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Synthesis of Monotrifluoromethyl-Substituted Saturated Cycles

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1. Introduction

Cyclic compounds including aromatic analogs form the backbone of important molecules of life and a framework on which bioactive compounds are based. Introduction of a trifluoromethyl group into cyclic compounds especially at a strategic position of drug molecules has become an important aspect of pharmaceutical research owing to the unique physical and biological properties of fluorine. The steric requirement of the fluorine atom resembles that of hydrogen (van der Waals radii: CF_3=1.35 Å versus CH_3=1.29 Å). Thus substitution of a methyl by a trifluoromethyl group in a drug candidate usually allows the trifluoromethylated analog to be comparable in size and follow similar drug–protein interactions of the parent methyl compound. However, the strong covalent bonding of the C–F bond (116 kcal/mol) versus that of the C–H bond (100 kcal/mol)[1] can often avoid unwanted metabolic transformations.

The high electronegativity of fluorine enables a trifluoromethyl group to decrease the electron density and the basicity or enhance the electrophilicity of the neighboring functional groups within a molecule. In many systems, the substitution by a trifluoromethyl group of the methyl group results in added lipophilicity (π_{CF3}=1.07 versus π_{CH3}=0.5),[2] which may lead to easier absorption and transportation of the molecules within biological systems and thereby improve the overall pharmacokinetic properties of drug candidates.

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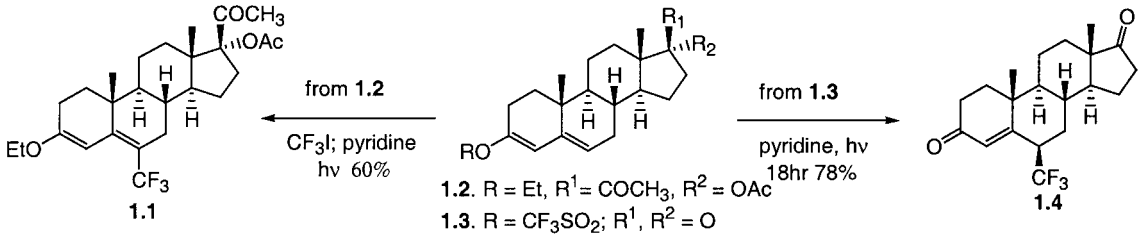


Scheme 1.

There have been several recent reviews[3,4] and books[5–8] focusing on several different aspects of organofluorine chemistry. One notable review by Resnati[4] contains an extensive list of references to the early organofluorine review literature. An excellent monograph for the organofluorine specialist covering recent developments in the organofluorine chemistry field was published in 1999. This book, edited by Soloshonok,[9] describes the rapid growth in asymmetric synthesis of organofluorine compounds and includes some literature citations relating to mono-CF_3-substituted compounds.

Although trifluoromethyl derivatives of aromatic compounds are well documented,[10,11] those pertaining to saturated ring systems are less well described.[12] It is toward these less well documented rings that this Tetrahedron Report is addressed. The preparation of monotrifluoromethyl substituted saturated cyclic molecules broadly falls into two classes. The first involves direct introduction of a CF_3-group into a non-fluorinated ring system, and the second draws from the CF_3-substituted reagent pool which requires the CF_3-group being incorporated before the ring construction of the cyclic system.

Rather than attempting a comprehensive survey, the present review serves to illustrate some practical methods, with particular emphasis on methods that have been developed in the past decade, for the selective introduction of a trifluoromethyl group into saturated carbocyclic or heterocyclic molecules. This review will be categorized according to the types of trifluoromethylated reagents used as far as possible. Many of the assignments are therefore inevitably arbitrary. The coverage in this review is limited to the synthesis of compounds in which a single trifluoromethyl group is incorporated on to a saturated carbon on the cycles.

2. Direct Trifluoromethylation of Non-Fluorinated Non-Aromatic Cycles

Direct introduction of the CF_3-group into aliphatic molecules is a powerful technique, particularly when used in the late stages of a synthetic sequence, and this technique has been widely used for the synthesis of trifluoromethylated acyclic compounds.[3,10,13] The following section will illustrate the use of some trifluoromethylating reagents for direct trifluoromethylation of non-fluorinated non-aromatic cyclic compounds. These CF_3-containing reagents may be considered as either nucleophilic, electrophilic, radical or carbene sources of CF_3-groups.

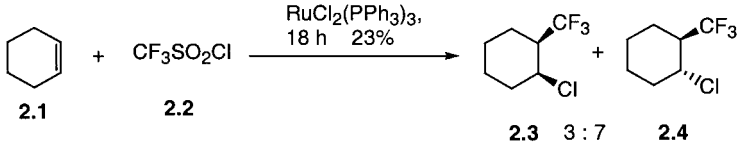
2.1. Trifluoromethyl groups introduced by radical reactions

Early work by Godtfredsen[14] on steroidal systems showed that a CF_3-group could be introduced into a steroidal dienol ether **1.2** using iodotrifluoromethane in pyridine, photochemically, to afford a CF_3-substituted dienol ether **1.1** in 60% yield (Scheme 1). More recently, Taguchi and coworkers[15] have used the method on a decalin structure for the synthesis of *s-trans* fixed retinal analogs. A related finding by Elliott and coworkers[16] concerned a dienyl enol triflate **1.3** of a steroidal system. Irradiation of the dienyl enol triflate **1.3** in the absence of CF_3I gave a 6β-CF_3-α,β-unsaturated ketone **1.4**. A radical process was suggested by Elliott for the fragmentation–rearrangement reaction.

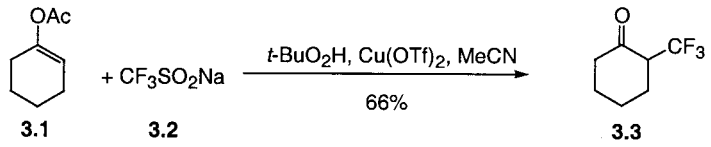
Trifluoromethanesulfonyl chloride has been used to introduce CF_3-groups onto olefin compounds (see Scheme 2). Trifluoromethanesulfonyl chloride **2.2** and an alkene in the presence of a ruthenium(II) chloride complex led to loss of SO_2 from the sulfonyl chloride and addition of a CF_3-group and a chlorine to the olefin. Four examples of this reaction relating to cyclic olefins were reported by Kamigata.[17] A radical chain reaction mechanism was proposed to account for the observed products.

Sodium trifluoromethanesulfinate **3.2** has been reacted with cyclohexanone enol acetate **3.1** in the presence of *t*-butyl hydroperoxide, copper(II) triflate in acetonitrile to give 2-trifluoromethylcyclohexanone **3.3**. A copper(I)/copper(II) redox system involving participation by trifluoromethyl radical was proposed as a plausible mechanism for the reaction[18] (see Scheme 3).

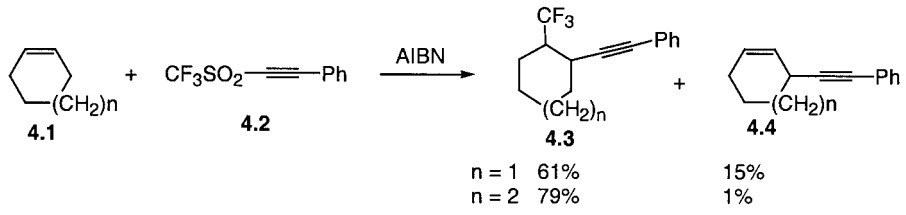
Fuchs and Gong[19] have developed a method for conjugate CF_3-alkynylation of olefins using acetylenic triflone **4.2** (see Scheme 4). A radical chain mechanism was proposed to



Scheme 2.



Scheme 3.



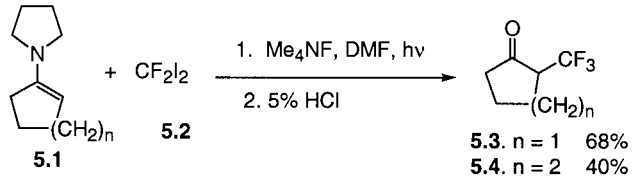
Scheme 4.

account for the observed products. The yields of adducts were dependent on the actual reaction time used, and the major by-products seen were derived from allylic hydrogen abstraction reactions.

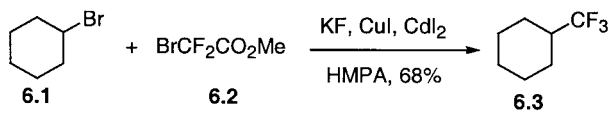
2.2. Trifluoromethyl groups introduced by difluorocarbene reactions

Chen[20] has developed a method that introduces a CF_3-group to pyrrolidine or morpholine enamines of a ketone by irradiation of difluorodiiodomethane and tetramethylammonium fluoride in DMF at 70°C to give, on work up, 2-trifluoromethylated ketones. The method was applied to enamines of cyclohexanone and cyclopentanone. A mechanistic scheme (Scheme 5) involving difluorocarbene was proposed to account for the observed reaction products.

A trifluoromethylation method[21] for saturated organic halides involving methyl bromodifluoroacetate in the presence of an equivalent of potassium fluoride, copper(I) iodide and cadmium iodide at 120°C in HMPA has been reported. In one case, cyclohexyl bromide was used as the saturated halide and the reaction run at 80°C. A 43% conversion of halide and 78% yield based on the conversion of the halide were obtained. The authors of the paper describe a mechanistic rationale invoking difluorocarbene (see Scheme 6).



Scheme 5.



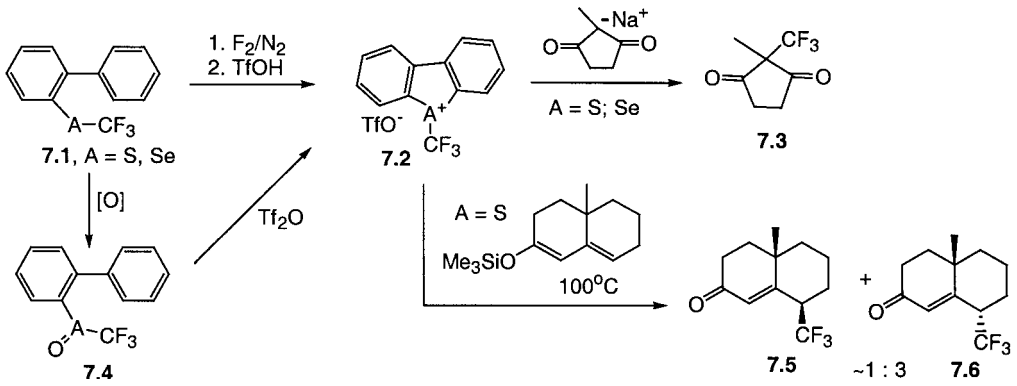
Scheme 6.

2.3. Trifluoromethyl groups introduced using electrophilic reagents

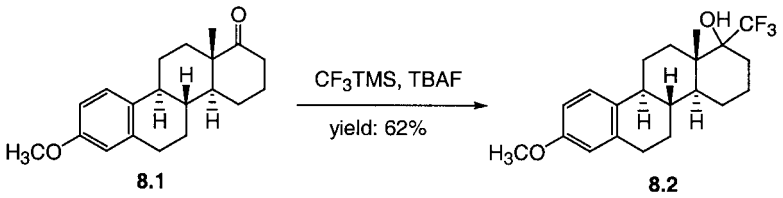
There have been few reports of developing reactions where a CF_3-group is introduced by an electrophilic reagent into an organic molecule. Umemoto and co-workers prepared (trifluoromethyl)dibenzothiophenium and (trifluoromethyl)-dibenzoselenophenium triflate salts **7.2** as electrophilic trifluoromethylating agents with various nucleophiles[22–24] ranging from sodium enolates of β-dicarbonyls, phenylacetylide, silyl enol ethers, enamines, aniline and thiolates (Scheme 7). Regio-, diastereo- and enantioselective trifluoromethylation may be achieved using boron-based Lewis acid reagents on enolate anions with the Umemoto sulfur and selenium trifluoromethylating agents.[25] The boron Lewis acid mediated reactions also allow the trifluoromethylation reaction to occur at lower temperatures in overall higher yields.

