chloride was applied for the preparation of 1*H*-pyrrole-2,3-diones **279**.[104] The reaction proceeds at room temperature and the yields of the products are not given.

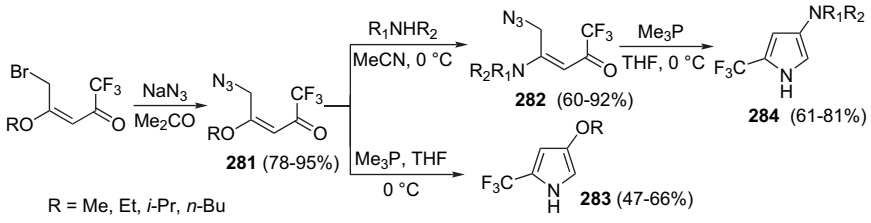


R_1 = Me, *t*-Bu; R_2 = H, Ph

A novel approach for the synthesis of pyrrole derivatives was published recently.[105] These heterocycles were prepared using the reaction of azidomethyl derivatives of β-alkoxy and

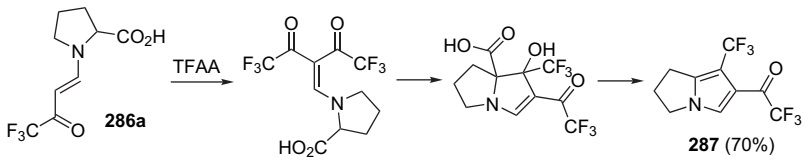
sis might be a one-pot procedure involving the sequence of trifluoroacylation of ethyl vinyl ether, enamine formation and final cyclization of the intermediate enamine. This three-step sequence was applied to pipecolic acid **285d** and thiaproline **285e**. The reaction was carried out without isolation of the intermediate enaminoketones **286d**,**e**. The corresponding pyrroles **288b**, **288c**, **289a**, **289b**, and **290** were obtained in moderate yields.

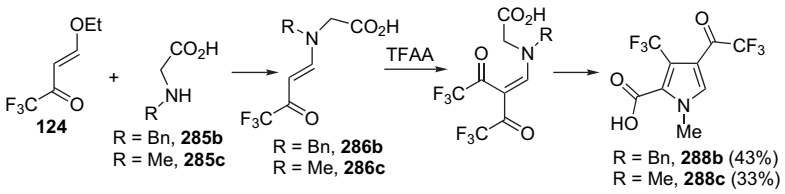


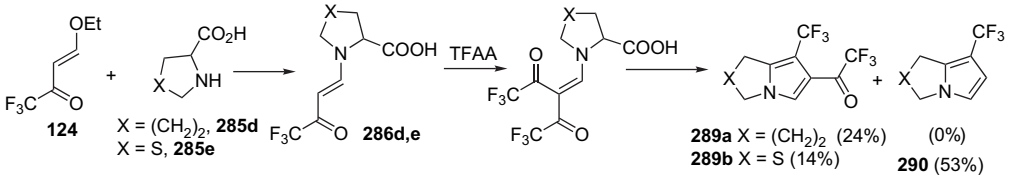


R = Me, Et, *i*-Pr, *n*-Bu

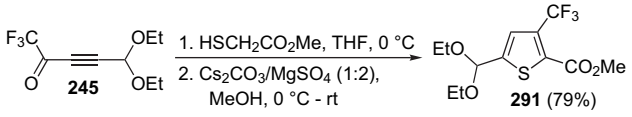
R_1, R_2 = Me, Me; Et, Et; -$(CH_2)_4$-; -$(CH_2)_5$-; -$(CH_2)_2$-O-$(CH_2)_2$-; Bn, Bn





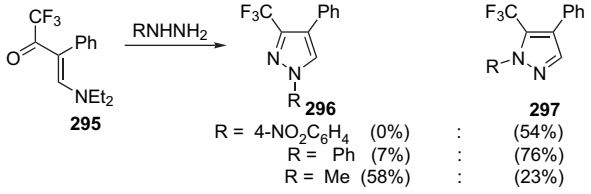


4.1.2.2. Synthesis of thiophene derivatives. Acetylenic ketone **245** was successfully used as a starting compound for the preparation of 3-CF_3-thiophene-2-carboxylate **291**. Treatment with methyl thioglycolate in THF and cesium carbonate in methanol leads to the target thiophen-2-carboxylic acid ester derivative **291** in good yield.[90]

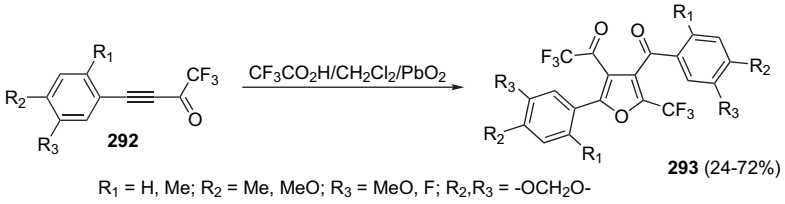


4.1.2.3. Synthesis of furan derivatives. The oxidative dimerization of acetylenic ketone **292** under treatment with lead dioxide in a methylene chloride/trifluoroacetic acid mixture was carried out.[107,108] The formation of the substituted furan **293** bearing CF_3 and $COCF_3$ groups was established in moderate yields.

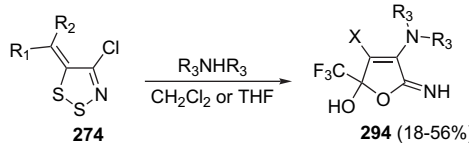
4.1.2.4. Synthesis of pyrazoles and their derivatives. β-Enaminoketones react with substituted hydrazines, opening up a simple and effective route to various pyrazoles. The reactions of ketone **295** with *N*-substituted hydrazines were carried out. The reaction leads, depending on the structure of the starting hydrazine, to individual pyrazoles or to a mixture of regioisomers **296** and **297**.[109]

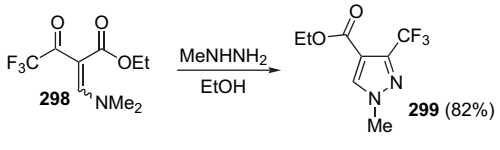


The reaction of enamine **298** with *N*-methylhydrazine was applied for the preparation of the 3-trifluoromethyl-4-pyrazolecarboxylate **299**.[110] The starting enaminoketone **298** was prepared from ethyl trifluoroacetoacetate and dimethylformamide dimethyl acetal (DMF-DMA). The reaction proceeds regioselectively and only one isomer was isolated in good yield.



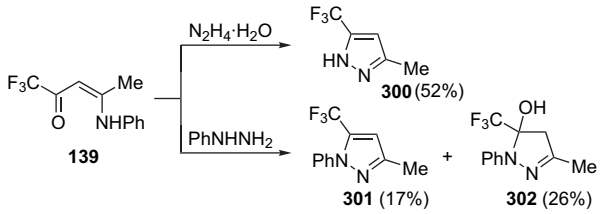
Trifluoromethylfuran derivatives **294** were also prepared by the reaction of ketone **274** with secondary amines.[102] The starting heterocyclic ketone **274** was prepared from the Appel salt **79**.[32]



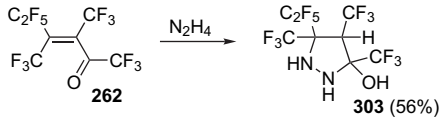


The formation of pyrazole **300** by the reaction of enaminoketone **139** with hydrazine hydrate and a mixture of pyrazole

301 and dihydropyrazole **302** in the reaction with phenylhydrazine was demonstrated.[111]



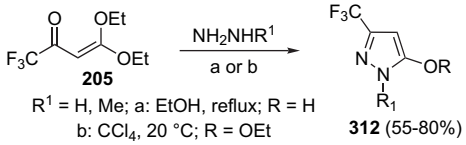
The numerous reactions of perfluorinated CF_3-enone **262** were studied including the reaction with hydrazine.[97] The perfluorinated derivative, pyrazolidine **303**, was obtained. This compound is a stable solid, subliming in a vacuum without decomposition. The stability of this compound can be explained by the presence of a number of fluorine atoms in the molecule.



The reaction of the primary β-ethoxy-CF_3-enone **124** with *N*-methylhydrazine has been re-investigated.[112,113] It was demonstrated that the earlier studies contained irreproducible results and that, in fact, the reaction of **124** with *N*-methylhydrazine gives two isomeric dihydropyrazoles **304** and **305** in various ratios. These pyrazolines **304** and **305** undergo dehydration with different rates to form the pyrazoles **306** and **307**. The yields of the products were not given.

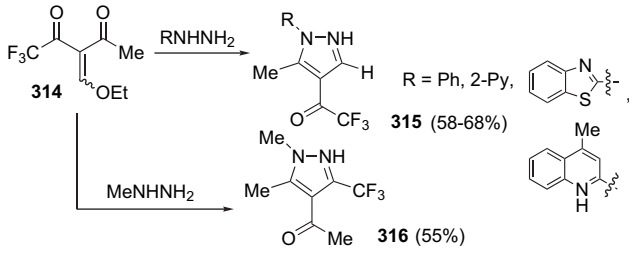
The investigation of the above reaction was continued for β-alkoxy-CF_3-enones **308**.[114] The formation of mixtures of pyrazole regioisomers **309**, **310** and the dihydro-derivatives **311** was observed in variable yields. It was found that, using THF or methylene chloride as the solvent, the yield of **309** containing a CF_3 group in position 3 is increased and so the selectivity of the reaction rises.

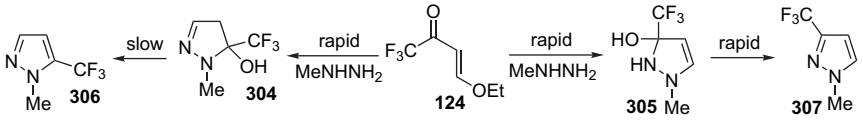
The corresponding ethoxy- and hydroxy-pyrazole derivatives **312** were obtained in good yields by the reaction of diethoxyenone **205** with hydrazine and methylhydrazine. Depending on the solvent used, the formation of the hydroxy or ethoxy derivatives **312** was observed.[98]

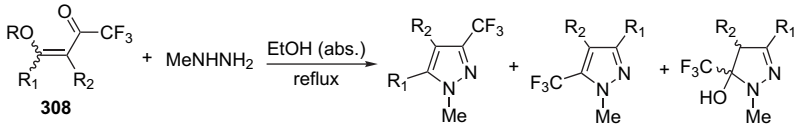


O,*N*-acetals-aminals of trifluoroacetylketene **206** obtained from diethoxyenone **205** and primary amines were used for the synthesis of aminopyrazoles. The target CF_3-containing pyrazoles **313** were prepared in good yields by the reaction with various hydrazines.[115]

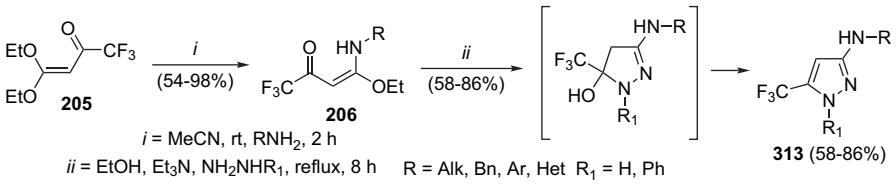
The reactions of various aryl- and hetaryl-substituted hydrazines with β-ethoxy-CF_3-enone **314** containing an acetyl group in the α-position were investigated.[116] It was established that the heterocyclization is directed to the acetyl group for arylhydrazines and to the trifluoroacetyl group for *N*-methylhydrazine. The corresponding pyrazoles **315** and **316** were obtained in moderate yields.







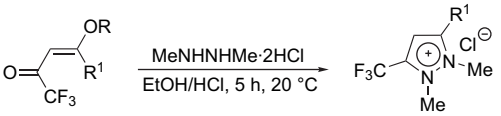
	309	310	311
a R = Et, R_1 = R_2 = H	(52%)	(0%)	(18%)
b R = R_1 = Me, R_2 = H	(32%)	(7%)	(0%)
c R = Et, R_1 = H, R_2 = Me	(40%)	(7%)	(7%)



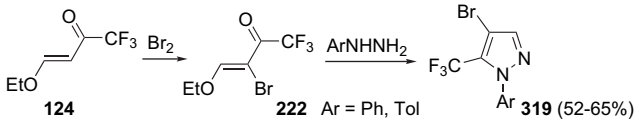
i = MeCN, rt, RNH_2, 2 h

ii = EtOH, Et_3N, NH_2NHR_1, reflux, 8 h R = Alk, Bn, Ar, Het R_1 = H, Ph

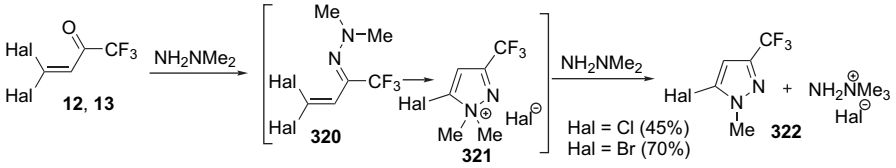
The synthesis of various *N*,*N*′-dimethylpyrazolium salts **317** in the reaction of enones **318** with *N*,*N*′-dimethylhydrazine dihydrochloride was reported.[117] The compounds **317** are very attractive, because of their potentially high herbicide activity.



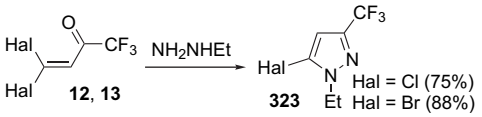
The reaction of α-bromo-β-ethoxy-CF_3-enone **222** with arylhydrazines was investigated.[118] The reaction was carried out by refluxing the reagents in ethanol solution, leading to the pyrazole **319** formation. The starting bromoketone **222** was prepared using bromination of ketone **124**. It should be noted that the heterocyclization proceeds 100% regioselectively to open up a new effective method for the synthesis of 4-bromo-5-CF_3-pyrazoles.



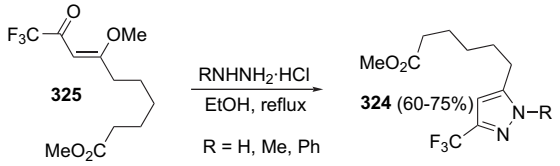
The reaction of β,β-dihalogen-substituted trifluoromethylketones **12** and **13** with *N*,*N*-dimethylhydrazine was investigated.[119] The mechanism of the reaction consists of initial dimethylhydrazone **320** formation with subsequent intramolecular attack of nucleophilic fragment on β-carbon atom of vinyl group. The *N*,*N*-dimethylpyrazolium chloride **321** formed is transformed into the aromatic pyrazole **322** by nucleophilic demethylation with a second mole of dimethylhydrazine. The target 5-halogen-substituted pyrazoles **322** were isolated in moderate-to-high yields.



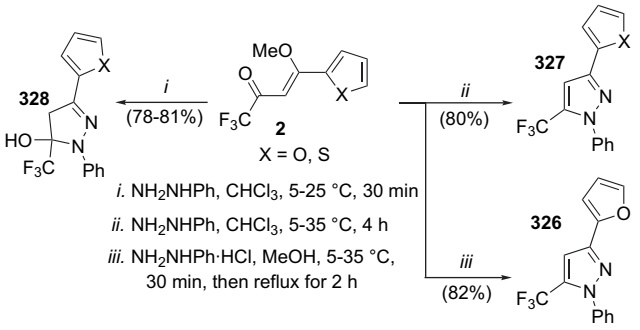
The same β,β-dihalogen-substituted trifluoromethylvinylketones **12** and **13** were studied in the reaction with *N*-ethylhydrazine.[120] The reaction proceeds analogously, but leads to the target 5-halogeno-derivatives of pyrazole **323** in higher yields.



Several pyrazoles **324** were prepared, starting from the corresponding trifluoromethylketone **325**.[121] The cyclocondensation of **325** with hydrazine hydrochloride, methylhydrazine, and phenylhydrazine was carried out in a molar ratio of 1:1.2 using ethanol as the solvent. The use of a small excess of the hydrazine derivative was essential for good yields of the target products.

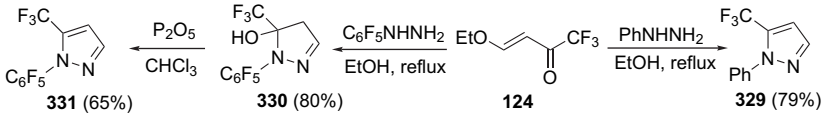


The reactions of β-ethoxy-CF_3-enones **2** with phenylhydrazine were studied. The conditions presented below were found to be best for the preparation of pyrazoles **326**, **327** and pyrazoline **328**.[122] A short reaction time and lower temperature in the reaction with pure phenylhydrazine results in the formation of pyrazoline **328**, whereas reaction under elevated temperature or using the hydrochloride salt of phenylhydrazine gives the pyrazoles **326** and **327**.



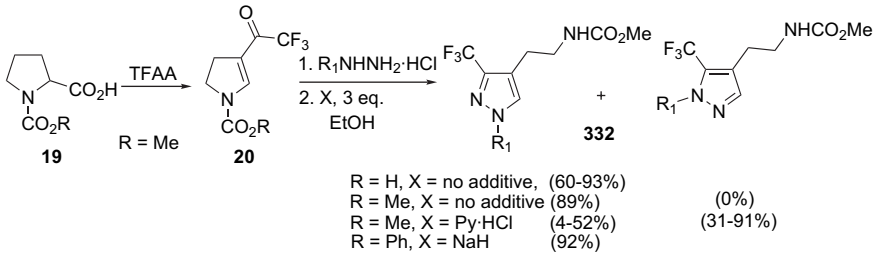
It was noted that the pathway of the reaction for ketone **124** with phenylhydrazine differs from the pathway of the reaction with the fluorinated analog.[123] As an example, the reaction of **124** with phenylhydrazine leads to the corresponding pyrazole **329**, while the same reaction with pentafluorophenylhydrazine leads to the formation of pyrazoline **330**. This difference was explained by the reduced basicity of polyfluorinated arylhydrazines. The pyrazolines **330** can be dehydrated into the pyrazoles **331** using phosphorus pentoxide in chloroform.

An interesting example of the application of trifluoroacetylpyrroline **20** for the preparation of pyrazoles **332** has been described.[124] The starting enaminoketone **20** can easily be obtained by trifluoroacylation of the *N*-substituted proline **19** with TFAA. It was found that this compound is a new 1,3-ambidentate electrophile reacting with bifunctional *N*-nucleophiles such as hydrazines and amidines to give CF_3-substituted pyrazoles bearing a β-aminoethyl side chain. The reaction sequence represents a special type of ring transformation by ring-chain transfer, where a ring and a chain

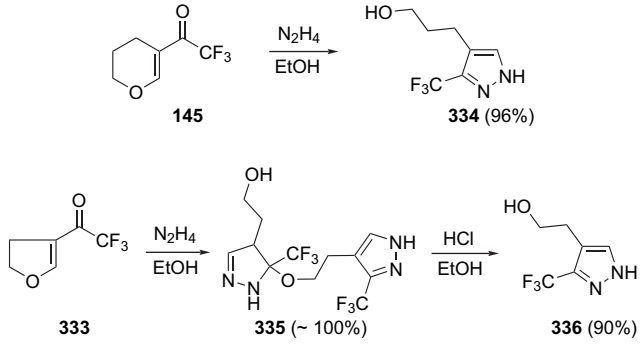


moiety in the adduct are transformed into each other, giving the product. In view of the pharmacological interest in heterocycles bearing both a CF_3 appendage and a β-aminoethyl side chain, the method is very attractive.