2.4. Trifluoromethyl groups introduced using nucleophilic reagents

Compared to the addition to a carbonyl group by simple alkyl groups using organometallic reagents, the direct introduction of trifluoromethyl halide to carbonyl compounds in the presence of a metal is more difficult and often ultrasound, electrolysis or use of metal complexes is required. Ruppert[26] reported the first synthesis of trifluoromethyltrimethylsilane (TFMTMS) but its use as a nucleophilic source of trifluoromethyl groups was later shown by Olah and Prakesh (Scheme 8).[27,28] TFMTMS with a catalytic amount of tetrabutylammonium fluoride (TBAF) adds a CF_3-moiety to carbonyl groups. Stahly and Bell[29] published similar findings on the trifluoromethyltriethylsilane and trifluoromethyltributylsilane reagents using a variety of bases and fluoride sources which added a CF_3-group to one of the two carbonyls of quinones. Sauvetre[30] also reported a similar observation with fluorotrialkylsilyl compounds and TBAF. Prakash[31] has also developed a one-pot procedure for the preparation of trifluoromethylated amides from ketones where the first formed CF_3 silyl-ether can undergo a Ritter reaction with acetonitrile and aqueous acid. Interestingly, β-amino ketones have been reported to react with TFMTMS without the need of fluoride catalysis for CF_3-addition to occur at the carbonyl group.[32]



Scheme 7.

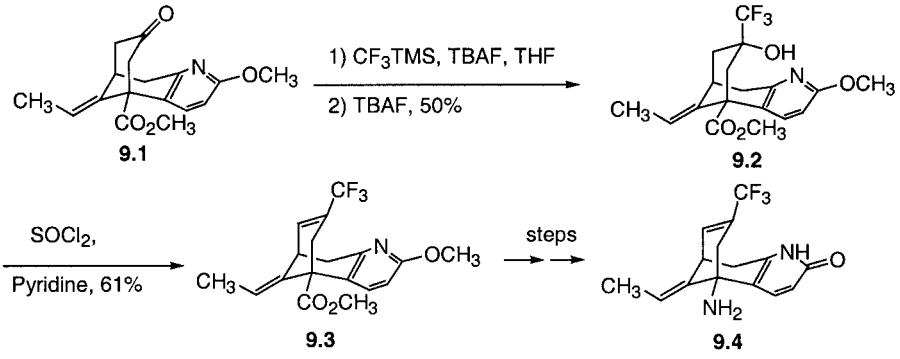


Scheme 8.

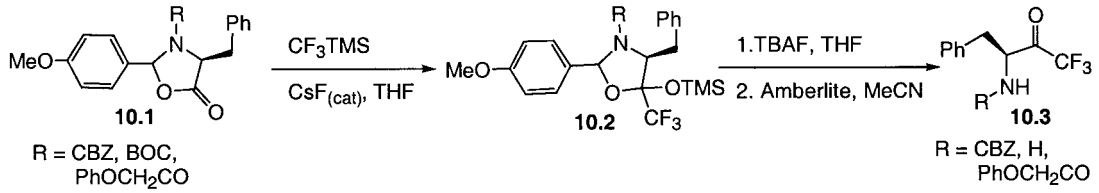
Further examples[33–35] of CF_3-addition to ketones and lactones using TFMTMS have been described. Terashima[36,37] used the fluoride-induced TFMTMS reaction in the synthesis of the trifluoromethylated Huperzine A analog **9.4** shown in Scheme 9.

Baldwin and Schofield[38–40] have used oxazolidin-5-ones **10.1** and TFMTMS with CsF catalysis to afford synthetically useful yields of trifluoromethyl substituted compounds **10.2** which served as precursors for trifluoromethylketone derivatives of amino acids **10.3** (see Scheme 10).

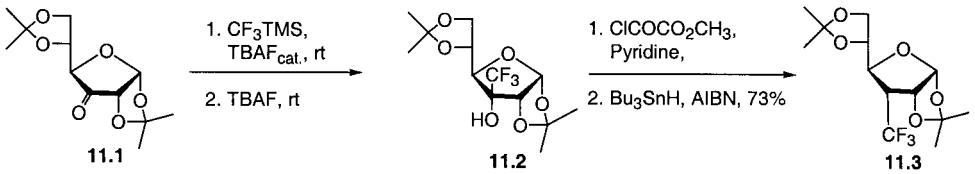
The reagent TFMTMS as a source of CF_3-groups has been used in synthesis of various trifluoromethylated sugars and deoxysugars.[41–45] A recent publication on synthesis of 3-deoxy-3-trifluoromethyl-D-ribose from an α-D-glucofuranose derivative involved a fluoride-catalyzed reaction of a ketone intermediate **11.1** with TFMTMS.[46] Deoxygenation at C-3 required a reduction of the methyloxalate ester derived from the secondary alcohol **11.2** and this led to a mixture of D-*ribo*- and D-*xylo*-derivatives **11.3** in the ratio of 98:2 (Scheme 11).



Scheme 9.



Scheme 10.



Scheme 11.

A classical method[12,47,48] for introduction of a CF_3-group is the use of a sulfur-based fluorinating agent to transform an acid functional group or an acid derivative into a trifluoromethyl group. An illustrative example of this method is shown in Scheme 12.[48]

3. Use of Trifluoromethylated Reagents as Synthetic Building Blocks

Chemical conversion of simple acyclic trifluoromethylated compounds into ring compounds is a useful strategy in preparation of trifluoromethylated saturated cycles and is more often suited for the synthesis of complicated molecules than the direct trifluoromethylation described above. These simple acyclic trifluoromethylated compounds are called CF_3-synthetic building blocks or CF_3-carrier reagents. This section is categorized according to the structures of the synthetic building blocks, most of which are trifluoromethylated olefins and carbonyl compounds.

3.1. Use of trifluoromethylated olefins

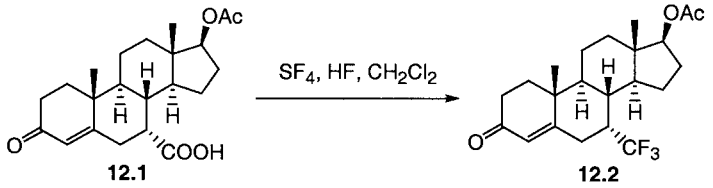
Most trifluoromethylated olefins discussed in this section possess a second electron-withdrawing group on the carbon–carbon double bond besides the trifluoromethyl group. Generally these olefins readily undergo Diels–Alder reactions or Michael addition reactions in an early stage of the reaction sequence for construction of the CF_3-substituted cycles. One reagent, 2-bromo-3,3,3-trifluoropropene is often converted into CF_3-substituted cycles by using it as a nucleophilic entity through its derived anion. Trifluoromethylated allylic alcohols are synthetically valuable and may be used in Claisen-type rearrangement reactions before the subsequent ring closure reaction that gives a CF_3-substituted ring.

3.1.1. From α,α-disubstituted olefins. 3,3,3-Trifluoropropene and its derivatives are useful trifluoromethyl-carrier reagents. The parent compound 3,3,3-trifluoropropene is itself a weak electrophile but introduction of another electron-withdrawing substituent at the α- or β-position decreases the LUMO energy level[49] and leads to reagents that have high reactivity as Michael acceptors with weak nucleophiles.

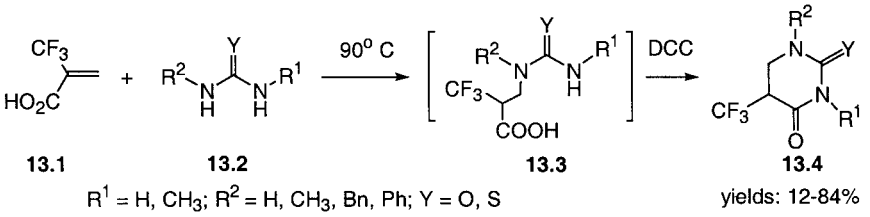
Michael addition of urea or *N*-substituted ureas and thioureas to 2-trifluoromethyl-2-propenoic acid (2-(trifluoromethyl)-acrylic acid) **13.1** on heating gave the corresponding 2-trifluoromethyl-3-ureidopropanoic acid **13.3** which was cyclized by treatment with dicyclohexylcarbodiimide (DCC) to give cyclic compounds **13.4**[50–52] (see Scheme 13).

Addition of water to 2-(trifluoromethyl)acrylic acid affords 3-hydroxy-2-trifluoromethylpropionic acid **14.2** in quantitative yield (Scheme 14). Kubota et al.[53] synthesized 3-trifluoromethyl-γ-butyrolactone **14.3** via a crossed Kolbe reaction of compound **14.2** with ethyl hydrogen malonate. The Kolbe reaction of the trifluoromethylated acid proceeded more smoothly than with 3-hydroxypropionic acid, thus implying that the α-trifluoromethyl group helps to facilitate the electrochemical cross-coupling reaction.

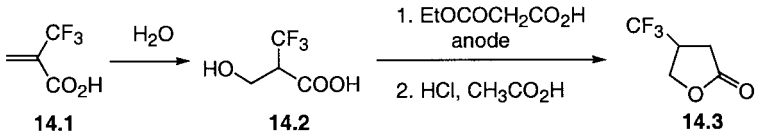
O'Hagan and coworkers[54] reported a single step procedure for the synthesis of 4-substituted 2-trifluoromethyl-γ-butyrolactones **15.3** and **15.4** by a photochemically induced addition of primary and secondary alcohols to 2-(trifluoromethyl)acrylic acid in the presence of benzophenone



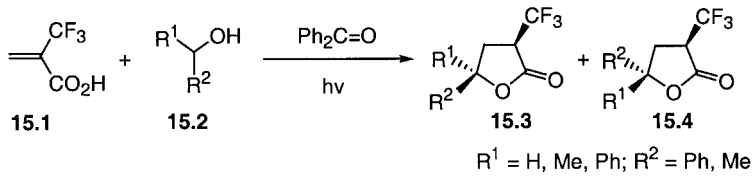
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

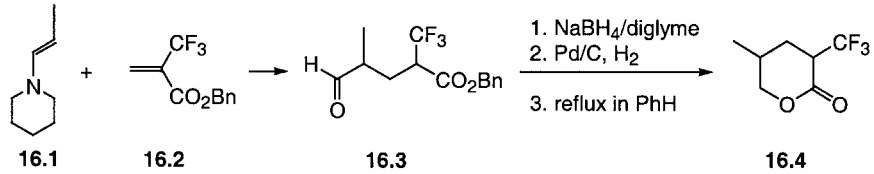
(Scheme 15). The diastereoisomers of the products formed can be separated by chromatography. The major isomers of the products have a *syn*-relationship between the trifluoromethyl group and the larger of the two substituents at C-4.

Kitazume and coworkers[49] described the Michael addition of piperidine enamine **16.1** to benzyl α-trifluoromethylacrylate **16.2** to give, on hydrolysis, Michael adduct **16.3** with 89:11 diastereoselectivity (Scheme 16). The adduct **16.3** was transformed in a three-step sequence to the corresponding trifluorinated lactone **16.4** in 53% yield. In the conversion of the 1,4-adduct **16.3** into the lactone **16.4**, the use of a protic solvent accelerates epimerization at the position C-2, while employment of an aprotic solvent leads to complete retention of the inherent stereochemistry generated in the first step.

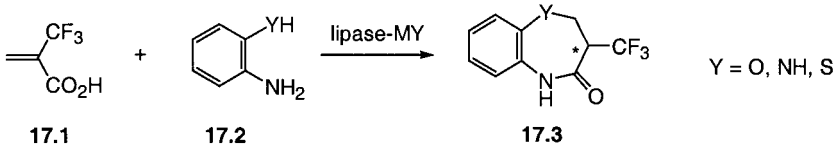
Kitazume et al.[55] have also described enzyme assisted Michael addition reactions of 2-(trifluoromethyl)acrylic acid. This approach has been applied to synthesis of optically active trifluoromethylated heterocycles via chiral Michael addition reaction. A bifunctional compound **17.2** is added to 2-(trifluoromethyl)acrylic acid in the presence of a lipase and the ensuing intramolecular condensation reaction of the first formed Michael adducts in situ leads to the asymmetric synthesis of the saturated heterocyclic ring (Scheme 17).

Trifluoromethylated olefins are of particular interest in synthesis of the trifluoromethylated cycles via Diels–Alder reactions and 1,3-dipolar cycloadditions. 2-(Trifluoromethyl)propenoic acid and its derivatives are more reactive as a dienophile than methacrylic acid itself owing to the presence of an extra electron withdrawing trifluoromethyl group. Substituted α-trifluoromethylpropenoic acid and its derivatives have been effectively used for the construction of cyclic quaternary carbons bearing a trifluoromethyl group.[56–59] Diels–Alder reaction of ester **18.1** with a methylated variant of Danishefsky diene **18.2** led to the 2-cyclohexenone **18.3**.[58] The α,β-unsaturated ketone **18.3** was taken through to trifluoro-β-cyclocitral **18.6** in several steps which involved a [2,3]-Wittig rearrangement en route for the introduction of an aldehyde group that is needed for the attachment of the side-chain. Thereafter, standard carotenoid chain-extension reactions on the aldehyde **18.6** introduced the side chain necessary for the completion of the synthesis of 16,16,16-trifluoro-retinal **18.7** (Scheme 18).