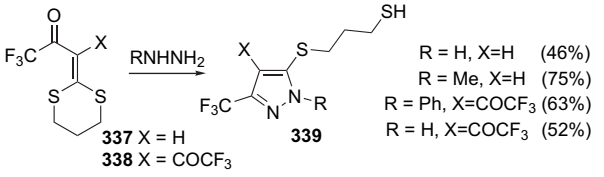
The reaction of 4-hydrazo-7-chloroquinoline **340** with various β-methoxy-CF_3-enones **341** was investigated.[126] The aim of the research was to generate new compounds for further antimalarial screening. The reaction was performed in



The reaction of hydrazine with cyclic CF_3-enones—β-trifluoroacetyldihydropyran **145** and β-trifluoroacetyldihydrofuran **333**—was studied.[88] The reaction was carried out in ethanol solution. It was demonstrated that, in the case of β-trifluoroacetyldihydropyran **145**, the reaction leads to the corresponding pyrazole **334**, while, in the case of β-trifluoroacetyldihydrofuran **333**, the formation of **335** at the first stage is observed. Monomeric pyrazole **336** can be prepared by treatment of an ethanol solution with hydrogen chloride.

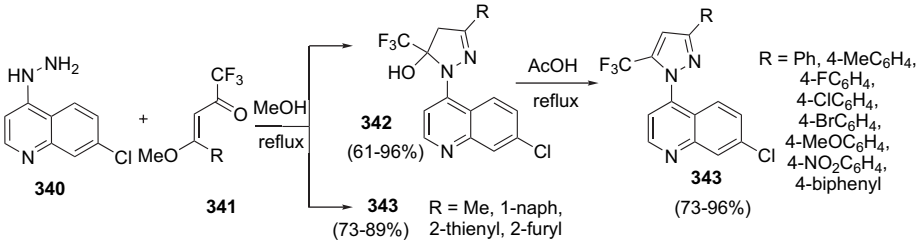


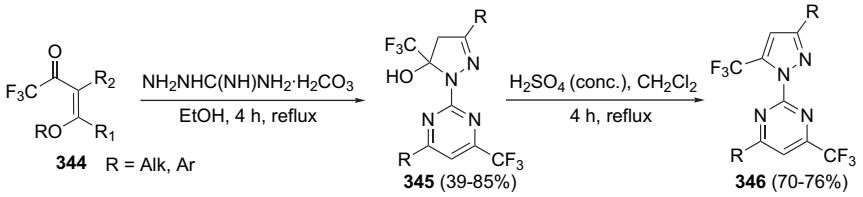
The reactions with various binucleophiles including the reactions with hydrazines were investigated for the CF_3-enones **337** and **338** containing a dialkyldithio fragment in the β-position (ketene dithioacetals) and so the possibility for the preparation of pyrazoles **339** or containing a 1,3-dithiopropyl substituent was shown.[125]



methanol at reflux. Depending on the substituent in the starting CF_3-enone, the dihydropyrazoles **342** were obtained in good yields. Dehydration into the corresponding pyrazoles **343** was performed under reflux in acetic acid. In some cases, simultaneous dehydration was observed at the stage of reflux in methanol. The same reaction of various β-methoxy-β-aryl-substituted CF_3-enones **341** with hydrazoquinoline **340** was applied for the preparation of several CF_3-containing pyrazoles **343** possessing high antimalarial activity.[127] The reaction proceeds with the formation of the intermediate pyrazoline **342**. The starting CF_3-enones **341** are available through trifluoroacylation of the acetophenone enol ethers.

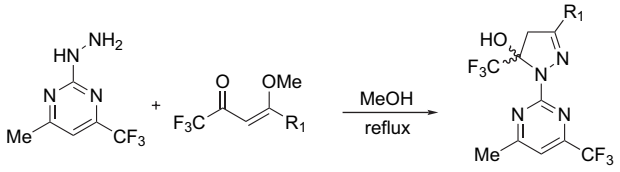
Using a twofold excess of the ketones **344** in the reaction with aminoguanidine hydrocarbonate, the formation of pyrazolinylpyrimidines **345** is observed. These compounds can be easily dehydrated into the corresponding pyrazolylpyrimidines **346**.[128] This transformation allows the simultaneous creation of two heterocyclic systems in one step. In addition, many of the 2-pyrazolylpyrimidine derivatives show a high physiological activity.





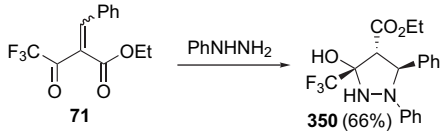
344 R = Alk, Ar **345** (39-85%) **346** (70-76%)

The reaction of enones **347** with a 2-hydrazo derivative of pyrimidine **348** proceeds in an analogous manner. The corresponding pyrimidine derivatives **349** containing a dihydropyrazole substituent in position 2 of the pyrimidine ring are formed.[129] These products are potential analgesics and antipyretics.



348 **347** R_1 = H, Me, Ph **349** (85-95%)

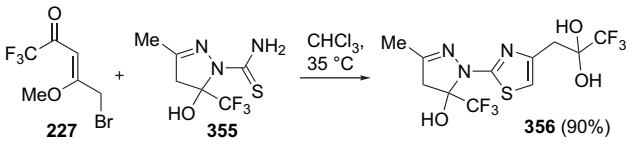
An interesting example is the reaction of ketone **71** with phenylhydrazine. The tetrahydropyrazole derivative **350** was obtained in moderate yield. The reaction proceeds with 100% stereoselectivity—only the diastereomer of **350** shown was obtained.[130]



71 **350** (66%)

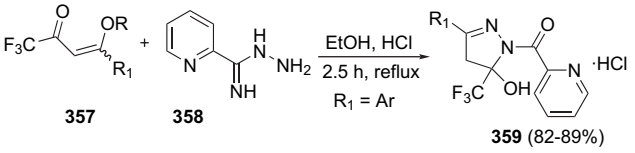
The reaction of β-alkoxy-β-aryl-CF_3-enones **351** with thiosemicarbazide as the hydrazine derivative **352** was studied.[131] The products of the reaction are the corresponding hydroxyl derivatives of dihydropyrazoles **353**. These compounds were obtained in high yields. They can be transformed into the *N*-substituted pyrazoles **354** in high yields using acidic hydrolysis.

The ketone **227** was obtained by allylic bromination with molecular bromine. Having a hidden bromoketone fragment in the structure, this compound was used for heterocylization using the reaction with **355**, forming a thiazole connected with pyrazoline **356**.[132]



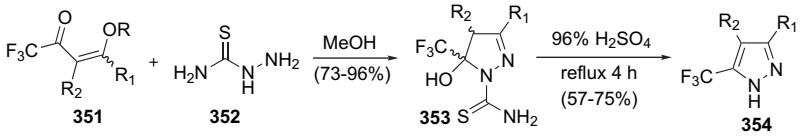
227 **355** **356** (90%)

The reaction of ketones **357** (R_2=H) with 2-pyridylcarboxamidrazone **358** leads to the predominant formation of the pyrazoline derivatives **359**,[133] regardless of the fact that amidrazones possess three reactive nitrogen atoms. The reaction is accompanied with imine fragment of amidrazone hydrolysis. The hydrochlorides **359** can be transferred into the free bases using triethylamine/diethyl ether solution. Attempts at dehydration of the free bases into the corresponding pyrazoles were unsuccessful.



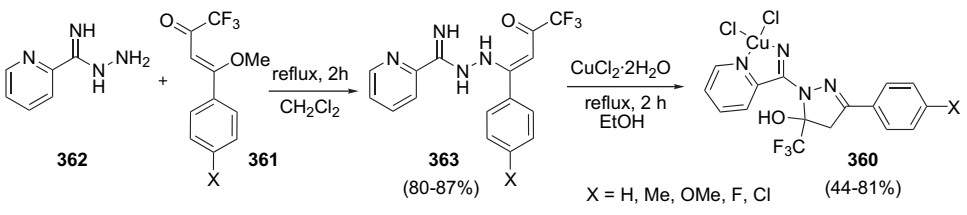
357 **358** **359** (82-89%)

The preparation of copper(II) amidrazone complexes **360** derived from CF_3-containing β-alkoxyenones **361** was described recently.[134] Ketones **361** react with 2-pyridylcarboxamidrazone **362** to produce the corresponding 1,1,1-trifluoro-4-aryl-4-(*N*-pyridine-2-carboxamidrazone)-3-buten-2-ones **363**. The compounds **363** react with copper(II) chloride to give 1:1 adducts, in which the donor molecules were shown to isomerize to their cyclic pyrazolic forms. The coordination chemistry of the products derived from this



351 **352** **353** **354**

R = Me, Et; R_1 = H, Me, Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$; R_2 = H, Me

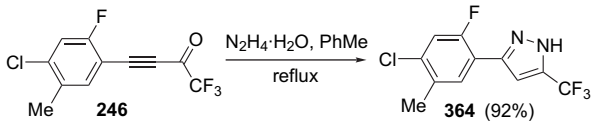


362 **361** **363** (80-87%) **360** (44-81%)

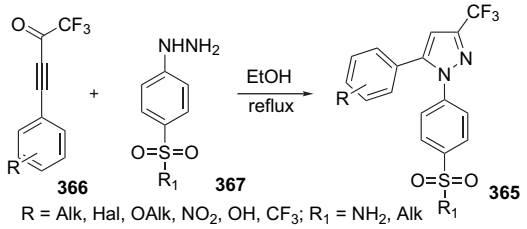
X = H, Me, OMe, F, Cl

reaction with copper(II) chloride was investigated. The adducts **360** containing the amidrazone pharmacophore have been tested as anticancer drugs.

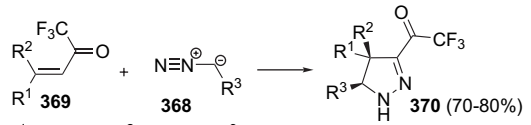
The reaction of acetylenic CF_3-ketone **246** with hydrazine hydrate was used for the preparation of the CF_3-substituted pyrazole **364**.[91] The reaction was performed in toluene under reflux. The corresponding pyrazole **364** was obtained in excellent yield.

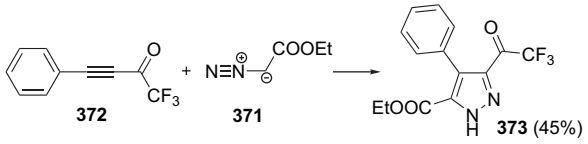


An analogous reaction was used for the preparation of pyrazoles **365** having aryl substituents on the nitrogen atom.[135,136] Acetylenic CF_3-ketones **366** react with *N*-arylhydrazines **367** under reflux in ethanol to give the pyrazoles **365**. The yields of **365** are not given.



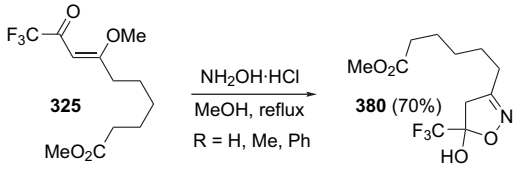
Work reported by our group in 2003[137] is devoted to [2+3]-dipolar cycloaddition of various diazo compounds **368** to α,β-unsaturated trifluoromethylketones **369**. The ketones **369** react with diazoalkanes **368** forming pyrazolines **370**. The reaction proceeds 100% regioselectively and with high stereoselectivity. In the case of phenyldiazomethane, the exclusive formation of the cis-isomers of pyrazolines **370** is observed. Ethyl diazoacetate **371** gives the cis-isomer predominantly (~75% of the mixture). The ketone **369** having R^1=Ph and R^2=Me does not react with aryldiazoalkanes, although it forms the cycloaddition product in the case of reaction with diazomethane (regiochemistry of the product is analogous to **370**). Using the trifluoroacetylated acetylene **372** in the reaction with ethyl diazoacetate **371** allows the preparation of the pyrazole **373**.[137]

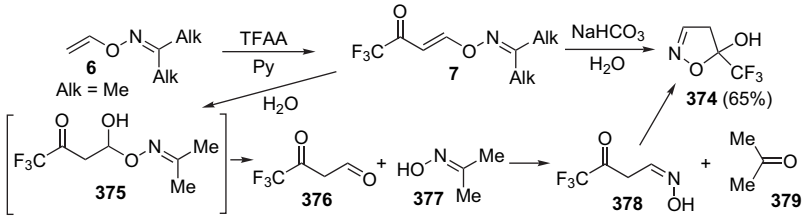


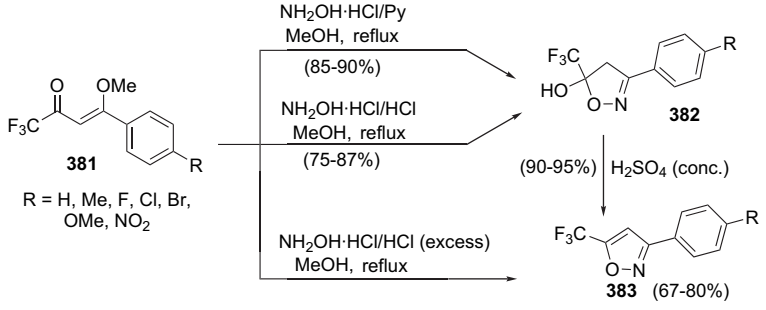


4.1.2.5. Synthesis of isoxazoles and their derivatives. *O*-Vinyl oximes **6** react readily with trifluoroacetic anhydride in the presence of pyridine at room temperature to give CF_3-enones. When the reaction mixture was treated, after trifluoroacylation, with aqueous $NaHCO_3$, 4,5-dihydro-1,2-oxazole **374** was isolated as the single product.[138] The formation of **374** implies the hydrolysis of **7** via an intermediate semiacetal-like adduct **375**, which decomposes to 3-oxo-4,4,4-trifluorobutyraldehyde **376** and acetoxime **377**. The two latter compounds undergo re-oximation to result in the corresponding aldoxime **378** and acetone **379**—the hydroxylamine exchange between oximes and aldehydes or ketones under solvolytic conditions is a well-established fact.

The isoxazoline **380** was synthesized starting from the CF_3-enone **325**.[121] The presence of a methoxycarbonyl group in the isoxazole obtained makes possible further transformations.

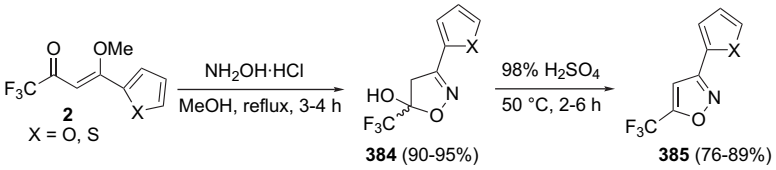




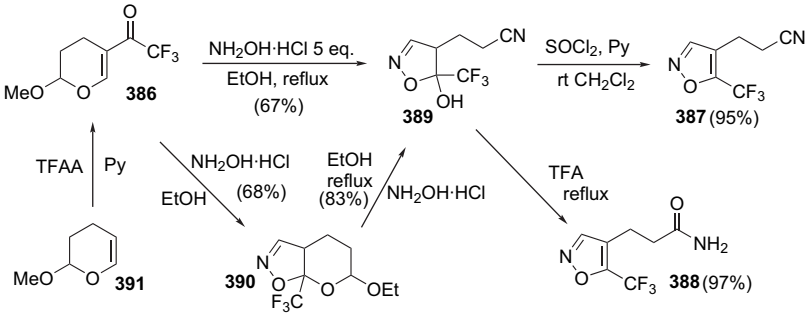


The reaction of a number of β-methoxy-β-aryl-CF_3-enones **381** with hydroxylamine hydrochloride was investigated.[139] The formation of 4,5-dihydroisoxazoles **382** was established. These compounds were obtained in high yields and can be transformed into the corresponding isoxazoles **383** in yields close to quantitative using concentrated sulfuric acid. In addition, the compounds **383** can be directly obtained using the reaction of β-methoxy-β-aryl-CF_3-enones **381** with hydroxylamine hydrochloride and an excess of hydrochloric acid.

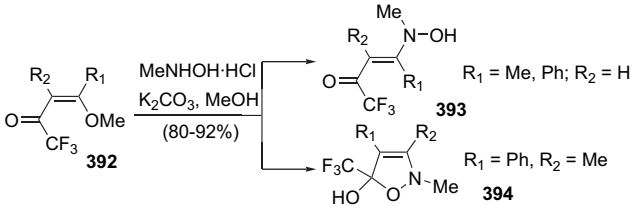
Analogous reactions were carried out for β-methoxy-CF_3-enones **2** containing 2-thienyl or 2-furyl substituents. The reaction with hydroxylamine hydrochloride leads to the dihydroisoxazole derivatives **384**.[122] Similarly, the products obtained can be easily dehydrated with concentrated sulfuric acid, forming the corresponding isoxazoles **385**.



An attractive sequence of reactions was carried out for a cyclic β-alkoxy-CF_3-enone **386**.[140] This allows the preparation of isoxazoles **387** and **388** and their dihydro-derivatives **389** and **390** containing functional groups. These compounds were obtained in high yields. The starting 3-trifluoroacetyl dihydropyran **386** can be easily prepared by trifluoroacylation of methoxydihydropyran **391** with trifluoroacetic anhydride in the presence of pyridine.



The reaction of β-methoxy-CF_3-enones **392** with *N*-methylhydroxylamine hydrochloride was investigated.[141] The reaction was carried out in methanol in the presence of potassium carbonate. Depending on the substituent in the starting ketone **392**, the reaction proceeds as a Michael addition, forming **393**, or successive heterocyclization takes place, with regioselective formation of the isoxazolines **394**.

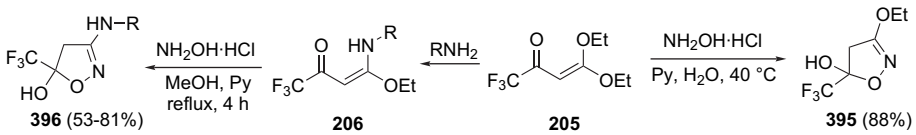


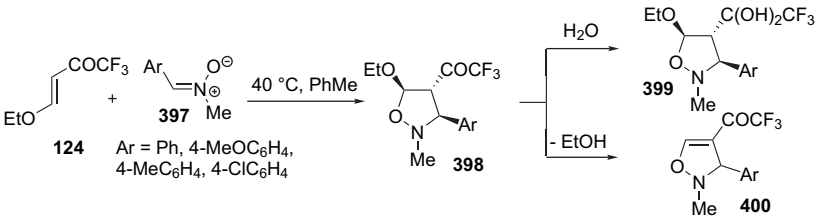
The reaction of diethoxyenone **205** with hydroxylamine hydrochloride has been investigated. The corresponding ethoxy derivative of isoxazoline **395** was synthesized in good yield.[98] Similarly, *O*,*N*-acetals-aminals of trifluoroacetylketene **206** were used for the synthesis of amino-substituted isoxazoles.[115] The target CF_3-containing isoxazolines **396** were prepared in good yields.

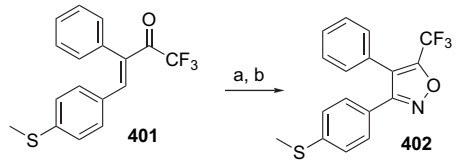
[2+3] Cycloaddition of β-ethoxy-CF_3-enone **124** with *N*-methyl-C-aryl nitrones **397** results in the isoxazolidines **398**. These compounds cannot be isolated in a pure form, due to transformation to the diol **399** and the ethanol elimination product **400** under column chromatography purification.[142]

Ketones containing no alkoxy groups in the β-position **401** can also be used for the preparation of isoxazoles **402**. The diaryl-substituted isoxazole **402** was synthesized using the reaction with hydroxylamine with further aromatization by treatment with iodine.[143] An unusual stereochemistry for the heterocyclization reaction is observed.

4.1.2.6. Synthesis of oxazoles. The reaction of acetylenic CF_3-ketones **245** and **403** with methyl isocyanoacetate





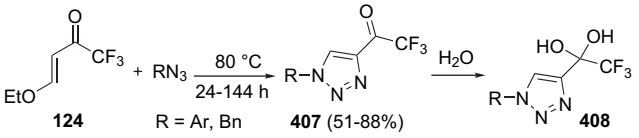


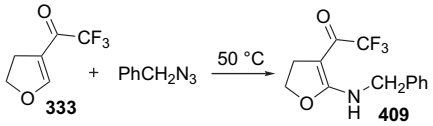
a = $NH_2OH{\cdot}HCl$, EtOH-H_2O, reflux, 90 °C (65%)

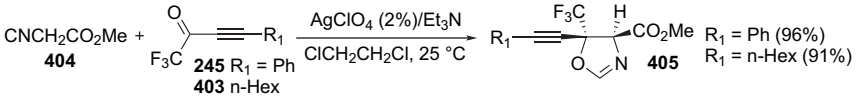
b = KI, I_2, $NaHCO_3$, H_2O-THF, reflux, 7 h, rt, 12 h (88%)

404 catalyzed with silver perchlorate was investigated. The reaction leads to the formation of the dihydrooxazole derivatives **405**.[144,145] It was found that the most effective catalyst in this reaction is a silver perchlorate/triethylamine system. It was shown that, in the case of CF_3-ketones, the reaction proceeds 100% stereoselectively. The target products are formed in high yields.

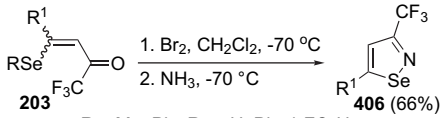
2,3-dihydro-5-benzylamino-4-trifluoroacetylfurane **409** as the minor component of an inseparable product mixture.







4.1.2.7. Synthesis of isoselenazoles. An approach to the synthesis of scarcely available heterocycles—isoselenazoles containing a trifluoromethyl group—has been described.[69] Isoselenazoles **406** can be easily prepared by successive treatment of enones **203** with bromine and ammonia. In the first stage, the compounds **203** react with bromine in dichloromethane at −70 °C and, in a second step, at the same temperature, an excess of gaseous ammonia is bubbled into the mixture.



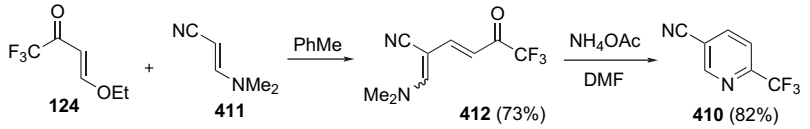
R = Me, Ph R_1 = H, Ph, 4-FC_6H_4

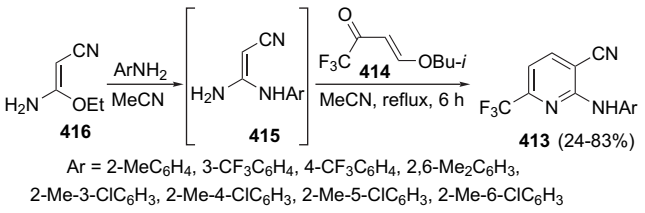
4.1.2.8. Synthesis of triazoles. The reaction of ketone **124** with various azides leads to the formation of the corresponding trifluoroacetyltriazoles **407**.[146] The ketones **407** obtained are easily hydrated at the carbonyl group, forming the diols **408**. Attempts to carry out the [2+3] cycloaddition for 2,3-dihydro-4-trifluoroacetylfuran **333** with benzyl azide led, instead of the expected triazole, to the formation of the

4.1.3. Synthesis of six-membered heterocycles.

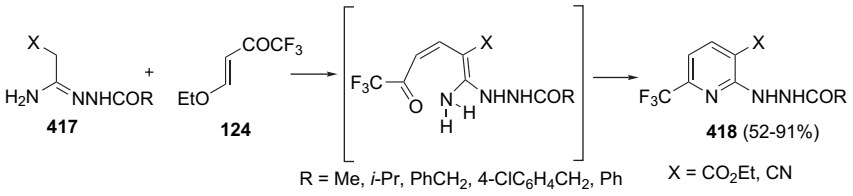
4.1.3.1. Synthesis of pyridines and their derivatives. Pyridines are a very important class of heterocyclic compounds and there are plenty of methods for their synthesis. There are, however, relatively few methods for the preparation of CF_3-containing pyridines. A method for the synthesis of 6-CF_3-nicotinonitrile **410**, based on the reaction of β-ethoxy CF_3-enone **124** with β-dimethylaminoacrylonitrile **411** followed by treatment of the intermediate product **412** with ammonium acetate, was proposed.[147] This sequence represents a convenient method for the regioselective preparation of 6-CF_3-nicotinonitrile **410**.

Recently, a method for the synthesis of 2-arylamino-6-CF_3 derivatives of nicotinonitrile **413** was elaborated.[148] β-*i*-Butoxy CF_3-enone **414** was employed as the CF_3-containing building block. The key step of the method is the reaction of the CF_3-enone **414** with β,β-diamino-substituted acrylonitriles **415** generated in situ in the reaction of **416** with anilines. The nicotinonitriles **413** containing various arylamino substituents in the α-position of the pyridine ring were obtained in low-to-high yields.

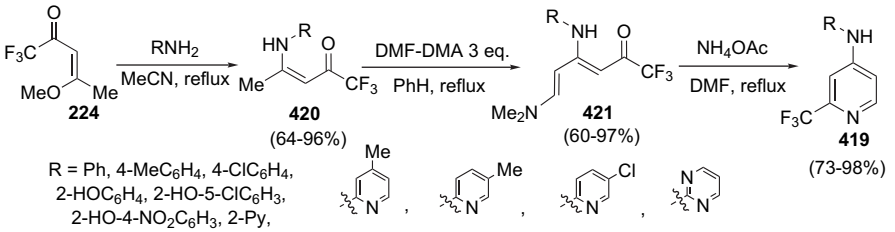




A novel method for the synthesis of CF_3-pyridines based on the reaction of enone **124** with *N*-acylacetamidrazones **417** was developed.[149] The reaction proceeds in good yields and allows the preparation of various 2-hydrazo derivatives of ethyl 6-trifluoromethylnicotinate and 6-trifluoromethylnicotinonitrile **418**.



A new approach to the synthesis of 2-CF_3 pyridines **419** containing various arylamino substituents in the 4-position of the pyridine ring was proposed.[150] This method exploits the reaction of β-methoxy CF_3-enone **224** with various aromatic amines including heterocyclic amines. The subsequent reaction of the formed enaminoketone **420** with the DMF dimethyl acetal leads to dienones **421**. The final stage is the reaction of the obtained dienones **421** with ammonium acetate in dimethylformamide, leading to the target 2-CF_3-4-arylaminopyridines **419** in high yields.



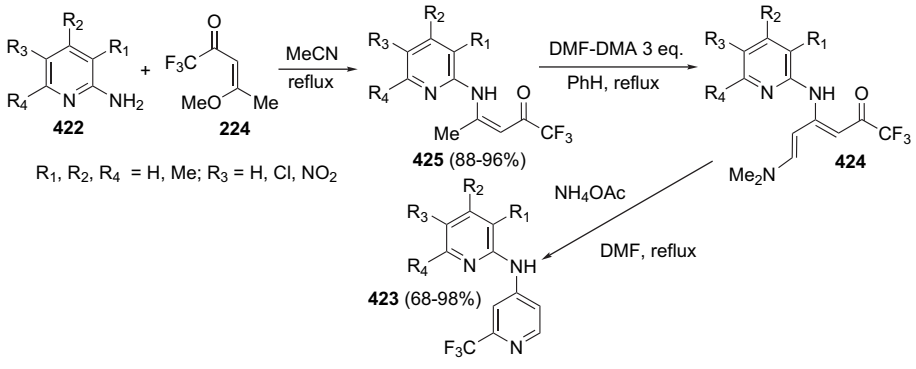
An analogous approach based on the use of 2-aminopyridine derivatives **422** as aromatic amines for the synthesis of the 2-CF_3-4-pyridylaminopyridine derivatives **423** was suggested.[151] The target products **423** are formed in high yields by reflux of the dienone **424** obtained from enaminoketone **425** with ammonium acetate in dimethylformamide.

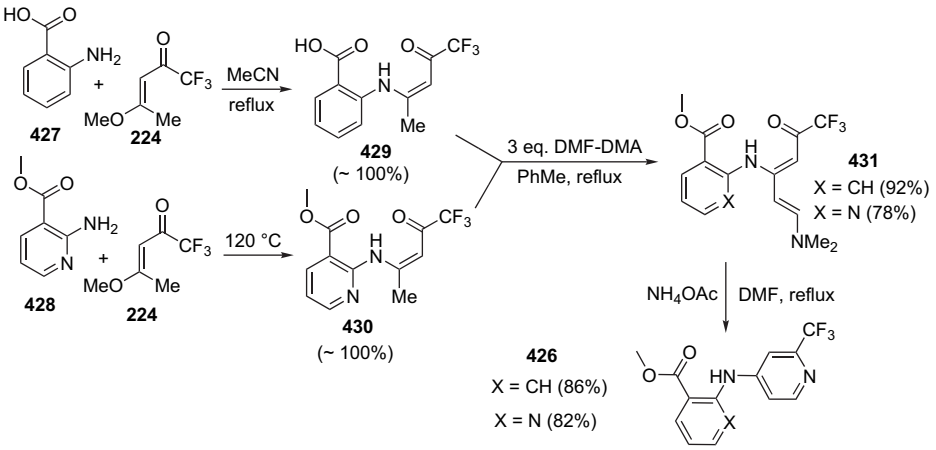
The same method was used for the preparation of 4-arylamino-2-CF_3-pyridine derivatives **426** possessing anticancer activity.[152,153] 2-Aminobenzoic acid **427** and 2-aminonicotinic acid methyl ester **428** were used as the aromatic amines. The intermediate enaminoketones **429**, **430**, and the dienones **431**, as well as the target pyridines **426**, were prepared in high yields.

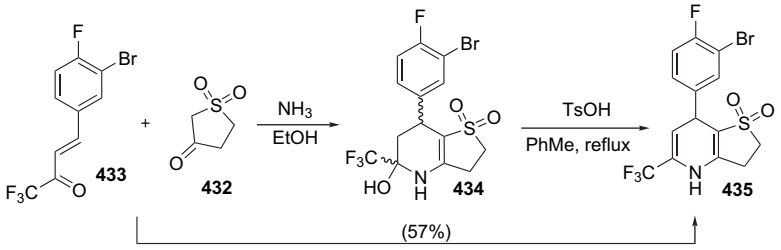
A Gantsch-type synthesis of 1,4-dihydropyridine derivatives has been suggested.[154] This method uses the reaction of dihydrothiophene-3(2*H*)-one-1,1-dioxide **432** with CF_3-enone **433**. The intermediate compounds **434** were isolated as a mixture of diastereomers and, without further purification, were utilized in the next reaction. The target 1,4-dihydropyridine derivative **435** was prepared in good yield.

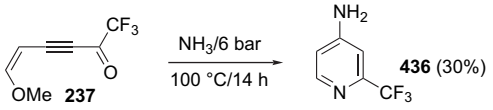
4-Amino-2-CF_3-pyridine **436** was prepared in moderate yield using the reaction of ketone **237** with ammonia under heating at high pressure.[87]

Several publications are devoted to methods for the synthesis of pyridine derivatives using lithium azaenolates. The application of ketone **205** for the synthesis of substituted 4-ethoxy-2-trifluoromethylpyridines **437** has been described. The ketone **205** was involved in the reaction with azaenolates **438** prepared from lithiated alkyltrimethylsilanes **439** and aromatic nitriles.[155]

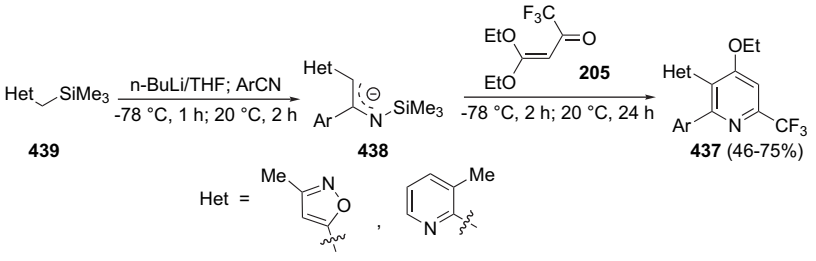




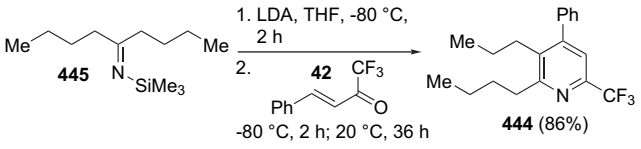


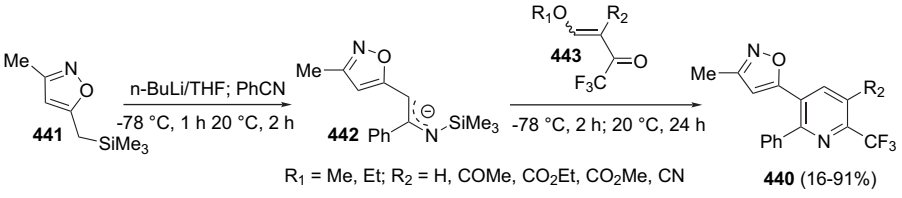


Besides the ketones **443**, some other α,β-unsaturated ketones react similarly in these conditions. In one example, the ketone **42** was used for the synthesis of the trifluoromethylpyridine **444** by the reaction of **42** with lithiated imine **445**.[157] The intermediate dihydropyridine derivative transforms spontaneously into the target pyridine.

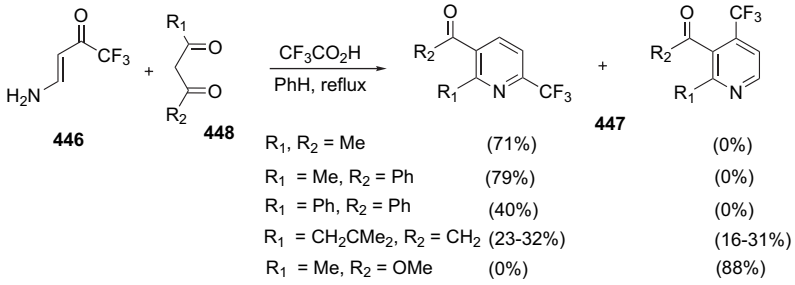


This method was extended to the preparation of various isoxazolyl-substituted pyridines **440**.[156] The method is based on metallation of 3-methyl-5-trimethylsilylmethylisoxazole **441**. The reaction with benzonitrile gives the azaenolate **442**. Subsequent treatment with CF_3-β-alkoxyenones **443** results in the formation of the target pyridines **440** in low-to-high yields.

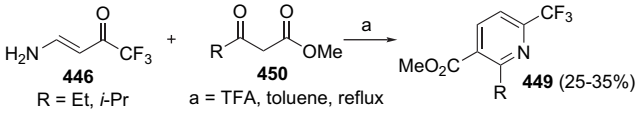




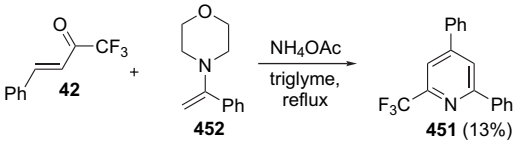
Enaminoketone **446** was studied as a building block for the preparation of 4-CF_3-containing pyridines **447**.[158] Ketone **446** reacts easily with various 1,3-dicarbonyl compounds **448** in the presence of trifluoroacetic acid under mild conditions to give the α-trifluoromethylpyridines **447** in moderate-to-high yields. In several cases, the formation of a mixture of regioisomers **447** was observed. This synthetic method provides a facile and convenient access to pyridines having a trifluoromethyl group at the α-position, which are not easily obtained by other methods. The peculiarities of the reaction regiochemistry are not discussed.



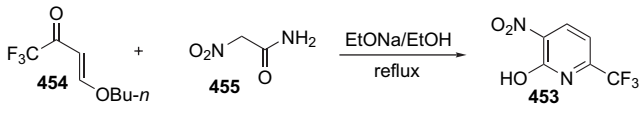
The same method for the preparation of nicotinates **449** involving the reaction of β-enaminoketone **446** with 1,3-ketoesters **450** was described.[159]



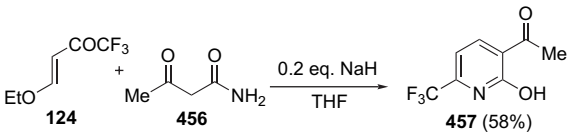
A 2-CF_3-pyridine derivative **451** was prepared in very low yield by the reaction of the enamine **452** with ammonium acetate and the ketone **42** by refluxing in triglyme.[160]



The synthesis of 2-hydroxy-3-nitro-6-trifluoromethylpyridine **453** starting from CF_3-enone **454** and nitroacetamide **455** has been described.[161] The yield for the pyridine **453** was not given.

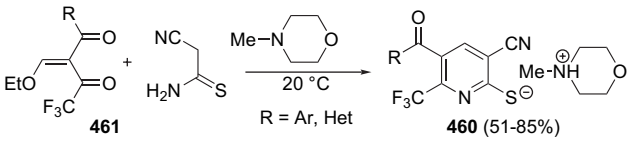


The reaction of enone **124** with acetoacetamide **456** was studied.[162] In the presence of catalytic amounts of sodium hydride, the formation of the pyridine derivative **457** was observed in moderate yield.



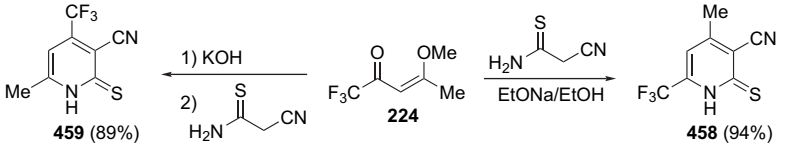
The reaction of CF_3-enone **224** with cyanothioacetamide was carried out.[163] Depending on the reaction conditions, the isomeric trifluoromethyl-substituted pyridinethiones **458** and **459** were prepared in good yields.

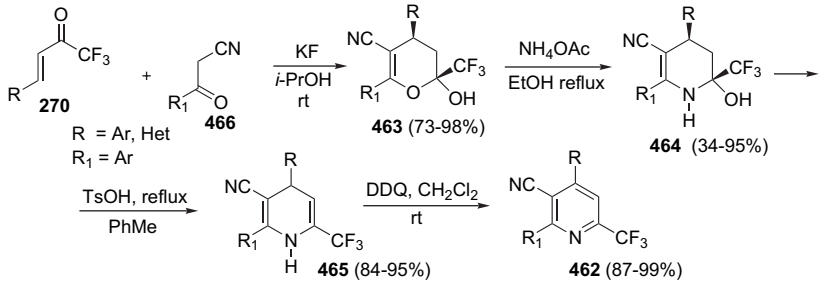
A similar method has been reported for the preparation of pyridine-2-thiols as their *N*-methylmorpholine salts **460** using the reaction of enones **461** and cyanothioacetamide in the presence of twofold excess of *N*-methylmorpholine.[164] The salts **460** can be involved in further transformations, forming thienopyridines in particular.



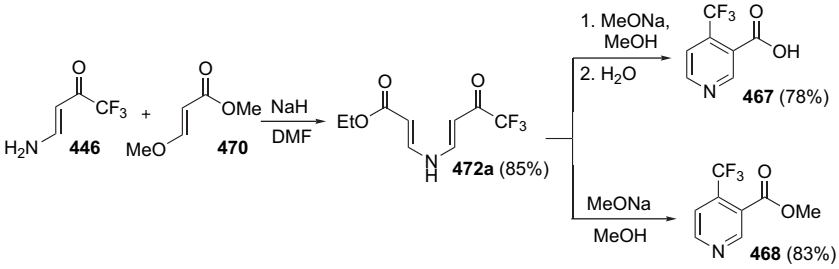
A novel method for the preparation of CF_3-containing pyridines **462** was elaborated recently.[165] The sequence includes several reactions. The first step is the synthesis of α-hydroxydihydropyrans **463** by the reaction of α,β-unsaturated ketones **270** and α-cyanoacetophenones **466**. The second step is transformation of **463** with ammonium acetate in ethanol to form the tetrahydropyridines **464**. The penultimate step is the dehydration of tetrahydropyridines **464** to give the dihydropyridines **465**. The final stage is oxidation into the target pyridines **462** with DDQ. All compounds were prepared in good yields. This sequence is a very effective and useful method for the preparation of CF_3-containing nicotinonitriles **462**.