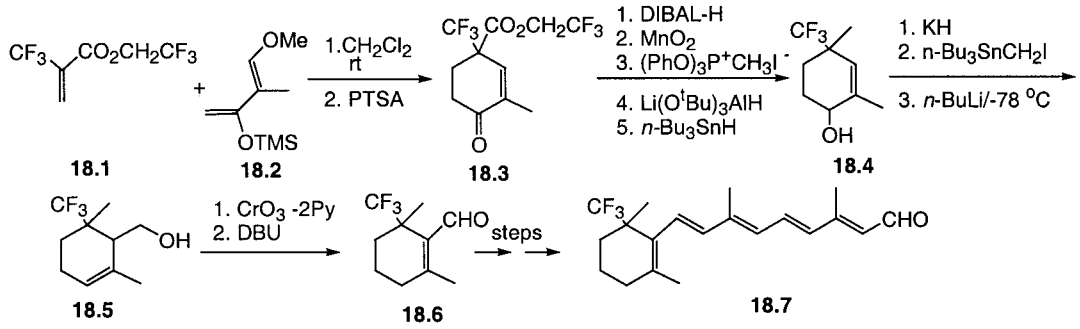
Taguchi and coworkers[60] used methyl 2-(trifluoromethyl)-propenoate in the preparation of angularly trifluoromethylated bicyclic compound **19.6** via a Diels–Alder reaction and an intramolecular Michael addition. Thus, the ring-forming reaction between methyl 2-(trifluoromethyl)propenonate **19.1** and Danishefsky diene **19.2** was followed by a three-step transformation to produce the key intermediate **19.4** in 89% yield over a four-step sequence. In two steps, **19.4** was converted into **19.5**. An intramolecular Michael addition of the methyl acetoacetate adduct **19.5** and



Scheme 16.



Scheme 17.

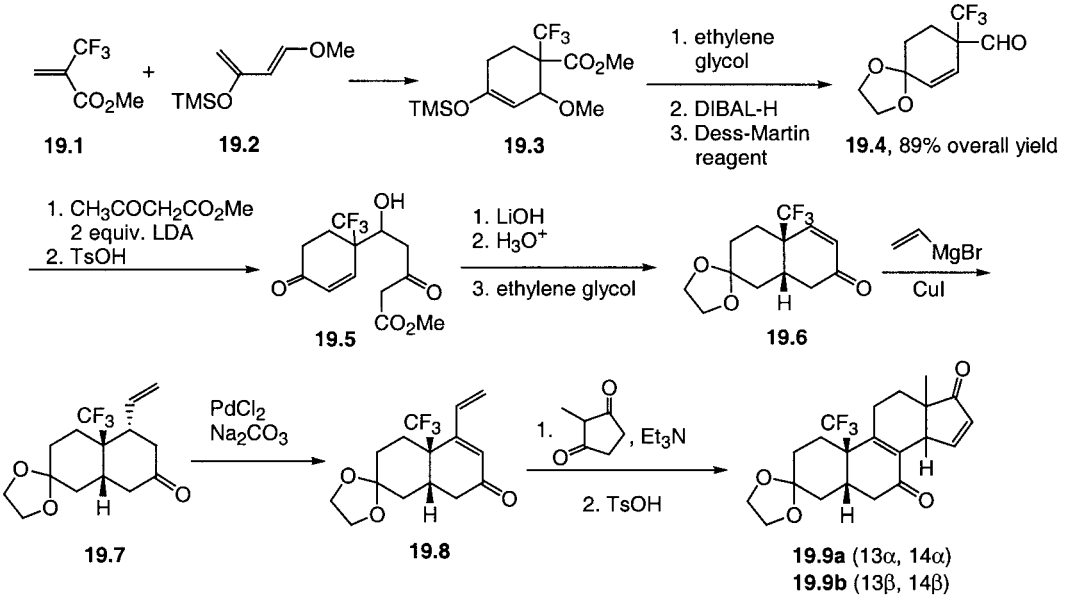


Scheme 18.

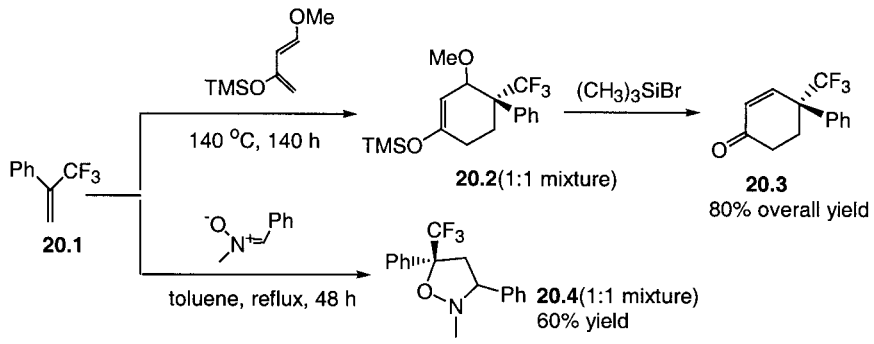
subsequent selective protection of the more reactive carbonyl group gave **19.6** in 83% yield as a single product. Bicyclic compound **19.6** was employed in a synthesis of a 19,19,19-trifluoromethylated steroidal system **19.9** where the trifluoromethyl group was placed at the steroid A,B-ring junction. The final compound **19.9** was obtained as a mixture of two diastereoisomers (Scheme 19).

Most trifluoromethylated olefins used in successful Diels–Alder and 1,3-dipolar cycloaddition reactions have at least one other electron withdrawing substituent present on the double bond apart from the trifluoromethyl group. Bonnet-Delpon et al.[61,62] described the electronic effect and steric effect of the CF_3-group on the course of cycloaddition reaction of trifluoromethylated alkenes. In α,α-disubstituted alkenes bearing a trifluoromethyl group solely as the electron withdrawing group, the electronic effect exerted by the CF_3-group can sufficiently lower the LUMO energy level to promote a cycloaddition to occur despite the steric hindrance. For instance, the reactivity of the α-trifluoromethylstyrene **20.1** is comparable to that of the 2-phenylacrylic acid in that both compounds react slowly with cyclopentadiene (Scheme 20). In cycloaddition reactions with nitrones, the reactivity of α-trifluoromethylstyrene **20.1** is similar to α-methylstyrene and this may indicate that the reaction occurs through different process: ($HOMO_{nitrone}$–$LUMO_{alkene}$) control is dominant for compound **20.1** while ($HOMO_{alkene}$–$LUMO_{nitrone}$) control occurs in the α-methylstyrene cyclization.[61]

Viehe and coworkers[63,64] have shown that 2-phenylthio-3,3,3-trifluoropropene **21.2**, its derived sulfoxide **21.5** and sulfone **21.8** are useful building blocks for the preparation of trifluoromethylated compounds in Diels–Alder and 1,3-dipolar cycloaddition reactions. The Diels–Alder reaction of the three olefins **21.2**, **21.5** and **21.8** is promoted by the sulfur substituents since, for example, vinylthioether **21.2** is much more reactive than 3,3,3-trifluoropropene itself toward pericyclic reactions. The vinyl sulfone **21.8** reacts with cyclopentadiene even at room temperature to give adduct in essentially quantitative yield. Together, the products obtained from **21.2**, **21.5** and **21.8** show that the stereochemistry of the reaction products is governed by the trifluoromethyl group. The *endo*-CF_3 adducts are formed preferentially with **21.5** and **21.8**. For the vinylthioether **21.2**, the lack of diastereoselectivity was rationalized by the possible stabilization by secondary orbital interactions of sulfur with cyclopentadiene in the transition state[63] (Scheme 21).



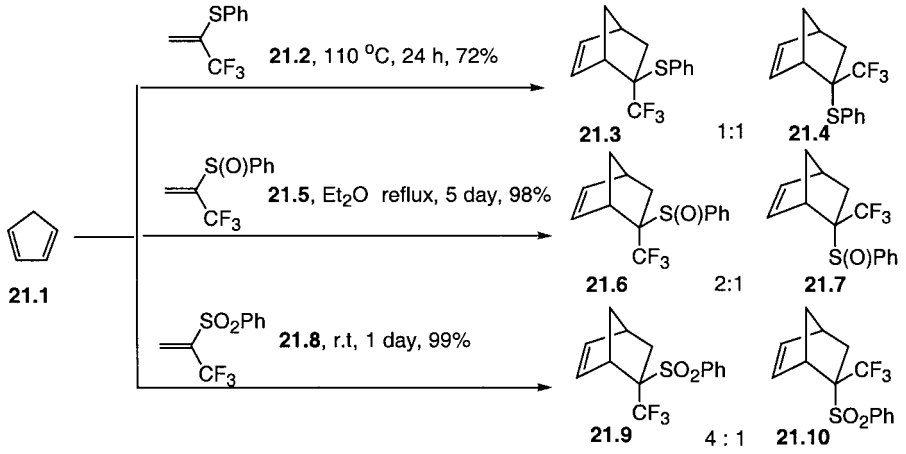
Scheme 19.



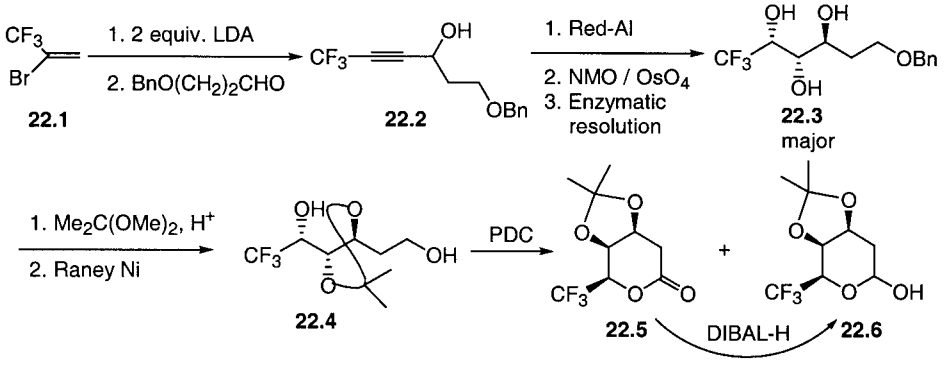
Scheme 20.

2-Bromo-3,3,3-trifluoropropene is readily available from 3,3,3-trifluoropropene.[65] 2-Bromo-3,3,3-trifluoropropene itself acts as a weak Michael acceptor. However, it can be transformed into nucleophilic forms that have synthetic utility. As shown in Scheme 22, treatment of 3,3,3-trifluoropropene **22.1** with LDA leads to the formation of lithiated 3,3,3-trifluoropropyne in situ. When this organolithium was reacted with 2-benzyloxypropanal it afforded 1-(benzyloxy)-6,6,6-trifluoro-4-hexyn-3-ol **22.2**.[66,67] Reduction of the acetylenic alcohol of **22.2** into its derived allylic alcohol followed by dihydroxylation with osmium tetroxide and an enzymatic resolution reaction gave an optically active triol **22.3**. Because of the presence of the trifluoromethyl group, the nucleophilicity of the 5-hydroxy group is diminished and therefore acetonide protection of the triol using 2,2-dimethoxypropane exclusively forms the 1,2-acetonide. The methodology here allowed a short reaction sequence for the synthesis of 2,6-dideoxy-6,6,6-trifluorosugar derivatives.

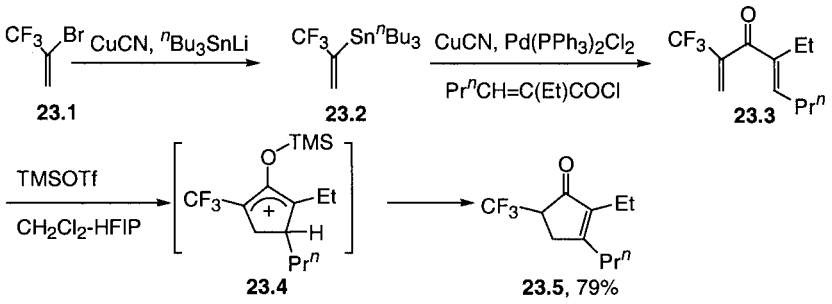
Stannylcupration of 2-bromo-3,3,3-trifluoropropene gave 1-trifluoromethylvinyltin **23.2** which in a Stille-type cross-coupling reaction gave the trifluoromethylated cross-conjugated ketone **23.3**.[68] Treatment of compound **23.2**



Scheme 21.



Scheme 22.



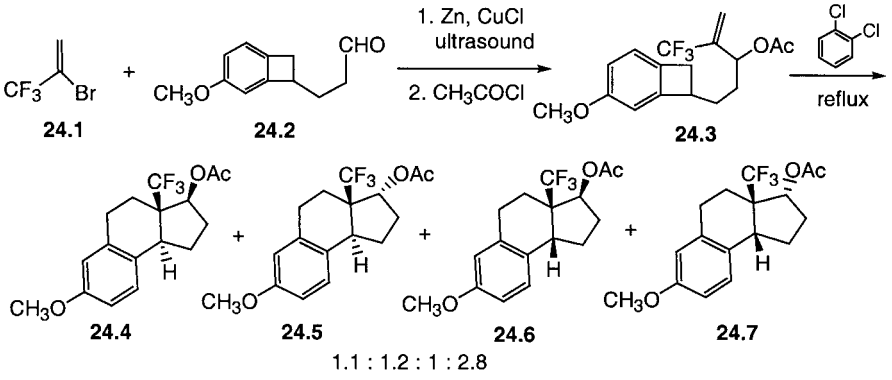
Scheme 23.

with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in a mixture of dichloromethane and 1,1,1,3,3,3-hexafluoro-2-isopropanol (HFIP) afforded 5-trifluoromethyl-2-ethyl-cyclopent-2-enone **23.5** in 79% yield as the sole cyclized product. The Nazarov cyclization of the non-fluorinated counterpart of **23.3** usually yields a mixture of regioisomers of the double bond in the five-membered ring. Here, the directing effect that the CF_3-group exerts leads to placement of the double bond away from the trifluoromethyl group. The reaction underscores the strong electronic bias imposed by the trifluoromethyl group on the direction of proton loss on the final reaction intermediate (Scheme 23).

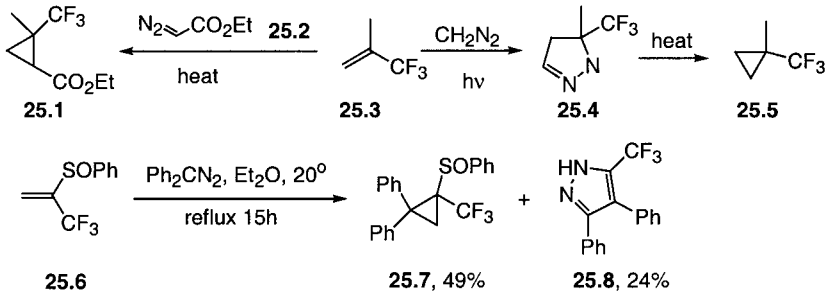
In another example trifluoroisopropenyl bromide in the presence of zinc, copper(I) chloride and ultrasound with a benzocyclobutenyl aldehyde **24.2** gave an allylic alcohol which was subsequently acylated to yield **24.3**. Fukumoto and coworkers[69,70] studied the stereochemical course of the intramolecular Diels–Alder reaction of *o*-quinodimethanes with trifluoromethyl allylic alcohols bearing various protecting groups on the hydroxy group such as **24.3** and have developed a novel approach to 18-trifluoroestrans. The thermal reaction of the acetyl protected **24.3** afforded all four possible isomers. The trifluoromethyl substituent on the carbon–carbon double bond enhanced the *cis*-selectivity about the ring junction and also the *anti*-selectivity between the trifluoromethyl and ester group, compared with the methyl analogs (see Scheme 24).

Addition of diazomethane and substituted diazomethane derivatives to CF_3-substituted olefins is well precedented with the earliest examples being reported by Misani[71] (Scheme 25). Some more recent examples have been reported by Fuchikami's group.[59] Viehe's group has studied reactions of sulfur substituted CF_3-olefinic compounds with diazomethane and substituted diazomethane derivatives[64] (Scheme 25).

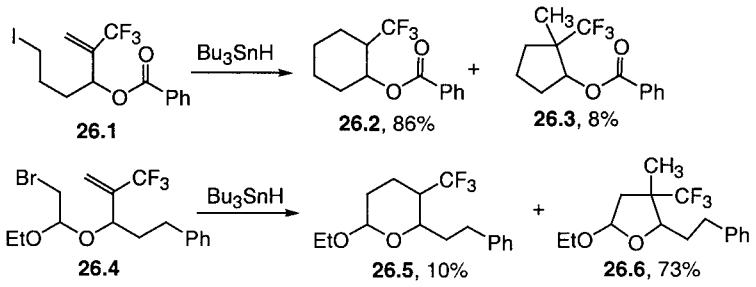
Radical reactions have distinct advantages over ionic reactions in the synthesis of trifluoromethylated cycles. Radical reactions avoid the problem of defluoridation that sometimes accompanies nucleophilic cyclization reactions[72]



Scheme 24.



Scheme 25.

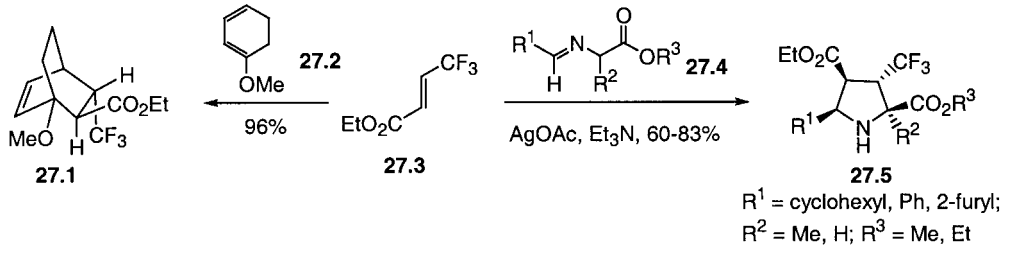


Scheme 26.

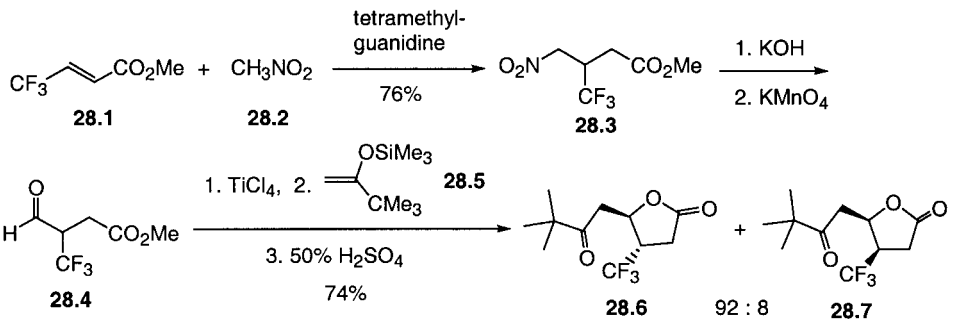
and also the problems associated with a strong electron-withdrawing effect from the CF_3-group encountered in electrophilic cyclization reactions. Kobayashi and coworkers[73] studied radical cyclizations of CF_3-double bond compounds for the synthesis of trifluoromethylated cyclic compounds. The carbon radical derived from iodide **26.1** predominantly attacks the carbon β to the trifluoromethyl group on the olefin via an *endo* ring-closure reaction to form **26.2**, that has a six-membered ring in 86%. The observed 6-*endo*:5-*exo* ratio was 11:1. The mode of cyclization reaction appears to be sensitive to the gross structure. An oxygen atom in the connecting chain overrode this 6-*endo* preference is seen in the radical cyclization of acetal **26.4**. The cyclization proceeded mainly by an α-attack and followed the 5-*exo* reaction pathway to give **26.6** (Scheme 26).

3.1.2. From α,β-disubstituted olefins. Diels–Alder reactions and 1,3-dipolar cycloaddition of (*E*)-4,4,4-trifluorocrotonate **27.3** and its derivatives have been extensively reported.[61,74–87] Scheme 27 shows just two examples, reactions with methoxy diene **27.2** and with a precursor to a metallo-azamethine ylid **27.4**. Thus the reaction of ethyl (*E*)-4,4,4-trifluorocrotonate **27.3** with diene **27.2** in refluxing benzene in the presence of dichloromaleic anhydride and *t*-butyl-*p*-cresole for 4 days gave the Diels–Alder adduct **27.1** with the CF_3-group situated *endo* to the bicyclic ring.[75] The regio- and stereo-specific cycloaddition of ethyl (*E*)-4,4,4-trifluorocrotonate **27.3** with metallo-azomethine ylids generated from imines of glycine or alanine ester in the presence of silver acetate, gave 3-trifluoromethylpyrrolidine derivatives **27.5**.[79] Despite the presence of the trifluoromethyl group, the regiochemistry of the Diels–Alder reaction of **27.3** is determined by the ester group. The relative stereochemistry at the C-4, C-5 centers and the C-2, C-3 centers indicates that the *endo*-approach of the ester group of the alkene is preferred.

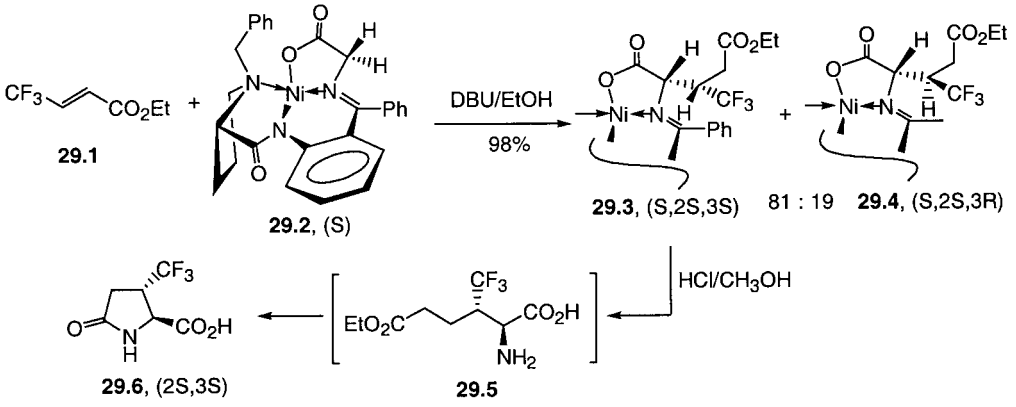
Michael addition of nitromethane **28.2** to ethyl (*E*)-4,4,4-trifluorocrotonate followed by base hydrolysis, oxidation with permanganate and careful distillation gave aldehyde **28.4** in 26% yield.[88] A $TiCl_4$-promoted Mukaiyama reaction of aldehyde **28.4** with enol ether **28.5** afforded γ-lactones **28.6** and **28.7** as a 92:8 *trans*:*cis* mixture. This is to be compared with the same reaction with the methyl-substituted analog which shows only a selectivity of 71:29 in preference for the *trans* lactone. The electron-withdrawing trifluoromethyl group is the main factor of the higher



Scheme 27.



Scheme 28.



Scheme 29.

trans selectivity. Addition of BF_3-etherate as the Lewis acid resulted in no formation of lactones (Scheme 28).

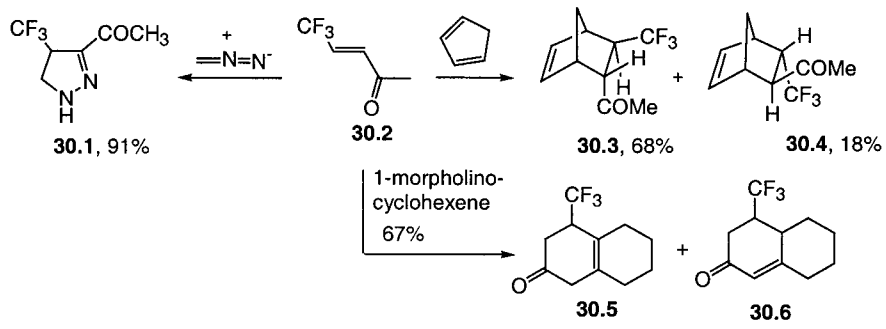
Soloshonok et al.[89] recently reported an asymmetric synthesis of (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid **29.6** via Michael addition of a Ni(II) complex of a glycine Schiff base with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (**29.2**) to ethyl (*E*)-4,4,4-trifluorocrotonate. The stereochemical outcome of the Michael addition was found to be subject to kinetic or thermodynamic control depending on the reaction conditions used. Under conditions of kinetic control, high diastereoselectivity of up to 94% d.e. of compound **29.6** was obtained, while the stereoselectivity obtained under conditions of thermodynamic control in comparison was only moderate (Scheme 29).