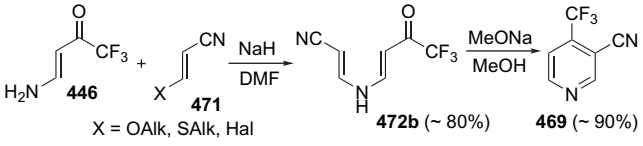
Original methods for the preparation of 4-CF_3-nicotinic acid **467**,[166] 4-CF_3-nicotinic acid esters **468**[167] and





4-CF_3-nicotinonitrile **469** were patented recently.[168] The synthetic sequence consists of the reaction of the parent enaminoketone **446** with β-substituted acrylic ester **470** or β-substituted acrylonitriles **471** having a leaving group in the β-position. Under treatment with sodium hydride in DMF these compounds produce enamines **472a** and **472b** after elimination of the leaving group. Compounds **472a**,**b** gave 4-CF_3-nicotinic acid ester **468** or nitrile **469** in excellent yields under treatment with sodium methoxide in methanol. If water is added to the reaction mixture after cyclization, 4-CF_3-nicotinic acid **467** is obtained.

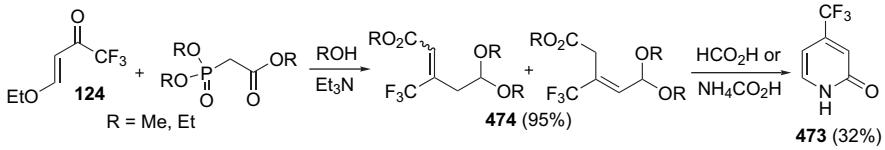


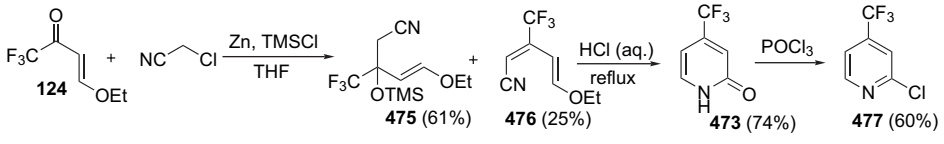


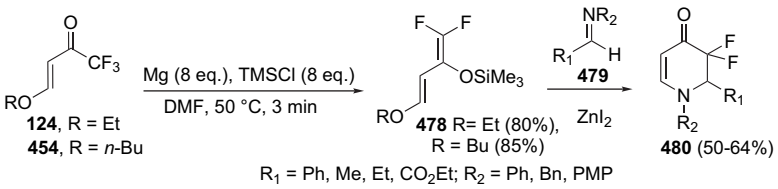
4-Trifluoromethyl-2(1*H*)-pyridone **473** has been synthesized recently.[169] The reaction sequence includes olefination of ketone **124** leading to a mixture of two products **474** in high total yield and the subsequent reaction with formamide or ammonium formate, leading to the target pyridone **473**.

An alternative one-pot synthesis of 4-trifluoromethyl-2(1*H*)-pyridone **473** using β-ethoxy-CF_3-enone **124** and chloroacetonitrile has been demonstrated.[170,171] It was found that chloroacetonitrile reacts with **124** in tetrahydrofuran as the solvent in the presence of zinc powder and trimethylchlorosilane to produce the β-trimethylsilyloxynitrile **475** accompanied by formation of the elimination product **476**. The mixture of **475** and **476** was heated under reflux in concentrated HCl to give 4-trifluoromethyl-2-pyridone **473** in good yield. It was suggested that the mechanism of heterocyclization involves a Reformatsky reaction to give the intermediate **475**, which undergoes elimination of TMSOH to give **476** and further cyclization to afford **473**. Chlorination of the pyridone **473** using $POCl_3$ resulted in the desired 2-chloro-4-trifluoromethylpyridine **477** in good yield.

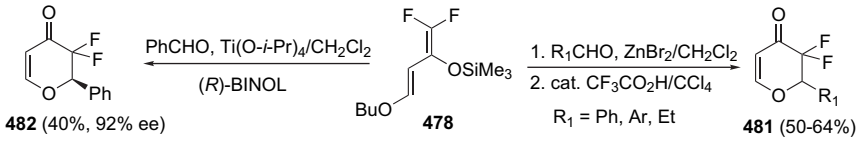
Treatment of the enones **124** or **454** with 8 equiv of magnesium and chlorotrimethylsilane in DMF leads to formation of difluoro derivative of Danishefsky diene **478**, which can be used in Diels–Alder reactions with various dienophiles.[172] In particular, various imines **479** can be used as dienophiles. The scarcely available 5,5-difluoro derivatives of dihydropyridone **480** were obtained in good yields by this method.



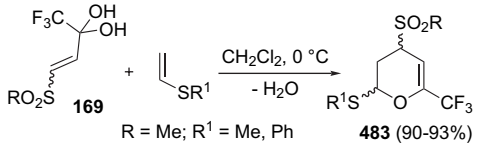




4.1.3.2. Synthesis of pyrans and their derivatives. Besides the above-mentioned work, Diels–Alder reaction of difluorinated Danishefsky-diene analog **478** was used in the reaction with various aldehydes. The corresponding pyran-4-ones **481** were obtained in moderate yields.[172] In the same work, the asymmetric synthesis of dihydropyrone **482** using a Ti(IV)-(*R*)-BINOL system is described. In the reaction with benzaldehyde, a sufficiently high ee was demonstrated for the prepared pyran **482**.

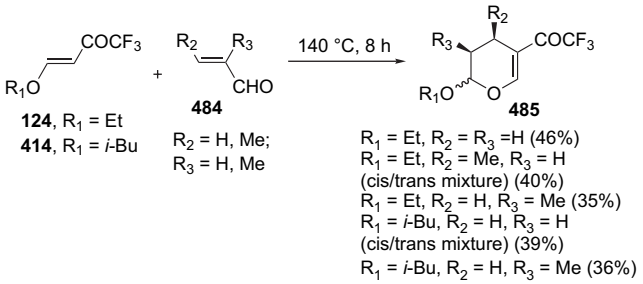


The ketone form of compounds **169** can be used as a heterodiene in the Diels–Alder reaction. This method has been used in the approach to dihydropyrans **483**.[173] The diol form of **169** can also be used in this reaction, because it exists in the equilibrium with its ketone form. The reaction at room temperature leads to the mixture of regio- and stereoisomeric products. As an example, the reaction with phenyl vinyl sulfide leads to a mixture of cis- and trans-isomers. The application of compound **169** having R=Ph leads to resinification of the reaction mixture.[173]



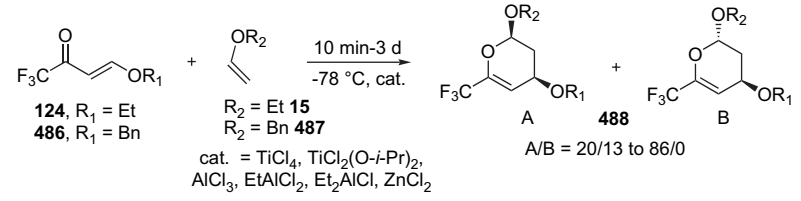
The cycloaddition reactions of α,β-unsaturated aldehydes **484** with β-alkoxy-CF_3-enones **124** and **414** were investigated.[142] The reaction leads to unexpected products—the cycloadducts **485** having the alkoxy group migrated. The formation of a cis-/trans-isomeric mixture of **485** is observed. The corresponding dihydropyrans **485** containing a trifluoroacetyl group were isolated in moderate yields.

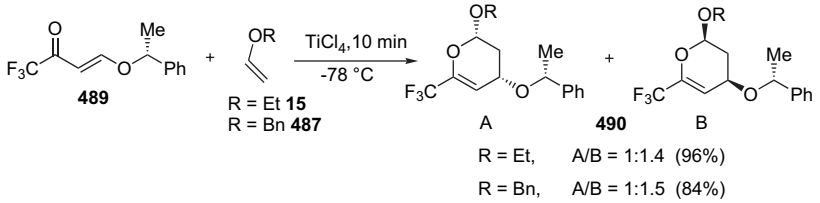
The influence of various Lewis-acid additives on the cycloaddition reaction of β-alkoxy CF_3-enones **124** and **486** with



vinyl ethers **15** and **487** was investigated.[174] The best results—the highest ratio of product diastereoisomers **488**-were obtained using titanium(IV) chloride.

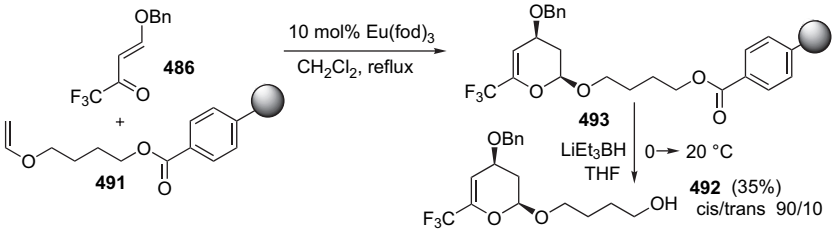
The preparation of chiral CF_3-dihydropyrans **490** was investigated. In this case, the reaction of CF_3-enone **489** containing a chiral substituent in the β-position was used.[175] The



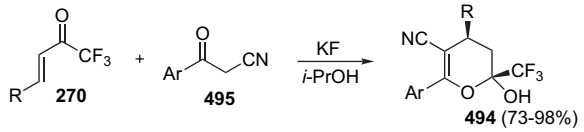


application of titanium(IV) chloride as the catalyst permits the preparation of the target pyrans **490** in high yields. The diastereoselectivity of the reaction is, however, very low.

Solid-phase methodology can be successfully applied to the cycloaddition reaction of β-benzyloxy-CF_3-enone **486** and vinyl ether **491**. The reaction is catalyzed with a europium(III) complex and proceeds in rather moderate yield, although with high stereoselectivity. The target pyran **492** was obtained from **493** after treatment with lithium triethylborohydride.[174]

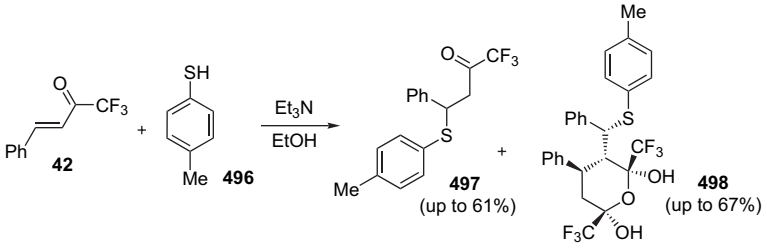


Cyano-substituted dihydropyrans **494** were obtained in the reaction of CF_3-enones **270** with aromatic α-cyanoketones **495**.[176] The reaction proceeds in *i*-propanol in the presence of calcinated potassium fluoride as the base. The reaction proceeds in good yields and 100% stereoselectively. The only diastereomer of the target dihydropyran **494** obtained had an equatorial orientation of the aryl substituent and the CF_3 group.

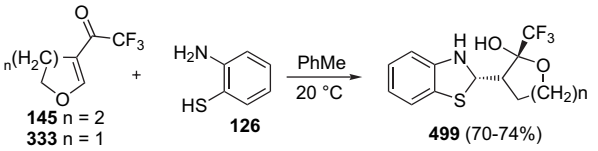


R = Ar, Het Ar = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

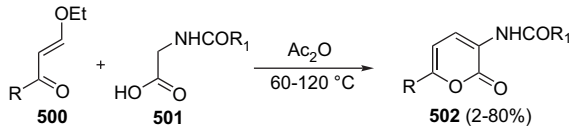
Pyran derivatives were also obtained in the reaction of CF_3-enone **42** with 4-methylthiophenol **496**.[177] A mixture of the Michael adduct **497** and the cyclic product of double addition **498** was formed. Depending on the reaction conditions, each of the two products can be obtained selectively. Although 32 isomers of **498** are possible to form in this reaction, the compound **498** was obtained as the single diastereomer and its structure was confirmed by X-ray analysis. Even the configuration of the carbon atom outside the pyran ring is fixed.



The reaction of 2-aminothiopenol **126** with two cyclic β-alkoxyenones **145** and **333** was investigated.[178] Using toluene as a solvent, the reaction leads to the formation of benzothiazolines **499** bound to a tetrahydrofuran or a tetrahydropyran ring. These compounds were obtained as a single diastereomer, the structure of which was confirmed using X-ray analysis. The trifluoromethyl group and the benzothiazoline substituent are oriented equatorially.



The investigation of reactions of β-ethoxyenones **500** with various *N*-aroyl glycines **501** in the presence of acetic acid anhydride was studied.[179] The heterocyclization proceeds upon heating and leads to 2*H*-pyran-2-one derivatives **502** in high yields.

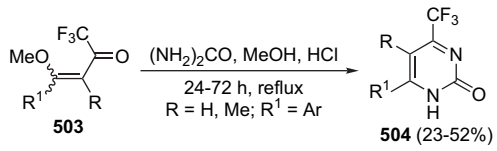


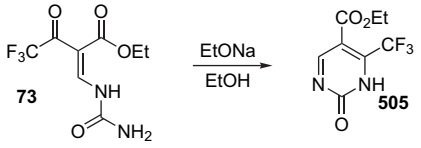
R = CF_3, $CClF_2$, C_3F_7, Me
R_1 = Me, Ph, 4-*t*-BuC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2-Th

4.1.3.3. Synthesis of pyrimidines and their derivatives. Bonacorso et al. reported the synthesis of pyrimidones **504** using the reaction of enones **503** with urea in acidic conditions.[180] In the case of ketones having R=Me, the yield of the pyrimidines **504** decreases and the reaction time increases. Apparently, this is due to steric hindrance caused by the presence of a methyl group in the α-position.

Enamidoketone **73** was used for the preparation of pyrimidine derivative **505**.[30] The heterocyclization was carried out under basic conditions. The yield of the product **505** was not given.

The reaction of a series of β-alkoxy CF_3-enones **506** with acet- and benzamidine **507** was carried out.[181] The formation of pyrimidines **508** or the mixture of **509** and their tetrahydro derivatives **509** is observed. The ratio of **508** and



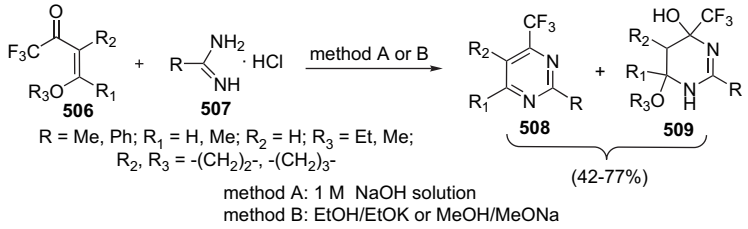


509 varies within wide limits, depending on the reaction conditions and the reaction time, as well as on the substituents in the starting compounds. The individual compounds **508**, **509** or their mixtures were obtained. The stereochemistry of the tetrahydropyrimidine products **509** has not been investigated.

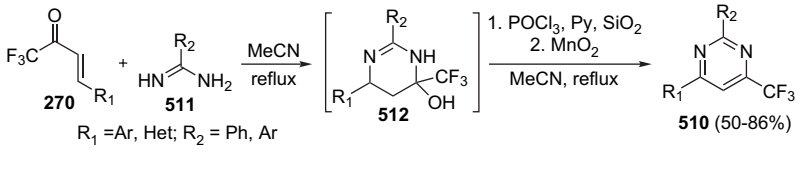
preparation of **510** in high yields.[182] The amidines **511** were generated in situ from the hydrochlorides by treating with sodium hydroxide.[182]

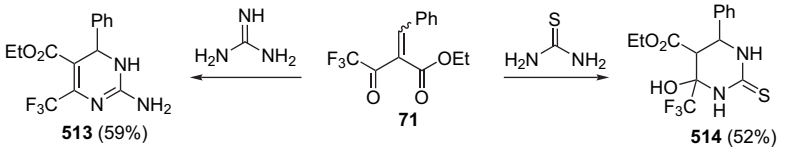
The reactions of CF_3-enone **71** containing an ethoxycarbonyl group in the α-position with thiourea and guanidine sulfate were investigated.[130] The corresponding dihydro **513** and tetrahydro derivatives **514** were obtained in moderate yields. The stereochemistry of **514** was not studied.

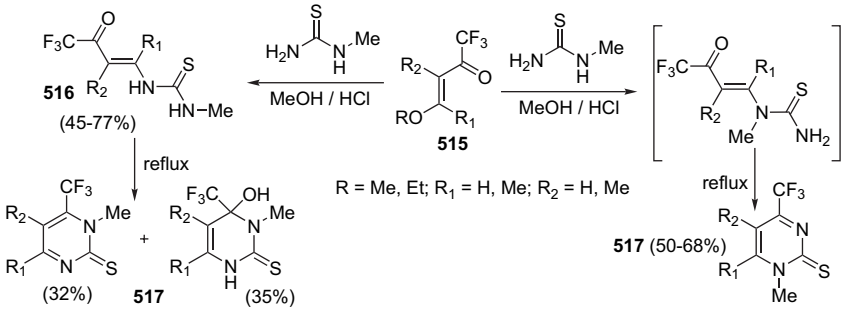
In order to study the regiochemistry of the cyclocondensation reaction of a series of β-alkoxyvinyl CF_3-ketones **515** toward an asymmetric dinucleophile, *N*-methylthiourea was chosen.[183] The cyclocondensation was carried out in methanol under acid catalysis. Depending on the temperature and the reaction time, the open-chain products **516** or pyridinethiones **517** were obtained. In general, a low temperature and a short reaction time promote the formation of the open-chain products **516**. Higher temperatures and longer reaction times results in the pyrimidinethiones **517**. The open-chain products **516** were isolated for the first time. These compounds are difficult to



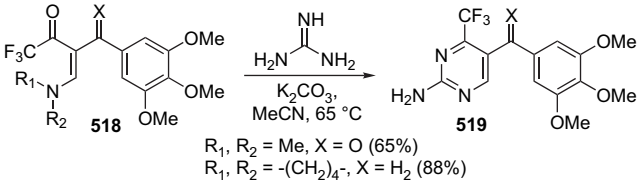
The synthesis of trifluoromethyl-substituted pyrimidines **510** was described using the reaction of enones **270** with amidines **511**. Subsequent dehydration and oxidation of the intermediate adducts **512** without isolation permits the isolate because the cyclization usually takes place very rapidly. The compounds were isolated probably due to the steric hindrance between the *N*-methyl group and the CF_3 group.



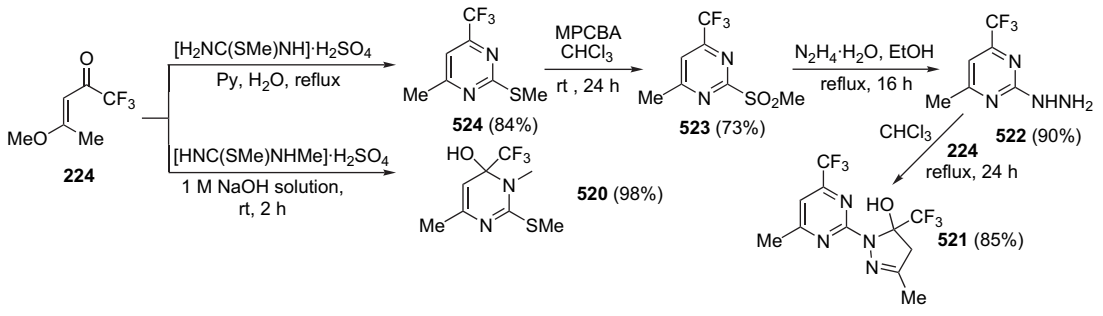




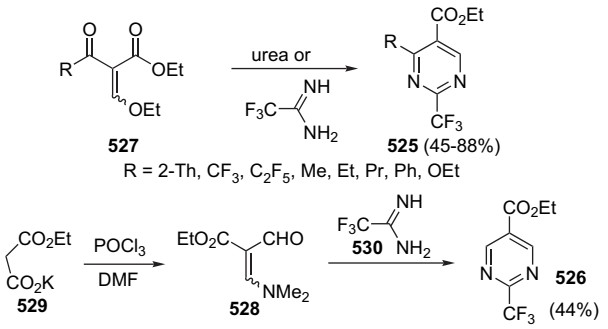
Some work[184] has been undertaken to apply the above methodology to the synthesis of fluorinated aminopyrimidines analogous to trimethoprim (TMP). TMP and pyrimethamine (PYR) have become the reference drugs for the prophylaxis and treatment of opportunistic infections due to *Pneumocystis carinii* and *Toxoplasma gondii*. Enaminoketones **518** were reacted with guanidine hydrochloride to give the pyrimidines **519**. Anti-*Toxoplasma* activities of the derivatives **519** were assessed in vitro using a tissue-culture model combined with an immunoenzymatic assay for quantification of *Toxoplasma* growth and TMP was tested in parallel as a reference drug.



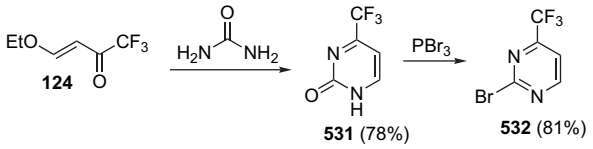
Four novel pyrimidines were prepared to investigate their effects on NTPDase activity in a synaptosomal fraction obtained from rat cerebral cortex.[185] The dihydropyrimidine **520** was prepared by the cyclocondensation reaction of **224** with 1,2-dimethyl-isothiourea sulfate in the presence of sodium hydroxide. The synthesis of **521** was achieved from the cyclization of the pyrimidin-2-yl-hydrazine **522** with the ketone **224** in chloroform under reflux for 24 h. The pyrimidine **523**, prepared by the oxidation of 2-methylsulfanyl-pyrimidine **524** with MCPBA, underwent nucleophilic displacement of the 2-methylsulfonyl group by hydrazine hydrate in ethanol and reflux to furnish the 2-hydrazinopyrimidine **522** in excellent yield. In general, all the novel pyrimidines tested as inhibitors of NTPDase showed a similar inhibition for both substrates ATP and ADP. It should be noted that the presence of the pyrimidine core was essential for enzyme recognizing of the compounds in both peripheral and active sites.



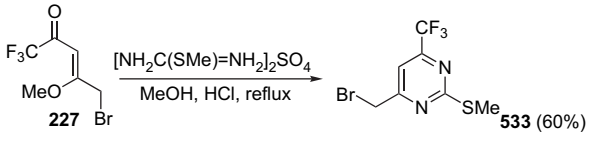
A library of pyrimidine derivatives including compounds **525** and **526** containing a CF_3 group was synthesized for an investigation of their physiological activity.[186] Two main approaches for the synthesis were used. The first approach was based on the reaction of β-ethoxy-CF_3-enone **527**, which is a derivative of trifluoroacetoacetic ester, with urea or amidines. The second approach was used for preparation of **526** is based on the reaction of formylenaminoester **528** obtained by formylation of malonic acid monoester potassium salt **529** with trifluoromethylamidine **530**.



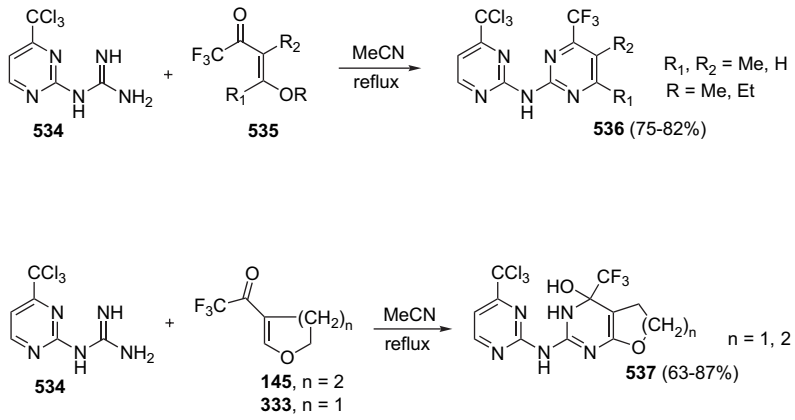
Recently, much attention has been devoted to the preparation and subsequent functionalization of chlorinated and brominated (trifluoromethyl)pyrazoles, (trifluoromethyl)pyridines, and (trifluoromethyl)quinolines.[187] An extension of this work to the pyrimidine analogs carrying a trifluoromethyl group and an additional halogen as substituents was reported. The condensation of urea with ketone **124** afforded 4-(trifluoromethyl)pyrimidin-2(1*H*)-one **531**, a known compound, in good yield. This was converted into 2-bromo-4-(trifluoromethyl)pyrimidine **532** by reaction with phosphorus tribromide. The analogous condensation of urea with 3-bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one **222** (X=Br) produced tars, rather than the expected 5-bromo-4-(trifluoromethyl)-2(1*H*)-pyrimidone.



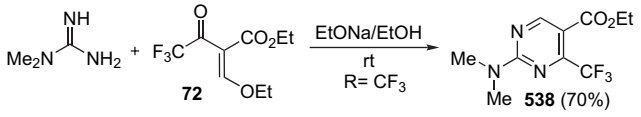
The bromoketone **227** has been applied for various heterocyclizations.[79] Compound **227** reacts with methylisothiouronium sulfate forming the corresponding pyrimidine derivative **533** in moderate yield.



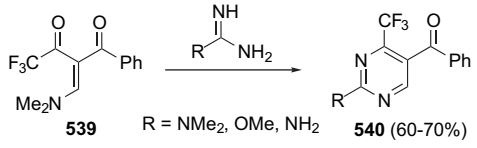
The reactions of 2-guanidinopyrimidine **534** with β-alkoxy-CF_3-enones **535** and cyclic enones **145** and **333** were investigated.[188] Depending on the substituents in the starting ketone, the reaction leads to dipyrimidylamines **536** or their condensed dihydrofuran and dihydropyran derivatives **537**.



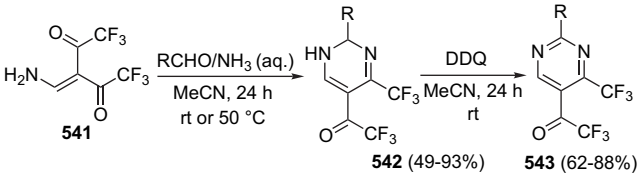
An analogous reaction was used for the synthesis of a 2-dimethylamino derivative of 4-CF_3-pyrimidine-5-carboxylic acid **538** showing cardiotonic activity.[189] The reaction of β-ethoxy CF_3-enone **72** with 2,2-dimethylguanidine was performed. The target product **538** was obtained in high yield.



The possibility of application of β-enamino-CF_3-enone **539** for the synthesis of pyrimidine derivatives was shown.[190] The pyrimidines **540** were obtained in good yields using the reaction with *N*,*N*-dimethylguanidine, guanidine, and *O*-methylurea.



It was found that β,β-bis(trifluoroacetyl)enamine **541** can be easily prepared in two steps with trifluoroacetic anhydride and isobutyl vinyl ether with a subsequent *i*-BuO–NH_2 exchange reaction with ammonia.[191] Enaminoketone **541** reacts with various aldehydes in the presence of ammonia to give the dihydropyrimidine derivatives in good yields. Oxidation of 1,2-dihydropyrimidines **542** with DDQ at room temperature for 24 h in acetonitrile caused smooth dehydrogenation to give the desired pyrimidines **543**. This synthetic method provides a facile and convenient access to pyrimidines **543**, having both trifluoromethyl and trifluoroacetyl groups, which are not easily obtained by other methods.

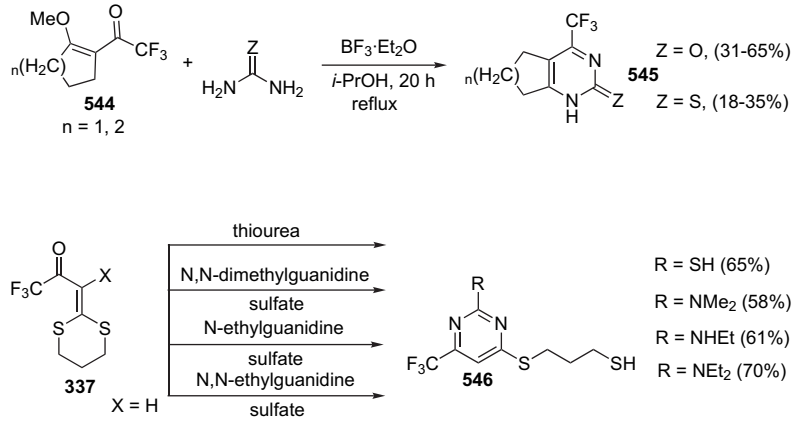


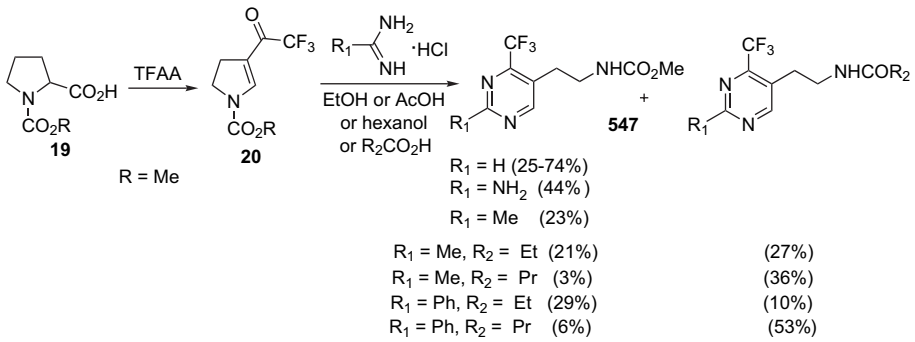
R = H, Me, Et, *i*-Pr, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, Ph, *p*-ClC_6H_4

Cyclic β-alkoxy-CF_3-enones **544** were applied for the preparation of 2-pyrimidones **545** and their thio analogs using the reaction with urea and thiourea.[192] The target compounds **545** were obtained in moderate yields.

The reactions of CF_3-enone **337** with several *N*,*N*-binucleophiles were investigated. Various 2-substituted pyrimidines **546** containing a 1,3-dithiopropyl substituent were prepared.[125]

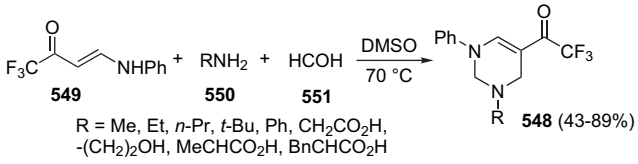
An example of the application of trifluoroacetylpyrroline **20** for preparation of pyrimidines **547** was also described.[124] In this case, the reaction is less selective. Nevertheless, the





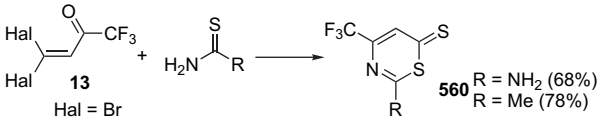
products **547** obtained are very attractive candidates for medicinal chemistry.

The multicomponent reaction was used for the synthesis of tetrahydropyrimidines **548**.[193] The components were β-phenylamino-CF_3-enone **549**, primary amines **550**, and formaldehyde **551**. The reaction proceeds by heating in DMSO and leads to the tetrahydropyrimidines **548** in moderate-to-high yields.

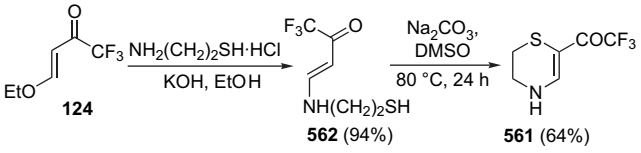


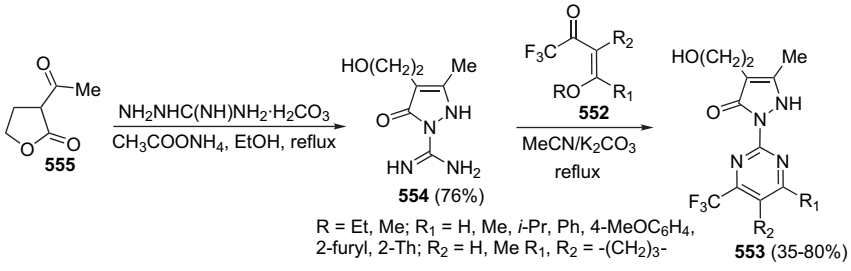
β-Alkoxy-CF_3-enones **552** were also used for the preparation of various CF_3-pyrimidines **553** containing a 3-oxo-2,3-dihydropyrazole substituent.[194] These compounds are of particular interest because of their potential use as anti-inflammatory non-steroidal agents. The starting 3-oxo-2,3-dihydropyrazole **554** derivative was prepared by the reaction of 3-acetylbutyrolactone **555** and aminoguanidine.

The reaction of β,β-dibromo-CF_3-ketone **13** with thioacetamide and thiourea was performed.[196] The reaction was carried out in an alcoholic medium using a 100% excess of the thio compound. The products of the reaction—the corresponding 1,3-thiazine derivatives **560**—were obtained in good yields. The reaction proceeds regioselectively, the nitrogen atom attacking the carbonyl group of **13**.



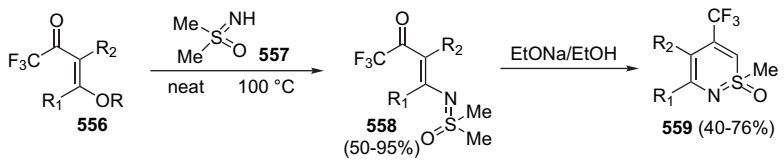
Dihydrothiazine **561** can be prepared using the reaction of ketone **124** with 2-aminoethanethiol with subsequent oxidative cyclization of the adduct **562**. The oxidative cyclization of **562** was performed by heating a DMSO solution in the presence of sodium carbonate.[178]

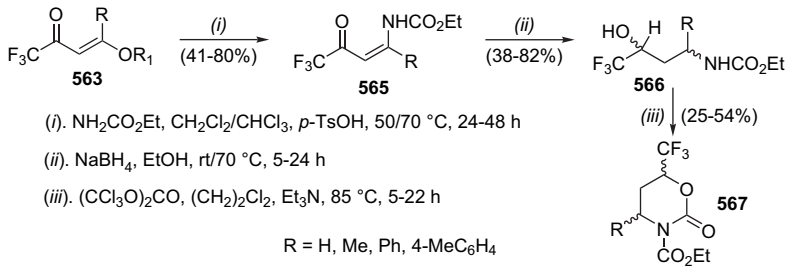




4.1.3.4. Synthesis of 1,2-, 1,3-, and 1,4-thiazines. The reaction of β-alkoxy-CF_3-enones **556** with *S*,*S*-dimethylsulfoximine **557** was studied.[195] Initially products **558** formed can be cyclized into the derivatives of 1,2-thiazine-1-oxide **559** in high yields.

4.1.3.5. Synthesis of 1,3-oxazines. The reaction of β-alkoxy-CF_3-enones **563** with ethyl carbamate leads to the formation of enamidoketones **565**. Subsequent reduction to the aminoethanols **566** and cyclization to **567** was performed.[197] One of the evaluated compounds **567** exhibited

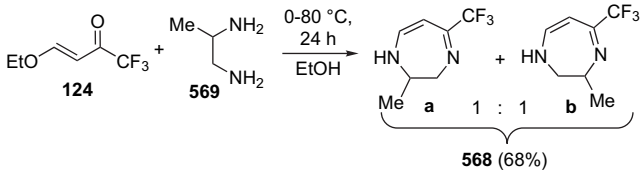




significant in vitro activity against the tested microorganism strains.

4.1.4. Synthesis of seven-membered heterocycles.

4.1.4.1. Synthesis of 1,4-diazepines. 5-Trifluoromethyl-2,3-dihydro-1,4-diazepine **568** was prepared by the reaction of CF_3-enone **124** with 1,2-propylenediamine **569**.[44] 1,2-Propylenediamine **569** reacted smoothly with **124** under mild reaction conditions to give **568**. As expected, the reaction gave two isomeric products **568a** and **568b** in an almost 1:1 ratio. They can be separated cleanly by column chromatography.

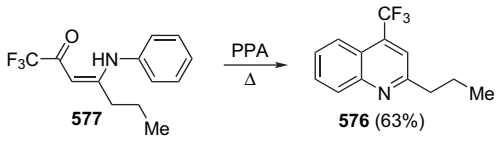


4.1.5. Synthesis of condensed heterocycles.

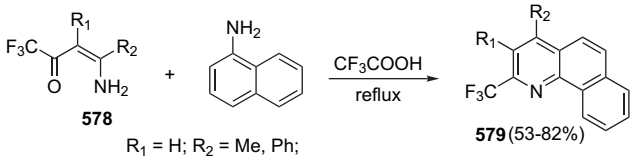
4.1.5.1. Synthesis of quinoline derivatives. A method for the synthesis of CF_3 derivatives of dihydrobenzo[*c*]acridine **570** has been suggested.[198] The approach is based on the application of β-methoxy CF_3-enone **571** obtained from tetralone. In the reaction of **571** with various substituted anilines, the formation of enaminoketones **572** is observed. The compounds **572** are cyclized into the target dihydrobenzo[*c*]acridines **570** in high yields on treatment with polyphosphoric acid (PPA).

treated with polyphosphoric acid. Noteworthy the corresponding unsubstituted benzo[*h*]quinoline having R_1=H cannot be prepared using this reaction.

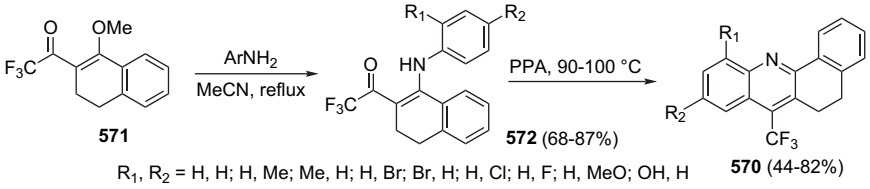
An analogous approach was used in work[200] on the synthesis of 2-propyl-4-trifluoromethylquinoline **576**. The enaminoketone **577** was prepared by the addition of aniline to the corresponding trifluoroacetylated propylacetylene.



Various enaminoketones **578** were used for the preparation of benzo[*h*]quinolines **579**. The reaction with 1-aminonaphthalene was applied. The target heterocycles **579** were obtained in good yields using TFA as the cyclizing agent.[201]

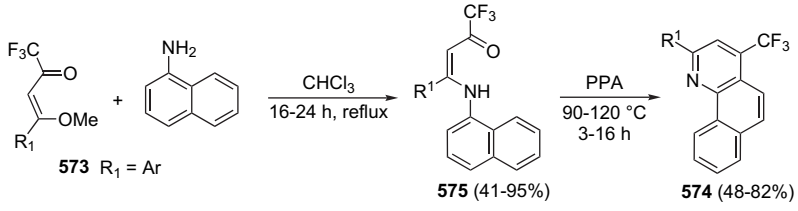


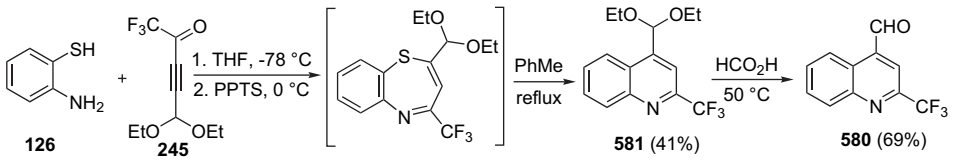
An effective method for preparation of 2-substituted 4-quinolinecarbaldehydes **580** was elaborated.[202] This method is based on the reaction of acetylenic ketone **245** with



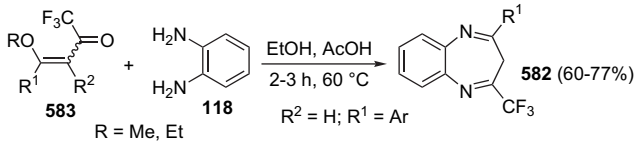
The ketones **573** can be also used for the synthesis of benzo[*h*]quinolines **574**.[199] The intermediate enaminoketones **575** prepared from the enones **573** and 1-naphthylamine are

2-aminothiophenol **126**. The reaction proceeds through the formation of a diacetal **581**, which is hydrolyzed with formic acid. Unfortunately, the yield of **581** is only moderate.