Another reagent that has been used as a reactant for Diels–Alder reactions and 1,3-dipolar cycloadditions in synthesis of the trifluoromethyl substituted cycles is (*E*)-1,1,1-trifluoro-2-penten-4-one **30.2**. Diels–Alder reaction of (*E*)-1,1,1-trifluoro-2-penten-4-one **30.2** and cyclopentadiene afforded the norborene derivatives **30.3** and **30.4** with a ratio of *endo*-acetyl **30.3** to *exo*-acetyl **30.4** of 79:21.[90] A facile 1,3-dipolar cycloaddition reaction of compound **30.2** with diazomethane gave the 2-pyrazoline derivative **30.1** which may be considered to result from isomerization of the first formed 1-pyrazoline. In a more classical annulation reaction, (*E*)-1,1,1-trifluoro-2-penten-4-one reacted with 1-morpholinocyclohexene in a Michael–Dieckmann reaction to give the trifluoromethyl substituted octalinone derivatives **30.5** and **30.6** in 67% yield[91,92] (Scheme 30).

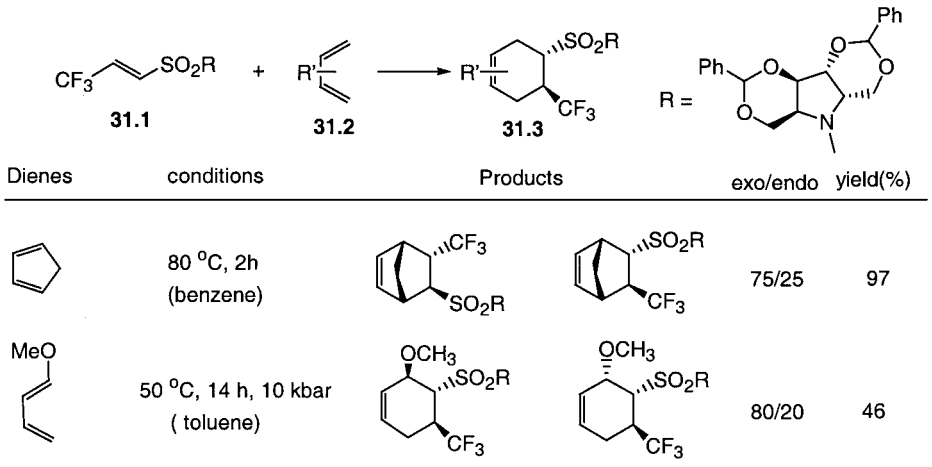
(*E*)-1,1,1-Trifluoro-3-phenylsulfonylprop-2-ene and (*E*)-1,1,1-trifluoro-3-phenylsulfinylprop-2-ene have been used in Diels–Alder and in 1,3-dipolar cycloaddition reactions.[93–97] The versatility and flexibility that is offered by the sulfonyl and sulfinyl groups have led to the two functional groups being exploited as temporary control elements for the introduction of chirality in asymmetric Diels–Alder and 1,3-dipolar cycloaddition reactions. Recently, Eguchi and coworkers[95] synthesized optically active trifluoromethylated cyclic sulfonamides through asymmetric Diels–Alder reactions of α,β-unsaturated sulfonamides **31.1** bearing a C2-symmetric pyrrolidine chiral auxiliary under high pressure conditions (Scheme 31). The stereochemical relationship between the trifluoromethyl and sulfonyl groups found in the reaction products is always *trans*, thus implying that a concerted reaction took place. Here again, the trifluoromethyl group plays a minor role in determining the regiochemistry of the cycloaddition reaction. The *endo* to *exo* selectivity is determined by steric repulsion, and in most cases the sulfonyl group preferentially occupies the *exo* position.

(*E*)-3,3,3-Trifluoro-1-nitropropene was synthesized for the first time by Shechter et al.[98] and it is a highly reactive Michael acceptor[99] and dienophile/dipolarophile.[84,99,100] Cycloaddition of (*E*)-3,3,3-trifluoro-1-nitropropene **32.1** with furan afforded diastereomeric 1:1 mixture of 6-trifluoromethyl-5-nitro-7-oxa-bicyclo-[2,2,1]hept-2-enes **32.3** and **32.4** in 60% yield (Scheme 32).

Shen[101] has reported a reaction of 2-trifluoromethyl vinylphosphonate **33.4** with isopropylidene triphenylphosphorane



Scheme 30.

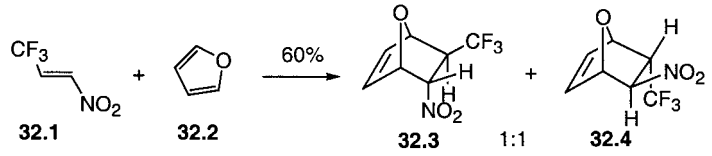


Scheme 31.

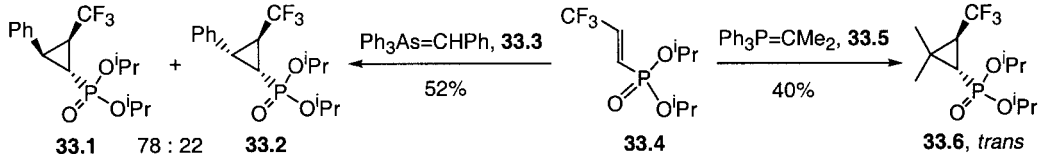
33.5. The isolated product is the CF_3-cyclopropyl phosphonate **33.6** wherein the phosphonate and CF_3-groups end up *trans* to each other is obtained in 40% yield. The reaction of the same vinylphosphate **33.4** with the corresponding triphenylarsorane reagent leads to a higher yield (60%) of the same product **33.6**. With benzylidene triphenylarsorane **33.3** and 2-trifluoromethyl vinylphosphonate **33.4**, a mixture of two cyclopropyl phosphonates **33.1** and **33.2** is obtained. The isomer with the phenyl group that is *trans* with respect to the phosphoryl group predominates (Scheme 33).

Reaction of trifluoromethylated allylic alcohol **34.1** with triethyl orthoacetate **34.2** led to an intermediate that underwent a Claisen rearrangement to give olefin ester **34.3**.[102] In a further four-step transformation, olefin ester **34.3** was converted into nitrone **34.5**. On heating in toluene, an intramolecular 1,3-dipolar cycloaddition of nitrone **34.5** occurred and a mixture of three bicyclic compounds **34.6**, **34.7** and **34.8** was obtained (Scheme 34).

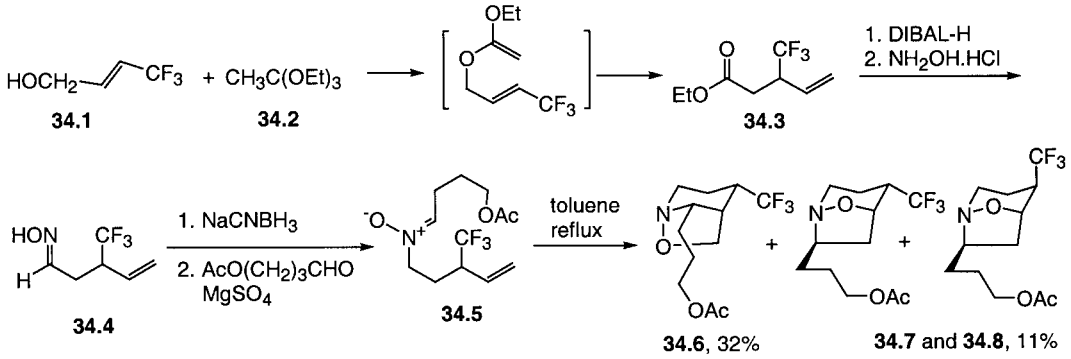
Kitazume and coworkers[103,104] reported a [3,3]-Ireland–Claisen rearrangement occurring on substituted α-methoxyacetic acid γ-(trifluoromethyl)allyl esters **35.1** and **35.4** that proceeded in a highly stereoselective manner to



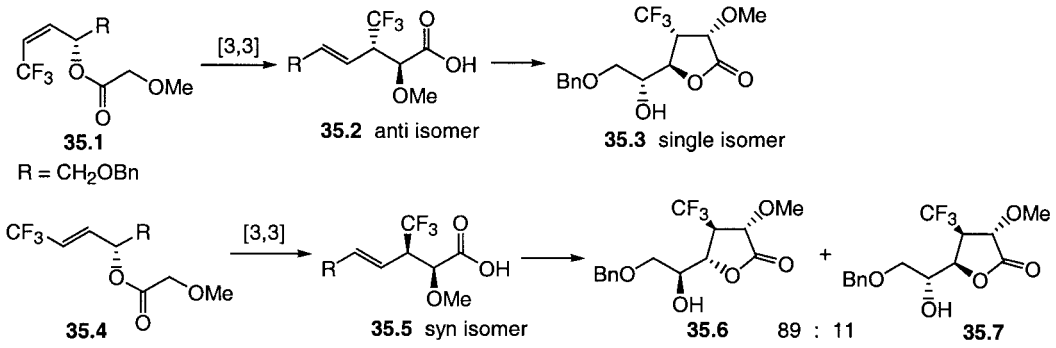
Scheme 32.



Scheme 33.



Scheme 34.

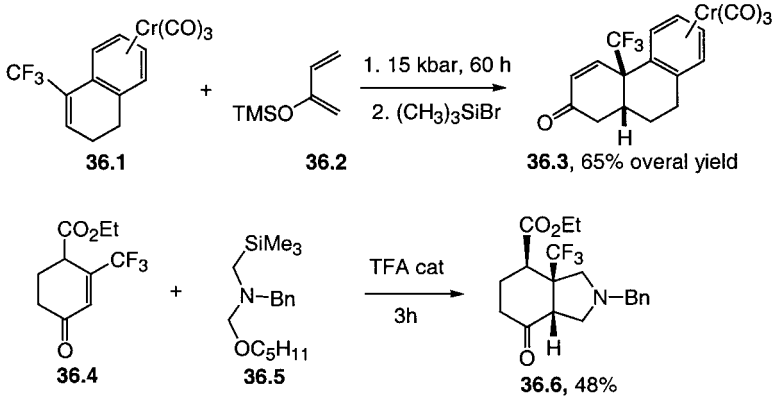


Scheme 35.

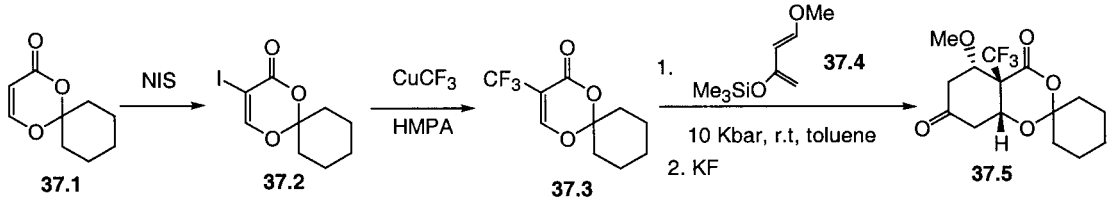
produce α-methoxy-β-trifluoromethyl-γ,δ-unsaturated carboxylic acid derivatives **35.2** and **35.5** in high yields. Osmylation of enantiomerically pure Ireland–Claisen products **35.2** and **35.5** gave γ-butyrolactones in moderate yields. The *anti*-isomer **35.2** afforded γ-butyrolactone **35.3** as a single isomer, while the *syn*-isomer **35.5** gave two γ-lactones, **35.6** and **35.7**, as a mixture of two diastereomers in the ratio 89:11 (Scheme 35).

3.1.3. From tri- and tetrasubstituted olefins. Trisubstituted alkenes that rely solely on the intrinsic electron withdrawing effect of the trifluoromethyl group are usually not sufficiently electron deficient enough to behave as dieneophiles in Diels–Alder reactions or as dipolarophiles in 1,3-dipolar reactions.[61] Lewis acid catalysis normally does not facilitate pericyclic reactions of trifluoromethyl-substituted olefins because the Lewis acid is not able to form a complex with the double bond bearing a trifluoromethyl group. However, as depicted in Scheme 36, the Diels–Alder reaction of chromium complex **36.1** with diene **36.2** occurs at high pressure. This is a special case. Formation of a chromium tricarbonyl complex with the phenyl ring of **36.1** leads to an increase in the reactivity of the carbon–carbon double bond bearing the CF_3-group. Trisubstituted olefins that possess both a trifluoromethyl group and another electron-withdrawing group are known to react only with highly reactive dipoles such as nitrones and diazomethane.