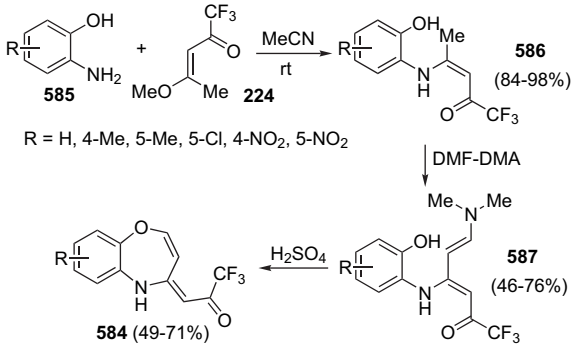




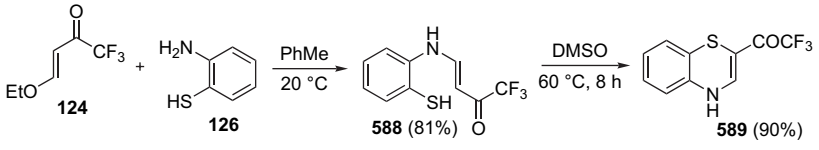
4.1.5.2. Synthesis of other condensed heterocycles. The preparation of benzodiazepines **582** by a one-step synthesis using the reaction of ketones **583** with -phenylendiamine **118** in an ethanol/acetic acid mixture as the solvent has been reported.[203] The yields of the target benzodiazepines **582** are sufficiently high.



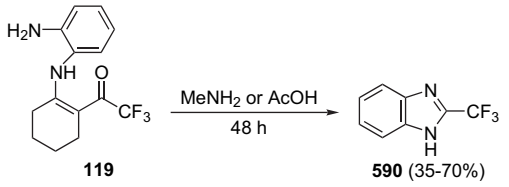
A useful approach to the preparation of new CF_3-containing 1,5-benzoxazepines **584** starting from *o*-aminophenols **585** and β-alkoxy ketone **224** was presented. An O–N exchange reaction gives the enaminoketones **586** in high yields. The reaction proceeds under mild conditions at room temperature. Further functionalization of **586** was achieved by heating with DMF-DMA. Thus, the corresponding dienaminoketones **587** were easily obtained. Cyclization of the resulting adducts **587** with aqueous sulfuric acid at 70 °C occurred smoothly to give the fluorinated 1,5-benzoxazepines **584** in good yields.[204]



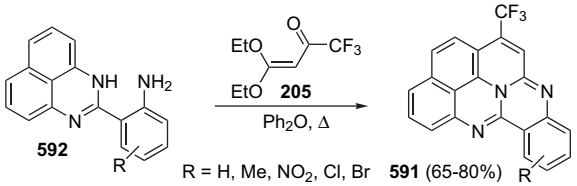
The enone **124** reacts with 2-aminothiophenol **126** in toluene solution at room temperature forming the enaminoketone **588**.[178] Heating of **588** in DMSO for 8 h leads to the product of oxidative cyclization—benzothiazine derivative **589**—in high yield.



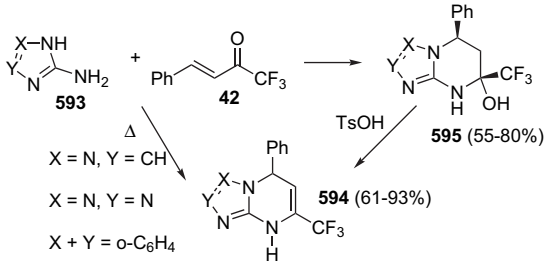
Treating enaminoketone **119** with methylamine or acetic acid leads to the formation of benzimidazole **590** containing a trifluoromethyl group in position 2.[41] It should be noted that destruction of the skeleton of the starting ketone **119** takes place.



The ketone **205** was applied for the synthesis of triazadibenzocrysenes **591**.[205] These polycondensed heterocycles containing various substituents were prepared in good yields in the reaction of ketone **205** with 2-perimidinylanilines **593**.



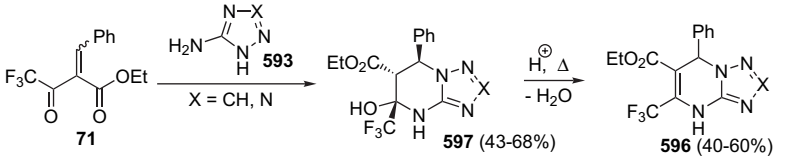
The reaction of CF_3-enone **42** with various amino derivatives of azoles **593**—aminotriazoles, aminotetrazoles, and 2-aminobenzimidazoles was used for the preparation of dihydro-**594** and tetrahydroazolopyrimidines **595**.[206] In the case of aminotriazoles and aminotetrazoles, the reaction proceeds 100% stereoselectively to form compound **595** having a cis-orientation of the CF_3 and phenyl groups as a single diastereomer. 2-Aminobenzimidazole gives a diastereomeric mixture of **595** in a ratio of 3:1.



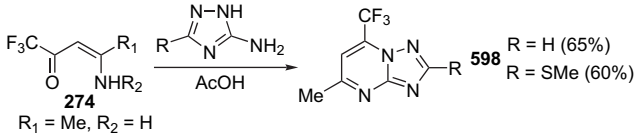
Treating enaminoketone **119** with methylamine or acetic acid leads to the formation of benzimidazole **590** containing a trifluoromethyl group in position 2.[41] It should be noted that destruction of the skeleton of the starting ketone **119** takes place.

The pyrimidine derivatives **596** can be prepared using the reaction of **71** with aminotriazoles and aminotetrazoles **593**.[207] The intermediate tetrahydro derivatives **597** were obtained

as single diastereomers. The structure was determined by spectral data analysis. The formation of a single diastereomer was explained by high conformational energy of phenyl, ethoxycarbonyl, and CF_3 groups. As a result, the formation of more favorable diastereomer having an equatorial orientation of these substituents was observed.

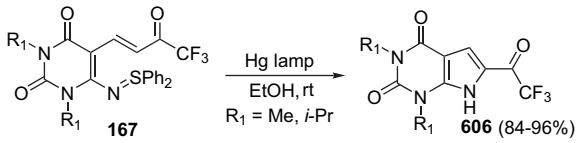


The analogous reaction was investigated for the β-enaminoketone **274**.[208] This reaction leads directly to condensed heterocyclic compound **598** formation, bypassing the intermediate tetrahydro derivatives. The structure of the compounds **598** was determined by analysis of their NMR data. The reaction proceeds 100% regioselectively and the yields of the products **598** are good. The causes of the observed regioselectivity are not discussed.

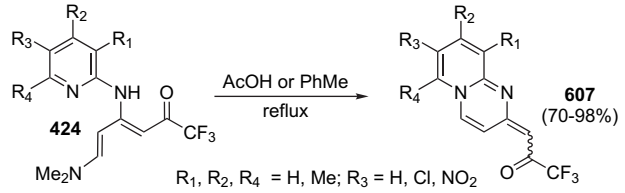


The preparation of CF_3 derivatives of pyrido[2,3-*d*]pyrimidines **599** and **600**, dihydro-derivative **601** and pyrazolo[3,4-*b*]pyridines **602** and **603** was studied.[209] The condensation of the corresponding 6-aminouracil **604** or 5-aminopyrazole **605** and CF_3-enones **42**, **124**, and **205** was used. The products were obtained in low yields, except for compounds **600**.

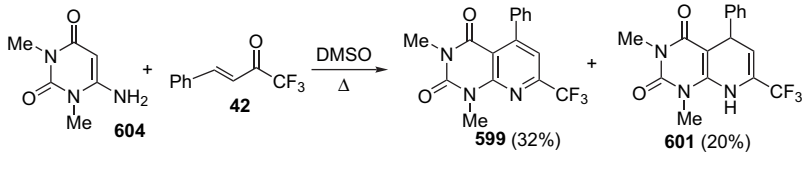
Photo-induced cyclization of uracil-substituted ketones **167** having a sulfimino substituent was used for the preparation of pyrrolo[2,3-*d*]pyrimidine-2,4-diones **606** containing a CF_3 group.[61] The reaction proceeds at room temperature using a mercury lamp.

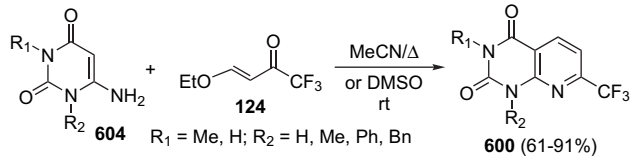


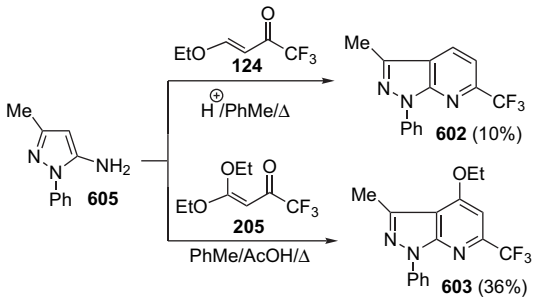
The corresponding pyrido[1,2-*a*]pyrimidine derivatives **607** are formed in good yields by heating the dienone **424** obtained from ketone **425** in toluene or acetic acid solution.[151]

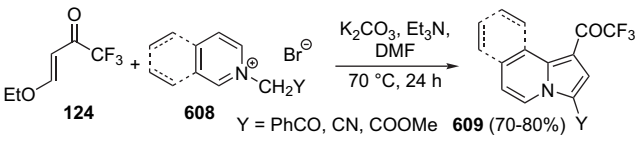


It was shown that the reaction of ketone **124** with pyridinium (isoquinolinium) salts **608** in the presence of base leads to the indolizines **609**.[210] The prepared indolizines **609** were obtained, due to the oxidation of the intermediate dihydro-derivatives with atmospheric oxygen. In the case of the compound with Y=COOMe, the partial transesterification of the product **609** is observed. Noteworthy is the fact that the reaction proceeds with low yields or does not proceed for the quinolinic salt.



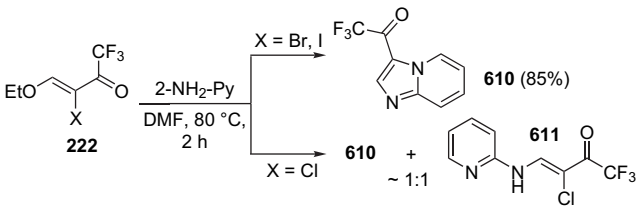






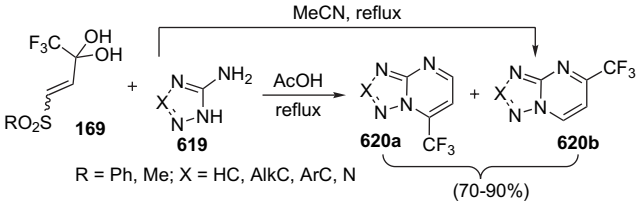
The reaction of ketones **222** (X=Br, I) with 2-aminopyridine was investigated.[211] The reaction leads in appropriate conditions to the imidazopyridine **610**. In the case of compound **222** having X=Cl, the formation of a mixture of two

products is observed. One of the products is the imidazopyridine **610**, and the second is the enaminoketone **611**—the product of ethoxy-group substitution (the ratio of these compounds is ~1:1).

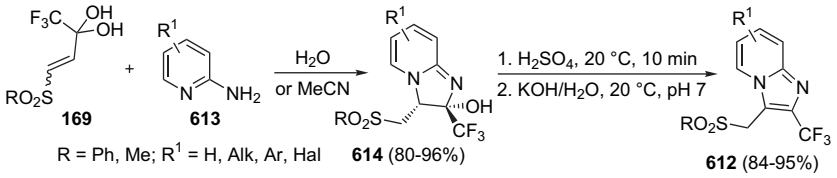


The synthesis of imidazopyridines **612** using the reaction of β-sulfonyl-substituted trifluoromethylketones **169** with several 2-aminopyridines **613** was described.[212] The reaction proceeds regio- and stereoselectively (the intermediate dihydro-derivatives **614** were isolated as a single diastereomer). This reaction is an exception in the commonly observed direction for the reaction of **169** with amines, because usually it leads to the products of sulfonyl-group substitution.[61] Noteworthy is the fact that the electrophilic attack is directed on C-3 of **169**. Commonly, the C-4 carbon atom is the object of electrophilic attack for most of the α,β-unsaturated trifluoromethylketones. Such regiochemistry is observed probably due to the electronegative properties of the sulfonyl group.

The analogous regioselectivity is observed in the reaction of enones **169** with various 3-amino-1,2,4-triazoles and 5-aminotetrazoles **619**.[214] The reaction was carried out in conditions similar to those used in the pyrazolopyrimidine **616** synthesis. The 7-trifluoromethyl-substituted cycloadducts **620a** dominate in most cases. A method for the synthesis of triazolopyrimidines **620b** was elaborated. Such an inversion of selectivity was achieved by carrying out the reaction in acetonitrile.

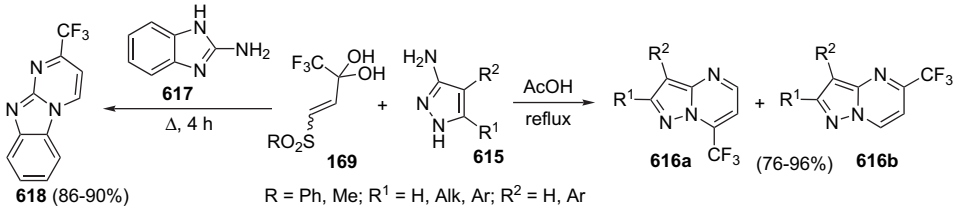


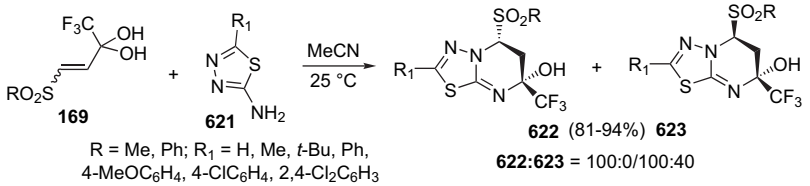
The reaction of 2-amino-1,3,4-thiadiazoles **621** with **169**, closely related to the reaction described above, was also investigated.[215] Although the products **622** and **623** contain two asymmetric centers, the reaction proceeds with high stereoselectivity. The target compounds **622** and **623** were obtained in high yields. The structure of compound **622** having R=Ph and R_1=H was established using X-ray analysis. The dihydropyrimidine cycle is positioned in an envelope conformation. The phenylsulfonyl group has an unusual axial orientation. This is probably due to an intramolecular hydrogen bond between the hydroxyl hydrogen atom and the phenylsulfonyl group oxygen atom.



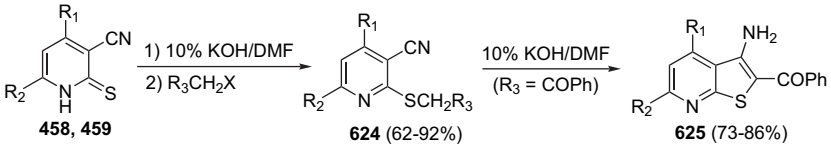
The synthesis of various heterocyclic systems using the reaction of enones **169** with several diazoles was investigated.[213] Reflux of **169** with 3-aminopyrazoles **615** leads to formation of the pyrazolopyrimidines **616a**. In several cases, the isomeric pyrazolopyrimidines **616b** were formed as the second product. Using aryl-substituted aminopyrazoles, the reaction proceed stereoselectively, forming **616a** as the only isomer. In the reaction of ketones **169** with 2-amino-1*H*-benzimidazole **617**, the formation of imidazopyridines **618** was observed.

The alkylation of pyridinethiones **458** and **459** with methyl iodide and ω-bromoacetophenones was studied.[163,164] The starting compounds were obtained from the ketones **224** and cyanoacetic acid thioamide. The corresponding methylthio and phenacylthio derivatives of nicotinonitrile **624** were obtained in good yields. The obtained compounds were also used for heterocyclization into the corresponding



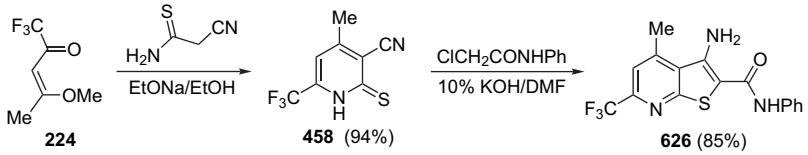


benzoylthieno[2,3-*b*]pyridines **625** by treating **624** with potassium hydroxide in DMF solution.



R1, R2 = Me or CF3 ; R3 = H, X = I; R3 = COPh, X = Br

The same approach was applied for synthesis of thieno[2,3-*b*]pyridine **626** containing an *N*-phenylcarboxamide group instead of a benzoyl group.[216] Chloroacetanilide was used in the second stage as the alkylating agent.



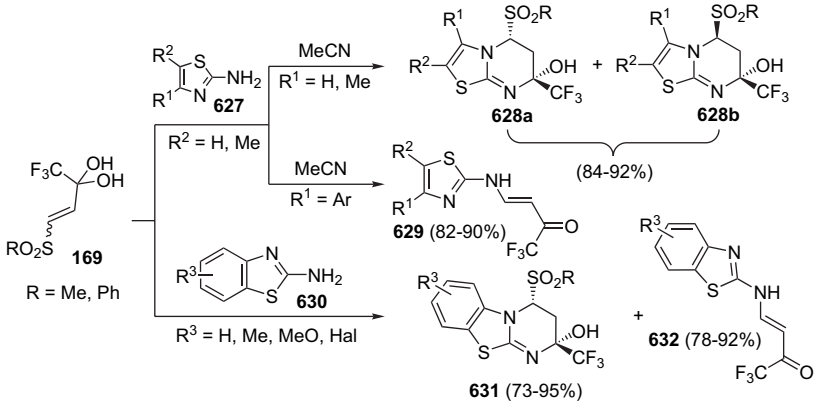
As a scaffold for the construction of condensed heterocyclic systems, several 2-aminothiazoles **627** were used.[217] The isomer **628a** dominates over **628b** among the products of this reaction. An attempt to use 2-amino-4-aryl-1,3-thiazoles failed because the reaction leads to predominate formation of the enaminoketones **629**—the products of sulfonyl group nucleophilic substitution. In the reaction of benzothiazoles **630**, the heterocycles **631** are formed as a single reaction product only in the case of compounds having the substituent in position 4, otherwise the formation of enaminoketone **632** is observed. In addition, the cyclization with 2-aminobenzothiazoles proceeds regio- and stereoselectively.

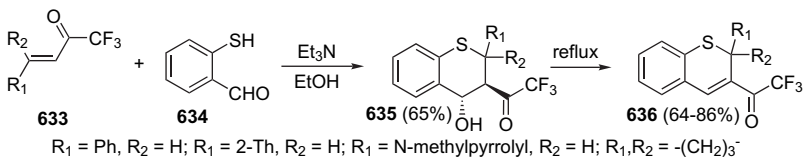
The reaction of ketones **633** with 2-mercaptobenzaldehyde **634** leads to the thiochromanes **635**, which can be easily transformed into the 2*H*-thiochromenes **636** by heating the reaction mixture. The intermediate thiochromanes **635** were isolated only in the case of the CF_3 enone having a phenyl substituent. It was established that all substituents in this compound have an equatorial orientation.[177]

The trifluoromethylketone **154** can be applied for the preparation of electrophilic reagent **637**, the vinylogous Vilsmeier-type reagent. The complex **637** can be used for different purposes. As an example, the reaction of 2,2′-bis-indolyl **638** with **637** leads to the formation of a pentacyclic compound **639**.[218] The reaction of *N*,*N*′-dipyrrolmethane **640** with **637** after alkaline treatment of the reaction mixture leads to aldehyde **641** formation.

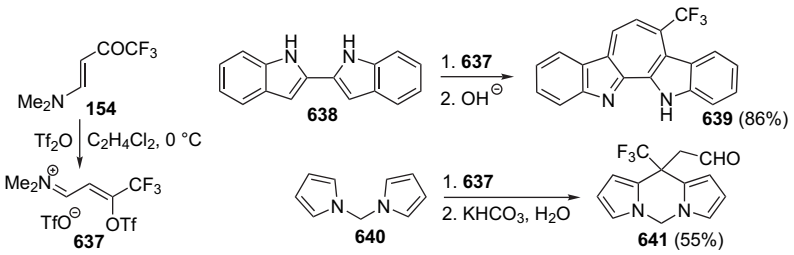
The benzimidazolyl and benzoxazolyl CF_3-ketones **642** and **643** were obtained in high yields in the reaction of *o*-phenylendiamine **118** or *o*-aminophenol **125** with β,β-dibromoketone **13**.[196]

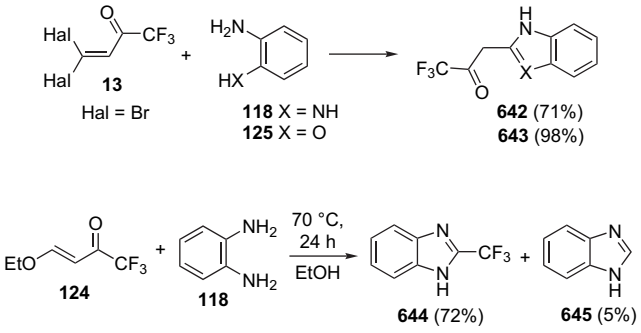
2-Trifluoromethylbenzimidazole **644** was prepared by the reaction of CF_3-enone **124** with *o*-phenylenediamine **118**.[44] *o*-Phenylenediamine **118**, the structure of which should favor 1,2-addition, reacted smoothly with **124**. It did not, however, give the corresponding 2,3-diazepine derivative. Instead, the products were 2-trifluoromethylbenzimidazole **644** and benzimidazole **645**.





R1 = Ph, R2 = H; R1 = 2-Th, R2 = H; R1 = N-methylpyrrolyl, R2 = H; R1,R2 = -(CH2)3-

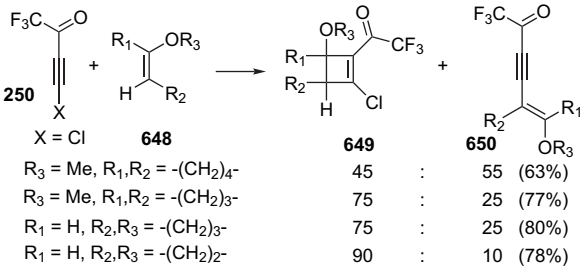




4.2. Synthesis of carbocyclic systems

4.2.1. [2+2] Addition reactions. It was found that bromotrifluoroacetylacetylene **257** reacts unexpectedly with alkenes **646a–h** to give the [2+2] cycloaddition adducts.[94] The reaction leads to the formation of trifluoroacetyl derivatives of cyclobutene **647a–h**. These products were obtained in moderate-to-high yields. Noteworthy is the fact that [2+2] addition is the anomalous pathway, because it is forbidden according to Woodward–Hoffman orbital symmetry rules. This is explained by high electronegativity of the trifluoromethyl group. In addition, the formation of ene-reaction products is observed as by-products.

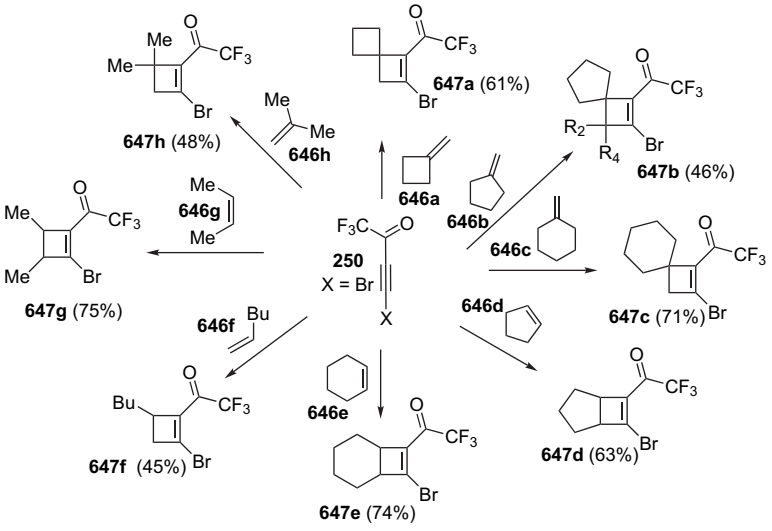
Analogously, chlorotrifluoroacetylacetylene **250** (X=Cl) [2+2] addition reactions with various vinyl ethers **648** have been carried out.[219] The reactions lead to the formation of mixtures of [2+2] cycloadducts **649** and ene-reaction products **650**. A method for isolation of the cycloaddition product **649** was proposed based on a selective low-temperature bromination of **650**.

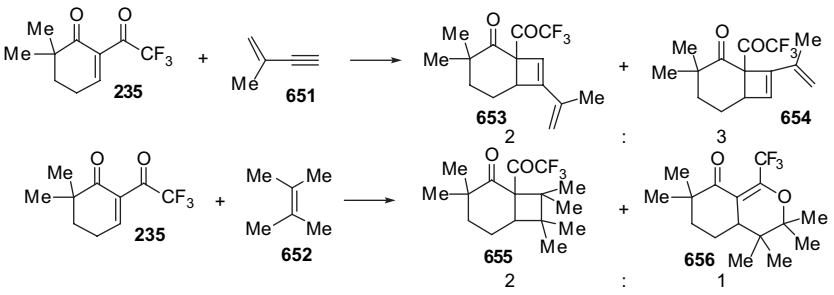


R_3 = Me, R_1,R_2 = -$(CH_2)_4$-	45	:	55	(63%)
R_3 = Me, R_1,R_2 = -$(CH_2)_3$-	75	:	25	(77%)
R_1 = H, R_2,R_3 = -$(CH_2)_3$-	75	:	25	(80%)
R_1 = H, R_2,R_3 = -$(CH_2)_2$-	90	:	10	(78%)

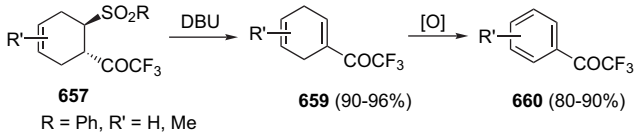
The photo-induced cyclization of vinylacetylene **651** or tetramethylethylene **652** with diketone **235** was studied.[86] The reaction was carried out until the conversion level of the starting enone became 40–45%. Mixtures of products **653**, **654**, **655**, and **656** were obtained. The individual compounds can be isolated using column chromatography. The yields of the products are not given.

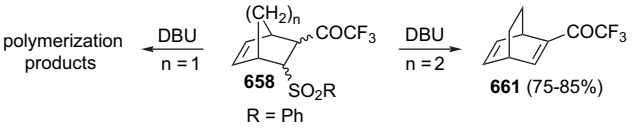
4.2.2. [4+2] Addition reactions. Due to the presence of two EWG groups, ketones **169** can also be used as dienophiles in Diels–Alder reactions.[220] The reaction of ketone **169** having R=Ph with various dienes leads to the corresponding cyclohexenes **657** and bicycles **658** in high yields. The regio- and stereochemistries of compounds **657** and **658** were studied in detail. The elimination of sulfinic acids from the products of the Diels–Alder reactions **633** under treatment with DBU followed by oxidative aromatization of the 1,4-hexadienes **659** leads to the benzenes **660**. Total resinification was observed for the reaction of

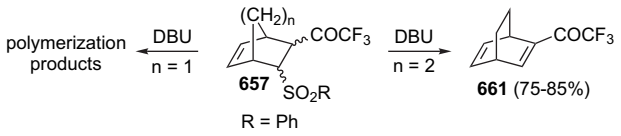




bicyclo[2.2.1]heptane derivatives **658**. Nevertheless, in the case of bicyclo[2.2.2]octane derivatives **658**, the corresponding dienes **661** were prepared in high yields.





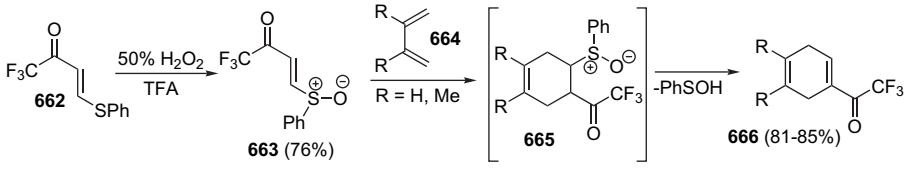


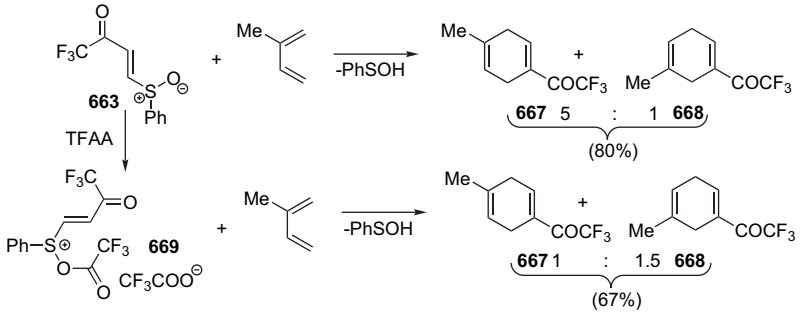
The enone **663** obtained by oxidation of the corresponding sulfide **662** with the equivalent of 50% hydrogen peroxide in trifluoroacetic acid solution was used as the dienophile.[221] The compound **663** reacts readily with dienes **664** forming the intermediate adducts **665**, which spontaneously eliminate the phenylsulfenic acid forming hexadienes **666** in high yields.

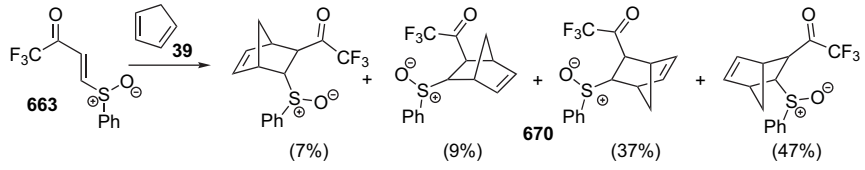
The reaction of ketone **663** with isoprene proceeds stereoselectively forming a mixture of isomers **667** and **668** in a 5:1 ratio. Activation of **663** by treatment with TFAA leads to the dienophile **669**, which gives the opposite stereoselectivity—the ratio of isomers **667**/**668** becomes 1:1.5.[221]

The reaction of cyclopentadiene **39** with ketone **663** is not selective, forming four isomers of the adduct **670**. The individual stereoisomers were not separated. The stereochemistry of the adducts **670** is discussed in detail.[221] In this case, elimination of a sulfinyl group did not take place. The results were explained by analyzing the theoretical calculations.

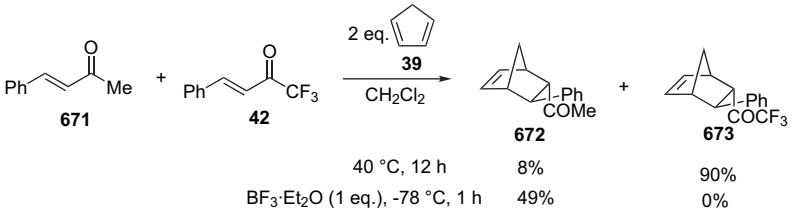
The influence of Lewis acids on the electrophilicity of carbonyl groups was investigated.[222] It is well known that the coordination of carbonyl groups to Lewis acids exerts a dramatic effect on the rates and selectivities. While much research into Lewis acid-mediated stereoselective or regioselective reactions has been carried out, less attention has been paid to chemoselective reactions in the presence



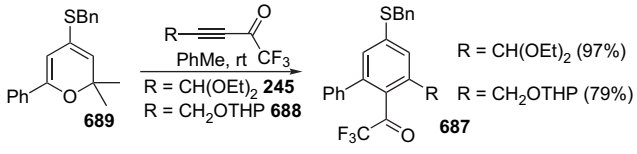


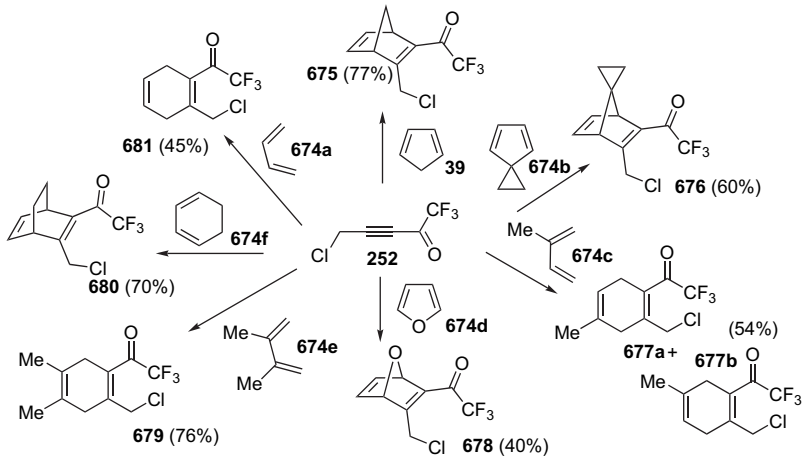


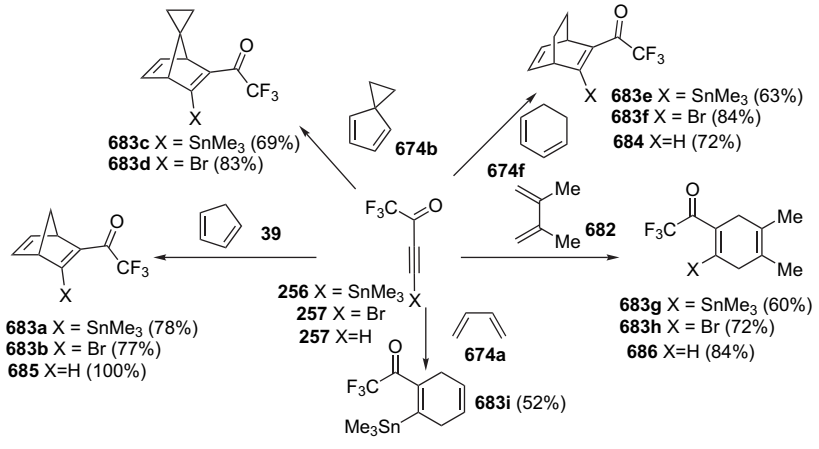
of Lewis acids. It is evident that the more electrophilic aldehydes and ketones react with nucleophiles much faster than the less electrophilic analogs. It was found that the reverse is the case for Lewis acid-mediated reactions: the more electrophilic aldehydes and ketones react much slower than the less electrophilic analogs in the presence of Lewis acids, with a chemoselectivity that is not attainable under ordinary conditions. A similar observation was also made in a Diels–Alder reaction. The thermal reaction of a 1:1 mixture of ketones **671** and **42** with cyclopentadiene **39** at 40 °C afforded the [4+2] cycloadduct **673** derived from **42** in 90% yield, along with a small amount (8%) of **672** derived from **671**. This is also an expected result, since **42**, which has an electron-withdrawing CF_3 group, is a better dienophile than **671**. The $BF_3\cdot Et_2O$-mediated reaction at −78 °C, however gave **673** as the sole product in 49% yield.



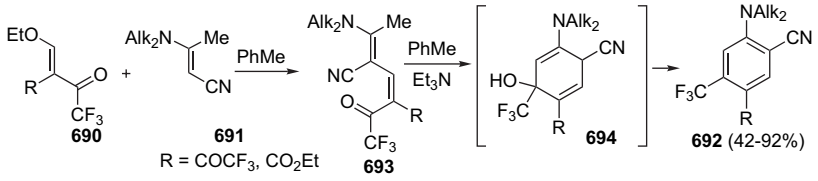
The Diels–Alder reaction of chloromethyltrifluoroacetylacetylene **252** with several dienes **39** and **674a–f** was studied.[93] Various carbocyclic compounds **675–681** containing CF_3 group were obtained in good yields.



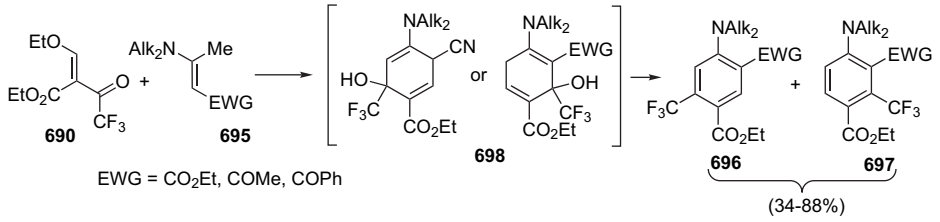




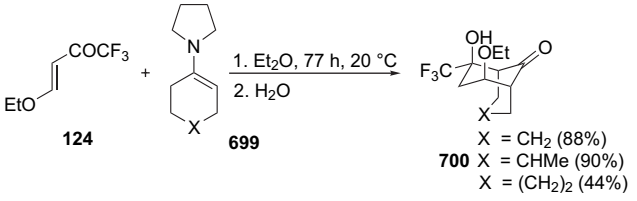
4.2.3. Michael-based cyclizations. Trifluoromethyl-substituted arenes can be synthesized using the reaction of alkoxyenones **690** with various enamines **691** containing an EWG group in the β-position.[225] In one example, the reaction of ketones **690** with nitriles **691** allows the preparation of anilines **692**. In the case of the compound having R=$COCF_3$, the cyclization and subsequent aromatization of dienones **693** proceed through the transition state **694** spontaneously. In the case of the compound with R=CO_2Et, the presence of triethylamine catalytic amounts is needed.



The formation of two regioisomers ('normal' **696** and the isomer **697**) is observed in the case of the reaction of ketone **690** with enamines **695** containing an ethoxycarbonyl, acetyl or benzoyl group instead of a cyano group.[225] The ratio of the products **696** and **697** varies over a wide range, but compound **696** predominates. The mechanism of formation of both products through the transition product **698** is reviewed in detail.



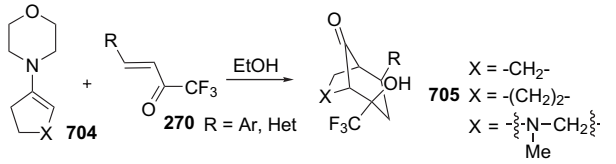
Work devoted to the construction of bicyclic systems containing trifluoromethyl substituents has been reported. The reaction of ketone **124** with 1-pyrrolidinocyclohexene **699** (X=CH_2) leads to the formation of bicyclo[3.3.1]nonane-9-one derivative **700** (X=CH_2) as the single diastereomer. The analogous products were obtained in the case of the reactions of the ketone **124** with 1-pyrrolydino-4-methylcyclohexene and 1-pyrrolidinocycloheptene.[226]



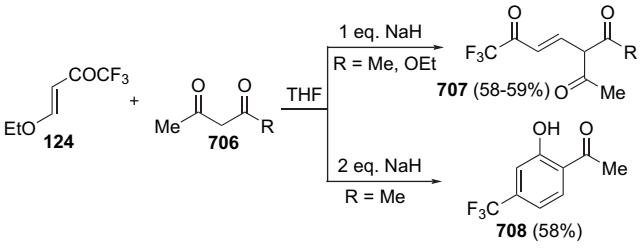
Similarly, the ketone **124** reacts with enamines of non-cyclic ketones, e.g., **701**.[226] The cyclohexanone **702** obtained can be further dehydrated into 2,6-dimethyl-3-trifluoromethylphenol **703**.

A similar reaction of enamines **704** with CF_3-enones **270** having aryl- and hetaryl substituents in the β-position was studied.[227] The corresponding bicyclic hydroxyketones **705** were obtained as a single diastereomer. The axial orientation of the hydroxy and aryl groups and the equatorial orientation of the CF_3 group was established using X-ray analysis.