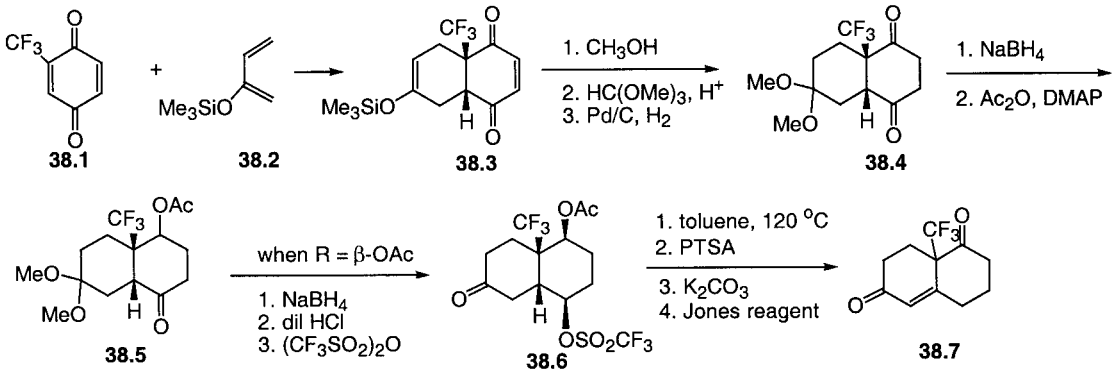
One example that demonstrates a CF_3-group actually promoting a Diels–Alder reaction is shown in Scheme 37. No observable reaction occurs between the 1,3-dioxin compound **37.1** and Danishefsky diene **37.4** even under high-pressures condition of 10 Kba at ambient temperatures.[105] After a trifluoromethyl group was introduced into the 5-position of dioxin **37.1** by iodination followed by a trifluoromethyl copper reaction to give **37.3**, the Diels–Alder reaction of the trisubstituted double bond of **37.3** with Danishefsky diene under a pressure of 10 Kba at room temperature gave a single adduct **37.5**. This suggests that the attachment of the trifluoromethyl group at the 5-position of the 1,3-dioxin ring enhanced the reactivity of the dioxin **37.1**. Also reported are some [2+2] photocycloaddition of the 1,3-dioxin **37.3**.[105,106]



Scheme 36.



Scheme 37.



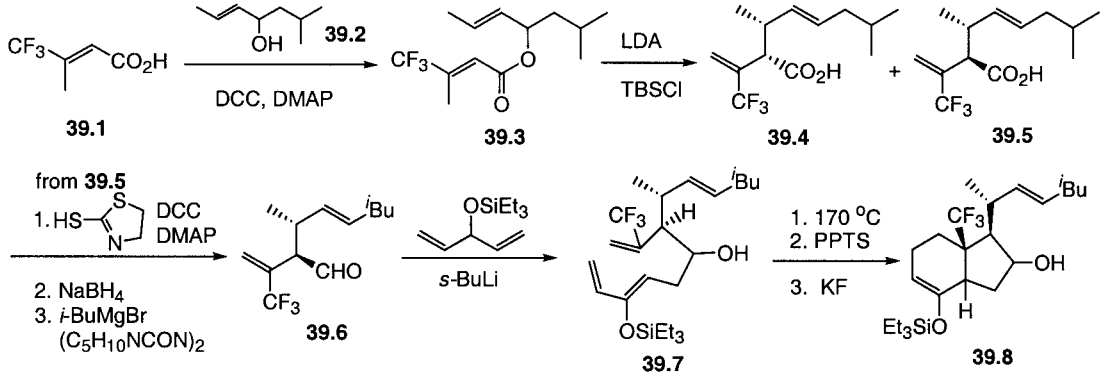
Scheme 38.

Quinone **38.1**,[107–109] bearing three electron withdrawing groups, readily reacted with 2-trimethylsiloxybuta-1,3-diene in methylene chloride at room temperature to furnish a single adduct **38.3** in 89% yield. Blazejewski et al.[110] were then able to synthesize a derivative of the 9,9,9-trifluoro analog of the Wieland–Miescher ketone **38.7** from the adduct **38.3**. The silyl enol ether **38.3** was converted into its corresponding ketone and protected as a dimethyl ketal, and then the C=C bond was reduced by catalytic hydrogenation to give **38.4**. Selective reduction of the 1,3-diketone **38.4** with sodium borohydride followed by treatment with acetic anhydride gave intermediate **38.5** in 75% yield. The preferential reduction of the carbonyl group that is shielded by the trifluoromethyl group may be ascribed to the enhanced reactivity resulting from the electron withdrawing trifluoromethyl group. Steps that resulted in the removal of the remaining ketone carbonyl, introduction of a carbon–carbon double bond and adjustment in the oxidation level led to ketone **38.7**. Ketone **38.7** was a key intermediate in the synthesis of 19,19,19-trifluoro-androstenedione derivatives reported by Blazejewski[111,112] (Scheme 38).

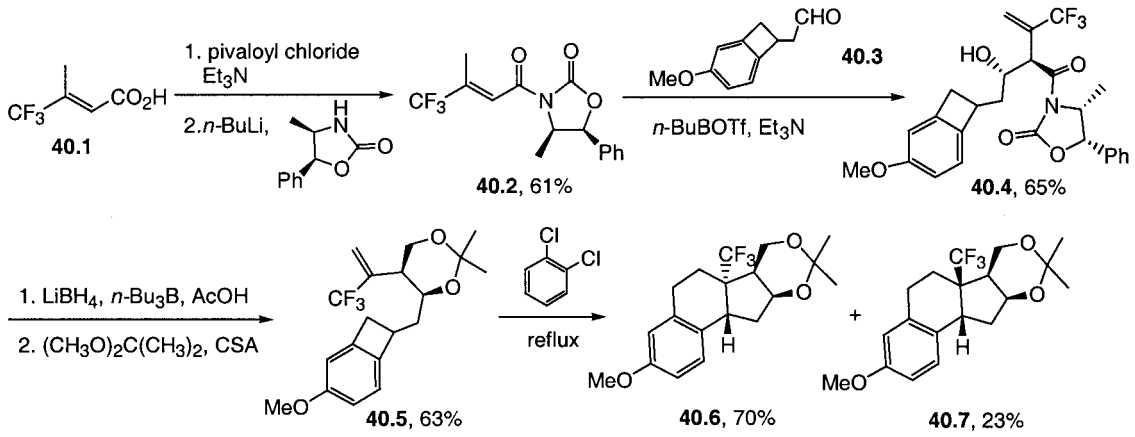
De Clercq[113] reported an intramolecular Diels–Alder reaction of 8-trifluoromethyl-1,3,8-nonatriene as a possible route to trifluoromethylated hydrindenes which have the CF_3-group situated at the ring junction. The key intermediate **39.6** that led to the triene was prepared by esterification of carboxylic acid **39.1** and allylic alcohol **39.2**. The resulting ester underwent an Ireland–Claisen rearrangement to give a mixture of carboxylic acids **39.4** and **39.5**. Conversion of carboxylic acid **39.5** into the aldehyde **39.6** followed by reaction of the aldehyde **39.6** with 3-triethylsilyloxypentadienyl lithium afforded the requisite triene **39.7** as a mixture of two diastereomeric alcohols in a 3:1 ratio. A thermally induced intramolecular cycloaddition reaction of the triene **39.7** produced predominantly *trans*-fused adducts **39.8** (Scheme 39).

In a synthesis of chiral, non-racemic, A-tetranor B-trienic 18,18,18-trifluorosteroidal system **40.6** and its epimer **40.7** shown below, Fukomoto and coworkers[114] used a chiral unsaturated imide **40.2** as a trifluoromethyl source and as an optical induction reagent. The chiral induction on the trifluoromethylated steroidal ring system was effected by chirality transfer from a chiral oxazolidinone on the adduct obtained from the chiral oxazolidinone **40.2** and the aldehyde **40.3** which gave rise to **40.4**. After conversion of compound **40.4** to the protected diol **45.5**, an intramolecular Diels–Alder reaction of the CF_3-substituted olefin with an *o*-quinodimethane that is generated thermally in situ afforded compounds **40.6** and **40.7** (Scheme 40).

Zecchi and coworkers[115] reported an intramolecular nitrone cycloaddition route to 3-(trifluoromethyl)isoxazolidino-[4,3-*c*]-chroman-4-ones and -quinolin-4-ones. A later report[116] described a variant of this synthetic approach that led to enantiomerically pure compounds. Thus, the trifluoromethylated substrate **41.1** was reacted with (*S*)-α-(phenylethyl)hydroxylamine oxalic acid salt to give homochiral nitrones **41.3**. Without isolation, nitrones **41.3** were heated in benzene to give a 9:1 separable mixture of



Scheme 39.



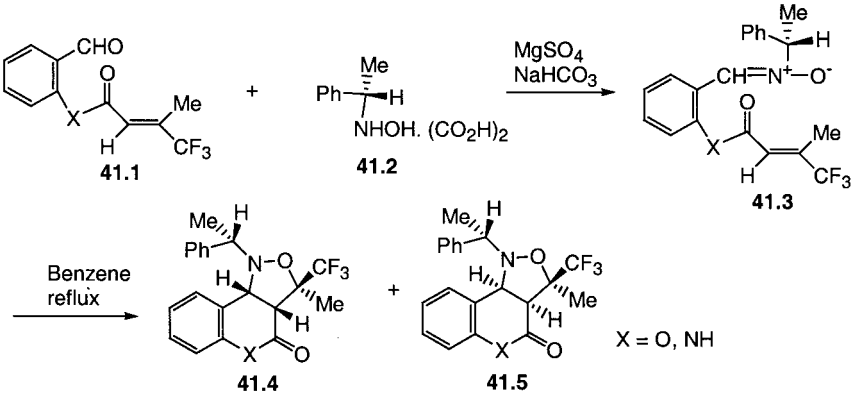
Scheme 40.

intramolecular cycloadducts **41.4** and **41.5** in 50% overall yield (Scheme 41).

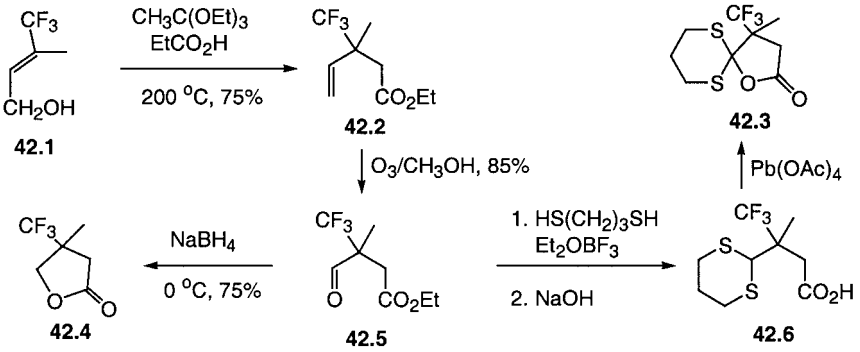
Claisen rearrangement of trifluoromethylated allylic alcohol **42.1** with ethyl orthoacetate for 3 h at 200°C afforded ethyl 3-methyl-3-trifluoromethyl-4-pentenate **42.2** in 75% yield.[117] An ozonolysis reaction of compound **42.2** afforded the aldehyde ester **42.5** in 87% yield. The ester–aldehyde **42.5** was converted into β-trifluoromethyl-γ-butyrolactones **42.3** and **42.4** (Scheme 42).

Trifluoromethylated cyclopropyl lactones have been synthesized by Faigl et al.. The synthesis is based on a cyclization reaction that involves single electron transfer.[118] Thus reaction of monoethyl malonate ester with *trans*-3-trifluoromethyl-2-butene-2-ol in the presence of DCC gave the ester **43.3**. Treatment of the ester **43.3** with iodine, potassium carbonate and tricaprylmethylammonium chloride (TCMC) in hot benzene gave **43.4** and **43.5** in an approximately 1:2 ratio (Scheme 43).

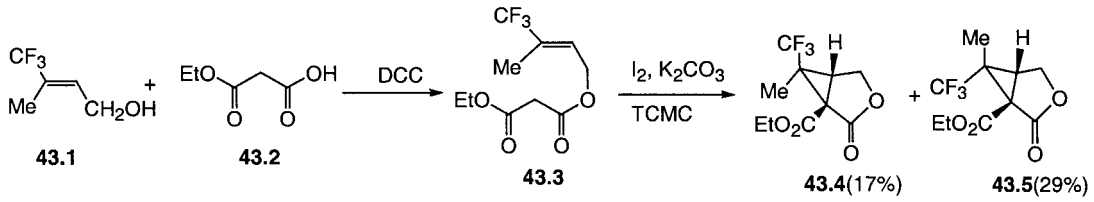
There are a few scattered reports of trifluoromethyl substituted olefins forming CF_3-substituted cyclopropanes by irradiation of the CF_3-olefin in an inert solvent and examples are depicted below in Scheme 44.[119–121]



Scheme 41.



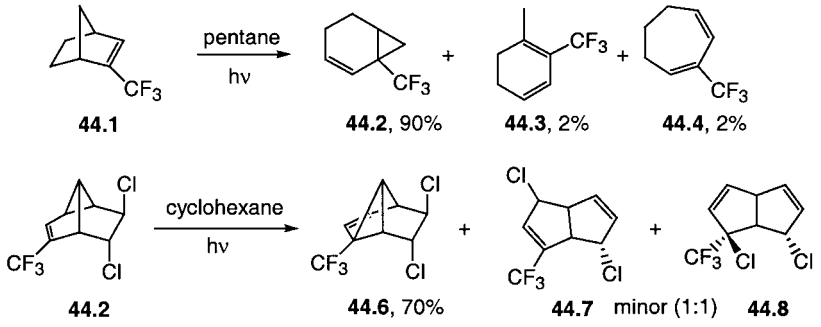
Scheme 42.



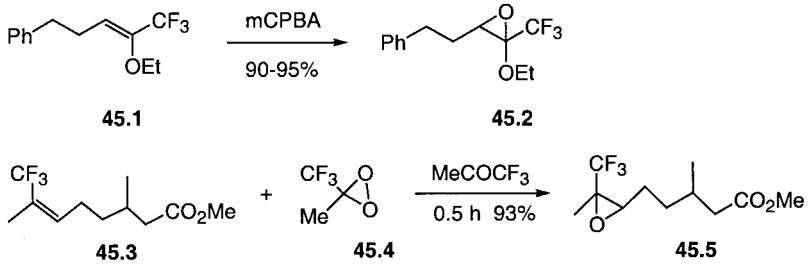
Scheme 43.

Oxidation of trifluoromethyl-substituted alkenes for the synthesis of 2-trifluoromethyl oxiranes is a well known reaction. As shown in Scheme 45, the oxidation has been achieved using *m*CPBA as an oxidant.[122–125] Epoxidations have also been achieved catalytically with a mixture of oxygen and chlorine.[126] Messeguer[127] has used Murray's reagent, dimethyldioxirane, to effect the epoxidation of CF_3-substituted olefins, however the reaction seems sluggish. As an improvement, trifluoromethyl methyl dioxirane epoxidizes CF_3-substituted olefins more rapidly.

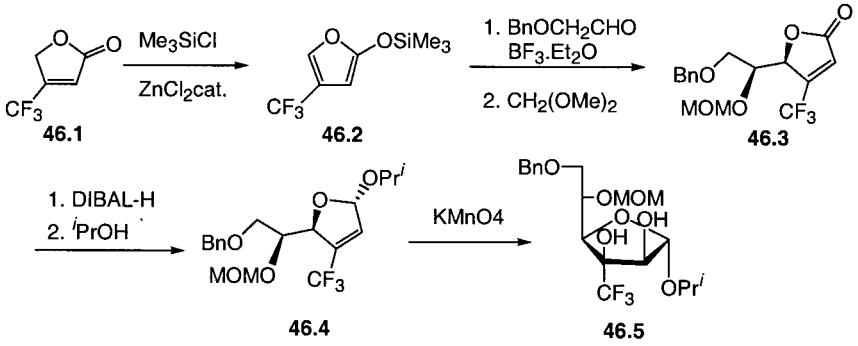
4-Trifluoromethyl-2(5*H*)-furanone **46.1** was synthesized by Kobayashi and coworkers[128,129] from (*Z*)-4-bromo-3-trifluoromethyl-2-butenoate and was converted to its silyloxyfuran derivative **46.2** using trimethylchlorosilane and triethylamine in the presence of a catalytic amount of zinc chloride.[130] A Lewis acid-catalyzed aldol reaction of the silyloxyfuran **46.2** with 2-benzyloxyacetaldehyde and subsequent lactone formation provided 5-substituted-4-trifluoromethyl-2(5*H*)-furanone **46.3** with high regio- and diastereo-selectivity. The aldol product of the lactone **46.3**



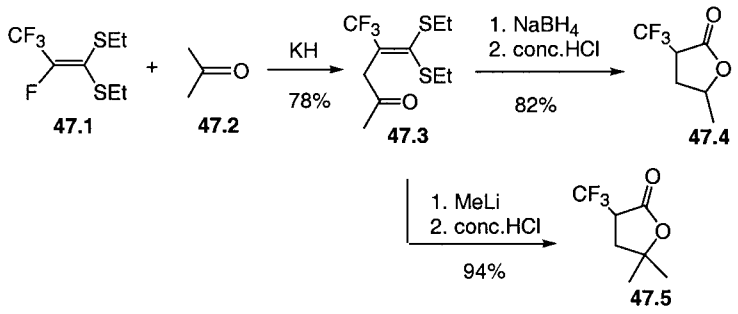
Scheme 44.



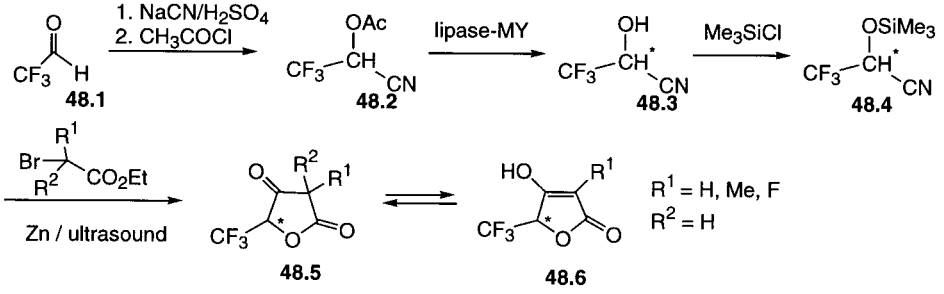
Scheme 45.



Scheme 46.



Scheme 47.



Scheme 48.

was transformed into a trifluoromethylated branched sugar derivative **46.5**[130] (Scheme 46).

Portella[131,132] reported substitution of the fluoride of perfluoroketene dithioacetal **47.1** by an acetonyl group using acetone and potassium hydride to generate ketone **47.3** in high yield. Reduction of the ketone **47.3** followed by hydrolysis using concentrated hydrochloric acid gave γ-butyrolactone **47.4** in 94% yield as a mixture of diastereomers. Addition of methyllithium to the ketone **47.3** followed by acid hydrolysis gave a more substituted lactone **47.5**. Noteworthy here is the hydrolysis of the dithioacetal moiety which was accomplished without assistance of mercuric salts (Scheme 47).

3.2. Use of trifluoroacetaldehyde and its imine derivatives

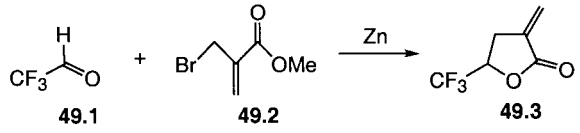
Trifluoroacetaldehyde is a useful building block for the preparation of organic compounds having a trifluoromethyl group. The aldehyde is commercially available as trifluoroacetaldehyde ethyl hemiacetal from which gaseous trifluoroacetaldehyde itself can be generated by dehydration.

Kitazume[133,134] reported Reformatsky-type reactions promoted by ultrasound between the optically active *o*-trimethylsilylated cyanohydrin **48.4** and α-substituted α-bromoacetic esters that gave chiral β-keto-γ-butyrolactone **48.5** and tetronic acid **48.6** bearing a trifluoromethyl group on the asymmetric carbon at C-4. The optically active cyanohydrin **48.3** was prepared by an asymmetric hydrolysis of the corresponding racemic acetic ester **48.2** with lipase-MY (Scheme 48).

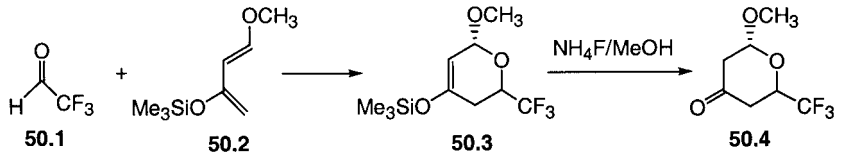
In a single-step Reformatsky reaction γ-trifluoromethyl-2-methylene-γ-butyrolactone **49.3** was obtained from trifluoroacetaldehyde with methyl 2-(bromomethyl)acrylate **49.2** and zinc dust in 32% yield[135] (Scheme 49).

The Lewis acid catalyzed diene–aldehyde cyclocondensation has proven to be one of the most reliable reactions for the preparation of pyranosic synthons. When this cyclocondensation was applied to trifluoroacetaldehyde[136,137] it occurred at room temperature and needed no Lewis acid activation. Unlike the reaction between a non-fluorinated aldehyde and Danishefsky diene **50.2** which leads to a γ-pyranone without isolation of the acid-labile intermediate similar to **50.3**, the trifluoroacetaldehyde reaction gave only the 6-trifluoromethyl-2-methoxy-4-trimethylsilyloxy-pyr-3-ene **50.3** as *cis/trans* mixture (70/30).[137] On forming the pyranosic ring, the inductive effect from the 2-trifluoromethyl group on the ring can exert an influence at a longer distance through the ring oxygen. The inductive effect of the CF_3-group situated at C-2 precludes the elimination of the methoxy group located at C-6 (Scheme 50).

Addition of *N*-methylhydroxylamine **51.2** to trifluoroacetaldehyde **51.1** followed by dehydration generates the nitrone **51.3** which has the *C*-trifluoromethyl and *N*-methyl groups in a *trans*-orientation.[138,139] The nitrone **51.3** has been shown to be a useful synthetic building block for constructing trifluoromethylated heterocycles. Reaction of the nitrone **51.3** with various alkyne dipolarophiles in refluxing benzene afforded 3-trifluoromethyl-4-isoxazolines **51.4**,



Scheme 49.



Scheme 50.

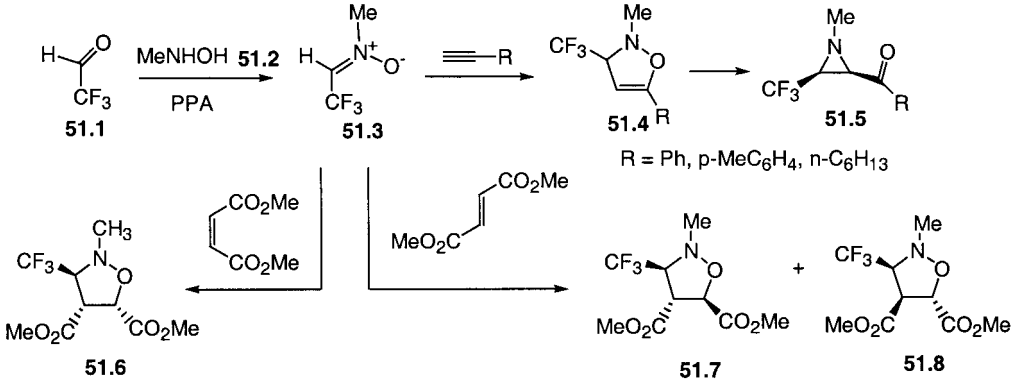
which can rearrange into 2-trifluoromethylaziridines **51.5**. Cycloaddition of **51.3** with dimethyl fumarate, a *trans* olefin, gave 3,4-*trans*- and 3,4-*cis*-substituted isoxazolidines **51.7** and **51.8** in an 1:1 mixture. Cycloaddition of *cis*-olefins such as dimethylmaleate proceeded with high stereoselectivity giving 3,4-*trans*-substituted cycloadduct **51.6**. The predominant formation of the 3,4-*trans*-trifluoromethylisoxazolidines **51.6** suggests that in the transition state, secondary orbital interactions between the trifluoromethyl group and the substituents including a phenyl or an ester group of the dipolarphiles are very weak and that the steric repulsion between these groups more than secondary orbital interactions that determine the product formed[140] (Scheme 51).

Bonnet-Delpon and coworkers[141,142] prepared CF_3-substituted β-lactam **52.4** by [2+2] cycloaddition of a ketene with the trifluoromethyl aldimine derived from trifluoroacetaldehyde. The ketene **52.2** used for the [2+2] reaction was generated in situ from α-benzyloxyacetyl chloride and triethylamine. When a chiral *N*-substituted imine **52.3** was used, this asymmetric Staudinger reaction showed low diastereoselectivity because the relatively long distance between the chiral center and the reaction centers precluded high optical induction. However, crystallization or chromatography followed by crystallization of the crude mixture of reaction products **52.4** in ethanol allowed a fine separation of the two isomers **52.5** and **52.6** to be performed (Scheme 52).