The reactions of enone **124** with 1,3-dicarbonyl compounds **706** were studied. In addition to the previously

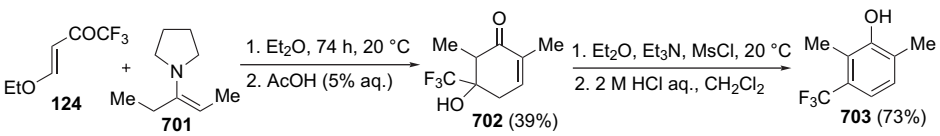


mentioned preparation of pyridine derivatives, the formation of primary substitution products **707** and the preparation of *o*-hydroxyacetophenone derivative **708** were demonstrated.[162]

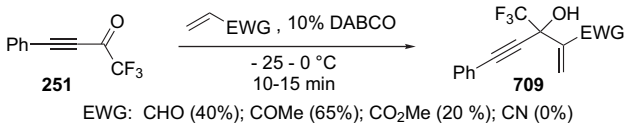


4.3. Synthesis of alicyclic compounds

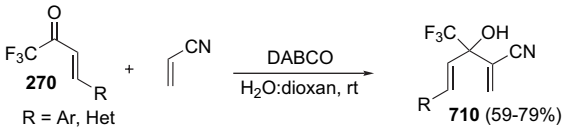
4.3.1. Reactions with C- and P-nucleophiles. The Baylis–Hillman reaction for acetylenic CF_3-ketone **251** with acrolein, methyl vinyl ketone, methyl acrylate, and acrylonitrile



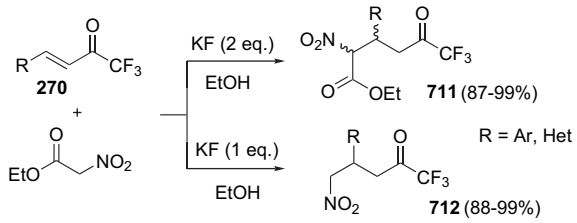
was studied.[228] In the case of acrylonitrile, the target product has not been isolated. For the rest of the substrates, the corresponding products **709** were obtained in moderate yields.



The same reaction was studied for the CF_3-enones **270** containing aryl substituents in the β-position.[229] Methyl acrylate, ethyl acrylate, methyl vinyl ketone, acrolein, phenyl vinyl sulfone, and acrylonitrile were studied as the activated alkenes. The reaction proceeds as a 1,2-addition of anion generated from the activated acrylonitrile to the carbonyl group of the CF_3-ketone while using DABCO and acrylonitrile. The products of acrylonitrile 1,2-addition **710** were obtained in good yields. In the case of ketones containing EtO and Me_2N groups only polymerization was observed and no target product was isolated. For the other activated alkenes, no reaction during a period of several months was observed.



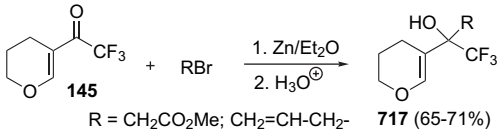
The reaction of CF_3-enones **270** containing various aryl substituents in the β-position with nitroalkanes was studied.[230] It was found that the reaction of α,β-unsaturated trifluoromethylketones **270** with ethyl nitroacetate proceeded in the presence of calcinated potassium fluoride (2 equiv) as the base in ethanol solution at room temperature to give the Michael adducts **711** in almost quantitative yields. Unexpected results were obtained while carrying out the reaction in aqueous ethanol in the presence of 1 equiv of KF. Instead of the Michael adduct, the product of the reaction was the corresponding CF_3-γ-nitroketone **712** and spontaneous hydrolysis and decarboxylation reactions had taken place. The reaction was carried out with several α,β-unsaturated trifluoromethylketones and excellent results were obtained, the yields of the nitroketones **712** being almost quantitative. Therefore, the esters **711** and the unsubstituted ketones **712** have been prepared from the same reagents. Noteworthy is the fact that the corresponding CF_3-γ-nitroketone **712** was obtained only in the case of CF_3-enone containing a Ph substituent **270** (R=Ph) using the reaction with nitromethane.



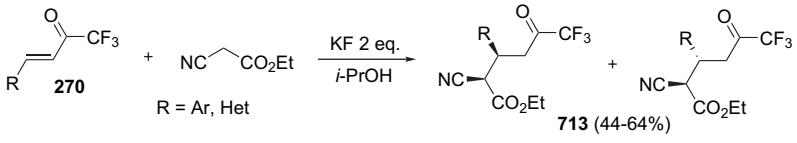
The reaction of CF_3-enones **270** with ethyl cyanoacetate has been studied.[231] Calcined potassium fluoride in *i*-propanol was used as the base. The reaction proceeds as a conjugated addition and the corresponding Michael adducts **713** were obtained in moderate yields. These compounds were formed as a mixture of diastereomers in approximately a 1:1 ratio. All attempts to perform the cyclization of the adducts **713** failed.

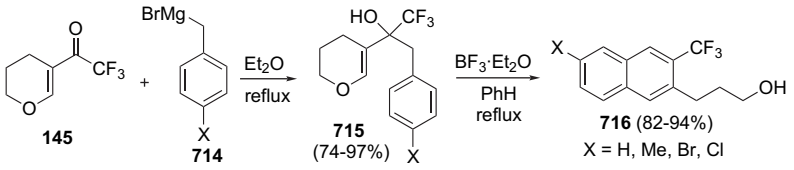
The reaction of enone **145** with benzylic Grignard reagents **714** in diethyl ether solution proceeds as a 1,2-addition,[232,233] forming the corresponding alcohols **715**, which can be transformed into the trifluoromethylnaphthalenes **716** in one step.[234] Aryl and alkyl Grignard reagents give in a opposite manner the 1,4-adducts.[235] The analogous reaction of enone **333** with **714** proceeds non-selectively, and products similar to **715** were obtained in lower yields. Nevertheless, these products can also be transformed into the corresponding trifluoromethylnaphthalenes **716**.[234]

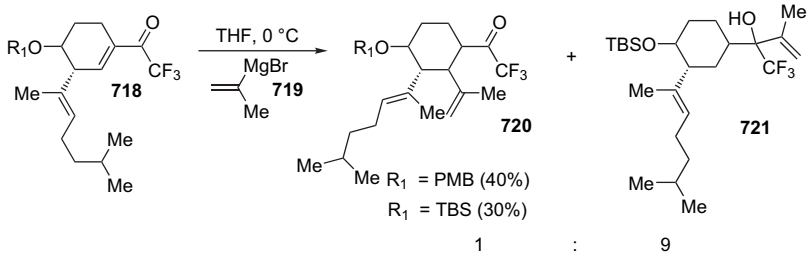
The reaction of cyclic enone **145** with organozinc reagents was also studied.[236] The reaction proceeds as a 1,2-addition, forming, similar to **715**, allylic alcohols **717** in good yields.



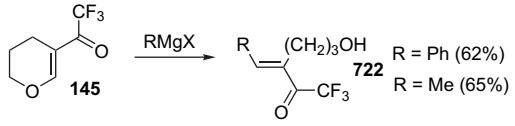
The reaction of ketones **718** with vinyl Grignard reagent **719** was carried out. Depending on the protective group, the reaction proceeds as a 1,4-conjugate addition or a mixture of 1,4-addition products **720** and 1,2-addition products **721** are formed.[75] In both cases, the yields of products are not high.





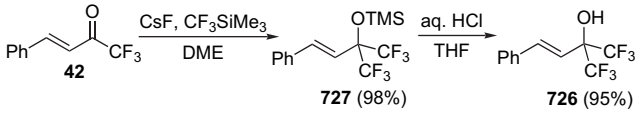


The reactions of 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran **145** with various nucleophiles have been studied.[52] The ketone **145** reacts readily with Grignard reagents to give the ring-opened products. The corresponding alcohols **722** were obtained in good yields.



A 1,3-strain has been recognized as a major factor determining the stereochemical pathway of reactions in both cyclic and acyclic systems. The different course of addition of Grignard reagents to the ketone **386** where ring opening affords products, thus exposing a stereochemical control of A 1,3-strain, is reported.[237] Reaction of ketone **386** with arylmagnesium bromides gave diols **723** as the mixture of two diastereomers. The structure of the crystalline diastereomer of diol **723** (Ar=4-MeC_6H_4) was determined by single crystal X-ray diffraction. When the reaction is conducted with 3 equiv of 4-tolylmagnesium bromide at −35 °C the ketone **724** can be isolated in good yield. By effecting the reaction at 0 °C, it is possible to isolate the aldehyde **725** in low yield.

Allylic alcohols are particularly useful intermediates for the synthesis of biologically active compounds. The trifluoromethylation reaction has been extended to the facile synthesis of *trans*-trifluoromethyl allylic alcohol **726** in excellent isolated yields by the CsF-catalyzed nucleophilic trifluoromethylation of enone **42** with TMS-CF_3.[238] Initially, a study was carried out on the optimization of the reaction conditions. Using the optimized reaction conditions, trans enones were reacted with TMS-CF_3 in the presence of catalytic amounts of CsF to give the corresponding trifluoromethyl silyl ethers **727**, hydrolysis of which with 6 N HCl at room temperature formed the trifluoromethyl allylic alcohols **726**. In the case of ketone **42**, the yields were almost quantitative.

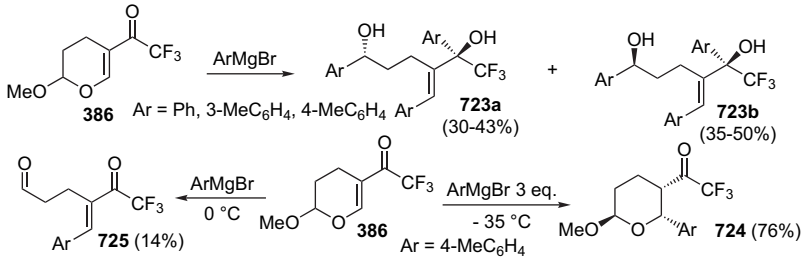


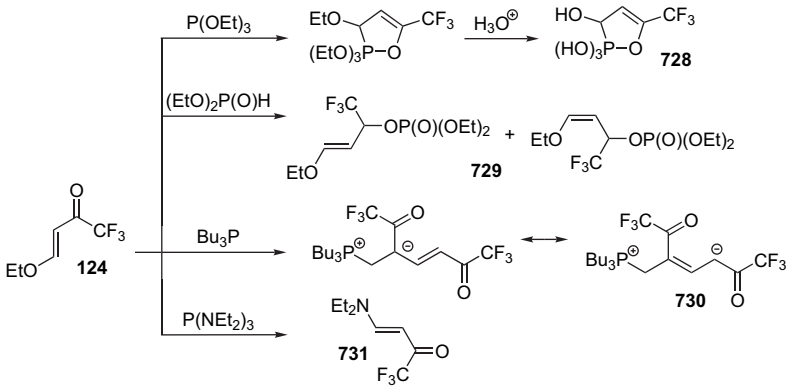
The reaction of CF_3-enone **124** with five different phosphorous nucleophiles was studied.[239] In the case of triethyl phosphate, the oxaphospholene **728** is formed. In the case of $(EtO)_2P(O)H$, the oxaphospholene initially formed underwent ring opening and rearranged to a diethyl allyl phosphate **729** mixture. In the reaction of Bu_3P with **124**, the initially formed anion attacked another molecule of **124** and finally gave the product **730**. A stronger nucleophile, $(Et_2N)_3P$, gave 4-(diethylamino)-l,l,l-trifluoro-3-buten-2-one **731** via nitrogen or phosphorus attack on the β-carbon atom of **124**. The less reactive nucleophile Ph_3P did not, however, react with **124**, even at higher temperatures and for longer reaction times.

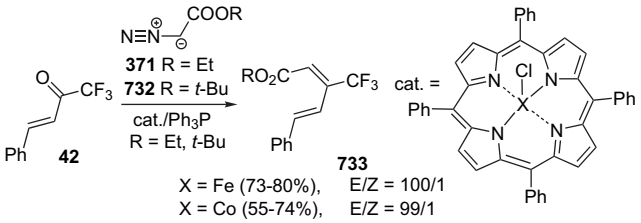
4.3.2. Olefination of CF_3-enones. α,β-Unsaturated β-trifluoromethyl esters have found numerous applications in organic, materials, medicinal, and agricultural chemistry, owing to their unique physical, chemical, and biological properties. Huang et al. have investigated[240,241] olefination reactions of various carbonyl compounds using alkyl diazoacetates **371** and **732** in the presence of Fe and Co porphyrin complexes. These porphyrin derivatives are efficient and versatile catalysts for the selective olefination of a variety of carbonyl compounds including aldehydes and activated and inactivated ketones with diazo compounds. In the case of CF_3-enone **42**, the corresponding alkenes **733** having an *E*-configuration are formed in good yields.

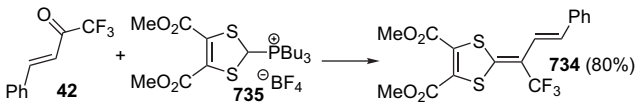
The same ketone **42** was converted into the diene **734** using a Wittig reaction with complex phosphorus ylide **735**.[242] The corresponding CF_3-diene **734** was prepared in high yield.

The application of CF_3-enone **124**, its α-bromo derivative **222** and α-phenyl-substituted ketone **736** for the synthesis of various CF_3-substituted derivatives of phthalic **737**, **741**,



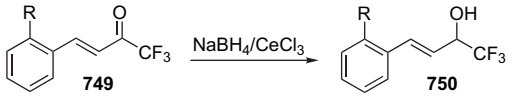






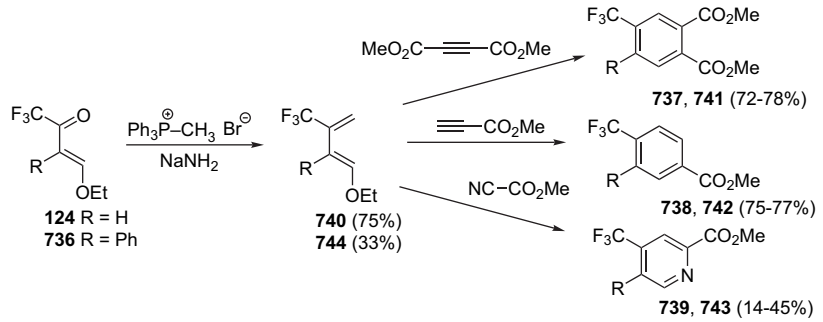
747, benzoic **738**, **742**, **745**, **746**, and picolinic acids **739** and **743** was described.[243] The method is based on the conversion of CF_3-enones into the conjugated dienes **740**, **744**, and **748** using Wittig reactions and causing these dienes to react with the corresponding dienophiles.

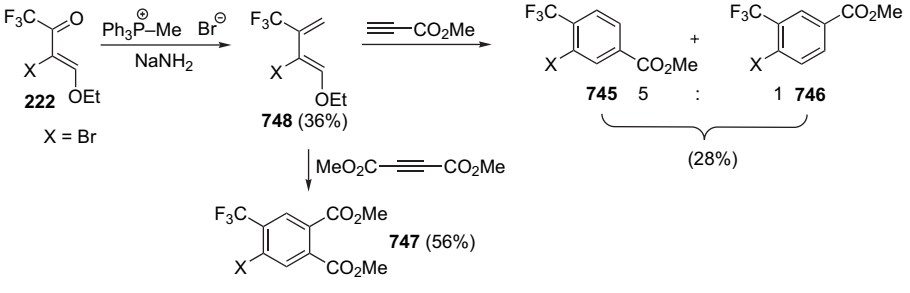
4.3.3. Reduction reactions of CF_3-enones. For several CF_3-enones **749** having a β-aryl substituent, the selective reduction of the carbonyl group has been performed.[244] As the reducing reagent, sodium borohydride in the presence of cerium(III) chloride was used. The corresponding allylic alcohols **750** were obtained in high yields.



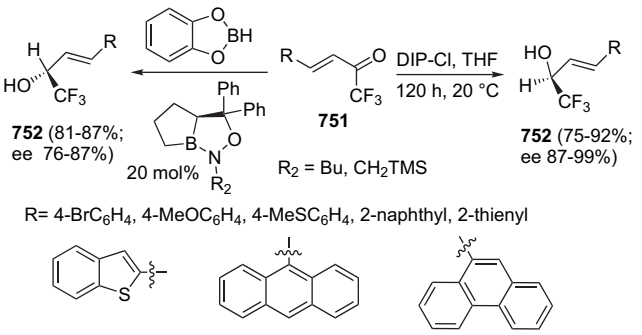
R = H (99%)
R = Me (90%)
R = OMe (75%)
R = OCH_2OMe (87%)

The enantioselective reduction of enones **751** proceeds with the formation of allylic alcohols **752** as the only products.[245] The highest enantioselectivity was obtained in the case of DIP–chloride. This reagent allows the preparation of the alcohols **752**, having an (*S*)-configuration. The configuration was established using X-ray analysis data for compound **752**, where R=4-BrC_6H_4, as well as using ^{19}F NMR

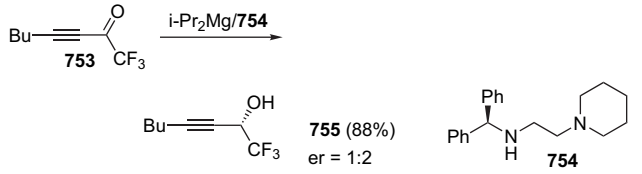




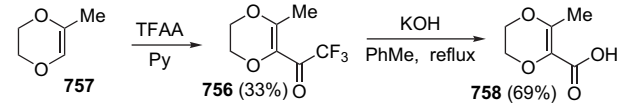
spectroscopy data of (*S*)-MPTA derivatives of alcohols **752**. The application of a reducing reagent based on a mixture of catecholborane with the 20 mol % of substituted oxazaborolidine additive allows the synthesis of allylic alcohols **752** having an (*R*)-configuration, although the optical purity is lower than in the case of DIP-chloride application.



Using the example of acetylenic ketone **753**, the possibility of chiral carbonyl group reduction was demonstrated.[246] A chiral magnesium amide was used as the reducing agent. This reagent was generated in situ from di-*i*-propylmagnesium and the chiral amine **754**. Despite the high ee ratio obtained in the case of non-fluorinated ketones, this system showed poor results in the reduction of the acetylenic CF_3-ketone—the high yield for the target propargyl alcohol **755** was 88%, although the ratio of enantiomers was only 1:2.



4.3.4. CF_3 group elimination reactions. The work of Dekeyser and Davis[247] is devoted to the synthesis of fungicidal carboxine analogs. The haloform reaction was carried out for cyclic α,β-dialkoxy-CF_3-enone **756** obtained by trifluoroacylation of 2-methyl-5,6-dihydrodioxine **757**. The product of this reaction is 3-methyl-5,6-dihydrodioxine-2-carboxylic acid **758**. The reactions described provide an example for the selective introduction of a carboxylic group using a trifluoroacylation/basic hydrolysis sequence.



5. Conclusions

Summarizing the facts given in this review, it might be concluded that elaboration of new of methods for the preparation of α,β-unsaturated trifluoromethylketones should be continued, although the trifluoroacylation of activated alkenes remains the most applicable method. The synthesis of some derivatives is hard and challenging work, but, nevertheless these compounds possess very high synthetic potential as molecular building blocks containing the trifluoromethyl group. α,β-Unsaturated trifluoromethylketones are widely used, especially in the synthesis of heterocyclic compounds. The application of these very useful molecular building blocks is, however, not restricted by this area.

The peculiarities of α,β-unsaturated trifluoromethylketones are their high reactivity in the reactions with nucleophiles, as well as the high chemo-, regio-, and stereoselectivity in these reactions. The distinctive feature is the stability of the *gem*-hydroxy-trifluoromethyl fragments, sometimes very resistant to the action of dehydrating agents. It was demonstrated that *gem*-diol fragments, containing a trifluoromethyl group in the α-position, are also very stable.

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