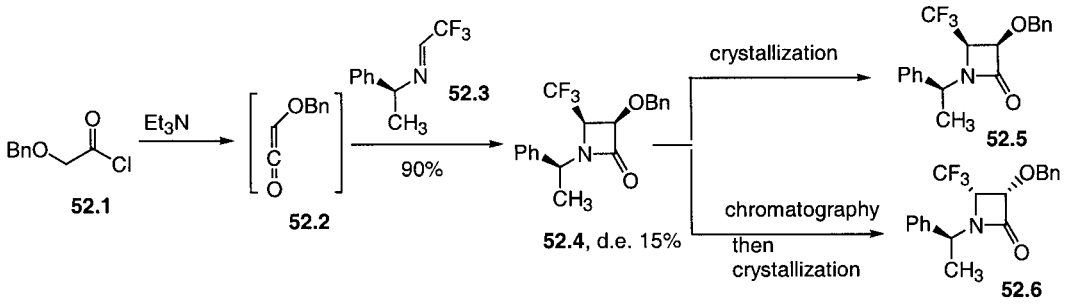
3-Fluoro-2-trifluoromethyl-β-lactams have been prepared by Ishihara by a condensation reaction of the lithium salt derived from 2-fluoropropanoic acid phenylthioester **53.2** with the benzylimine **53.3** derived from trifluoroacetaldehyde. Reaction of imine **53.3** with the (*Z*)-lithium enolate **53.2** gave 4-trifluoromethylated 2-azetidones **53.4** and **53.5** as a 97:3 *trans*:*cis* mixture in 44% yield[143] (Scheme 53).

3.3. Use of trifluoromethylated ketones

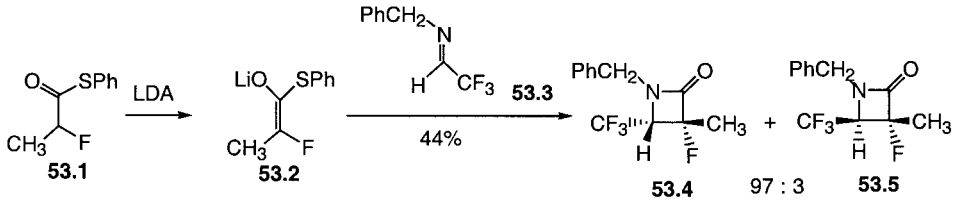
This section covers ketones that have the trifluoromethyl group directly attached to the carbonyl group. Arbitrarily we have also included in this section methyl or ethyl trifluoromethylpyruvate and ethyl 1,1,1,-trifluoroacetoacetate compounds that have a trifluoromethyl ketone present. The trifluoromethylated ketone carbonyl is more electrophilic than their corresponding methyl counterparts and the initial step when trifluoromethylated ketones are used for the construction of rings in most cases involves a



Scheme 51.



Scheme 52.



Scheme 53.

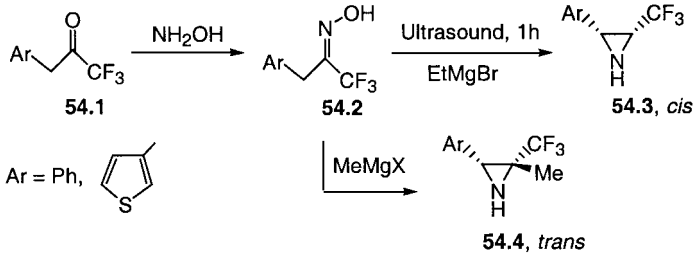
nucleophilic addition reaction to the trifluoromethyl carbonyl group.

3.3.1. From simple trifluoromethylated ketones. Trifluoromethyl ketones **54.1** were prepared by Laurent[144] by condensation reaction of 2-phenylacetonitrile and 2-(3-thienyl)-acetonitrile with ethyl trifluoroacetate followed by sulfuric acid hydrolysis with a concomitant decarboxylation reaction. The oximes **54.2**, prepared from the ketones **54.1**, were reacted with Grignard reagents. Ethyl- or isopropylmagnesium bromide and ultrasound led cleanly to *cis*-aziridine **54.3** without incorporation of either an ethyl or isopropyl group. An in situ reduction of a 2*H*-azirine intermediate was proposed. With methylmagnesium bromide, no *cis*-aziridine product formed by reduction was observed; instead the methylated *trans*-aziridine **54.4** was obtained. There was no reaction of the trifluoromethyl oximes **54.2** with phenylmagnesium bromide. Allylmagnesium bromide appears to add to across the C=N bond of the oximes **54.2** and/or reduce the carbon–nitrogen double bond rather than form a three-membered nitrogen heterocyclic ring[145] (Scheme 54).

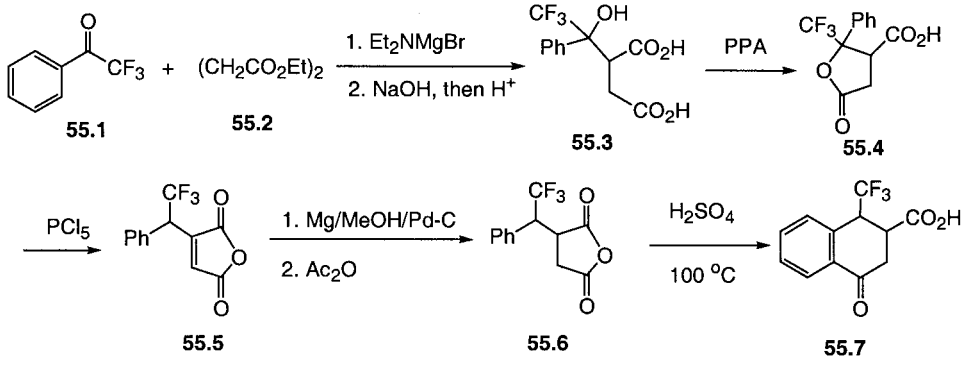
Trifluoroacetophenone **55.1** has been reported to react with diethylsuccinate to give 3-carboxy-5,5,5-trifluoro-4-hydroxy-4-phenylpentanoic acid **55.3**, which was then converted into 3-carboxy-4-phenyl-4-(trifluoromethyl)butanolide **55.4** on treatment with PPA. Heating the substituted γ-butyrolactone **55.4** with phosphorus pentachloride gave 2,5-dihydro-2,5-dioxo-3-(1-phenyl-2,2,2-trifluoroethyl)furan **55.5**. The carbon–carbon double bond in **55.5** was removed to give the succinic anhydride derivative **55.6**. Treatment of **55.6** with concentrated sulfuric acid led to the formation of 3-carboxy-4-(trifluoromethyl)tetralone **55.7**[146,147] (Scheme 55).

Azeotropic removal of water from a reaction mixture of trifluoroacetophenone **56.1** with (*R*)-phenylglycinol **56.2** by heating in toluene gave a chiral 2-trifluoromethyl-1,3-oxazolidines **56.3** as a 1.6:1 diastereomeric mixture.[148–150] The diastereomers were separated by column chromatography. A stereospecific substitution reaction of **56.3** with organolithium reagents on the carbon adjacent to the trifluoromethyl group proceeded with retention of configuration. Hence control of the newly created quaternary chirality center was achieved (Scheme 56).

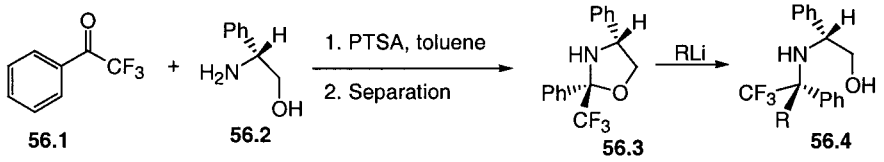
Stable 1,2γ^4-oxaselenetanes **57.7** and **57.8** have been thermally converted into CF_3-substituted epoxides **57.5** and **57.6**.[151] The selenium heterocyclic compounds **57.7** and **57.8** are derived from the substituted phenyl benzyl selenide **57.1** and trifluoroacetophenone **57.2** to give a



Scheme 54.



Scheme 55.



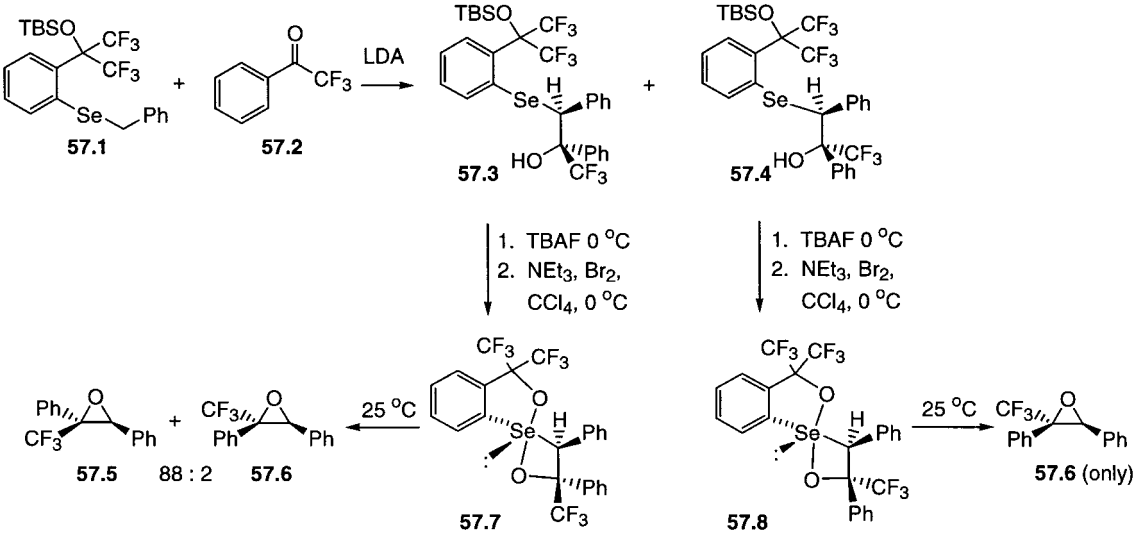
56.1 56.2 56.3 56.4

Scheme 56.

mixture of diastereomers **57.3** and **57.4**, which are separable. The individual diastereoisomers were each reacted with TBAF to remove the silicon group and a bromine oxidation reaction at 0°C formed the 1,2γ^4-oxoselenetanes **57.7** and **57.8**. At 25°C the epoxide **57.5** is formed selectively over epoxide **57.6** from 1,2γ^4-oxoselenetane **57.7** and, specifically, the trifluoromethylated epoxide **57.6** was obtained from the other 1,2γ^4-oxoselenetane **57.8**. A *syn* ligand coupling reaction of the 1,2γ^4-oxoselenetanes is proposed to account for the observed stereoselectivity of the CF_3-substituted epoxide formed (Scheme 57).

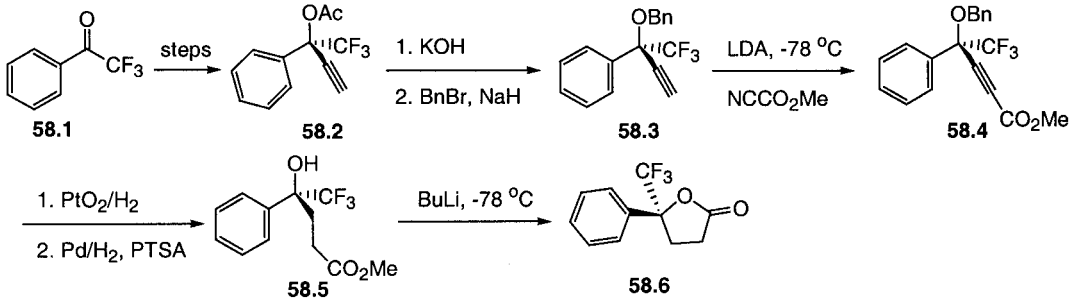
Trifluoroacetophenone **58.1** has been transformed into optically active acetate **58.2** via a hydrolytic resolution of the corresponding racemic acetate with a lipase.[152] Compound **58.2** was converted to (*R*)-γ-phenyl-γ-(trifluoromethyl)-γ-butyrolactone **58.6** in high optically purity (Scheme 58).

A general procedure for the preparation of the diazirine involves treatment of the trifluoromethyl ketone with hydroxylamine, *p*-toluenesulfonyl chloride and ammonia to give the diaziridine, which was then oxidized to diazirine. Scheme 59 shows the preparation of a diazirine peptidyl photo-affinity label that Baldwin et al.[153] required for biosynthetic studies on penicillin synthetase. The trifluoroacetyl ketone **59.1** was converted into its corresponding oxime and was then reacted with toluene-*p*-sulfonyl chloride. The diaziridine **59.2** was prepared from the tosylate using ammonia. A RuO_2-oxidation converted the heterocyclic ring into a diazirine **59.3**. Some further transformation steps were required to incorporate a peptidic portion onto the piece containing the diazirine in order to obtain the full structure of the photo-affinity label. Other photoaffinity labels based on CF_3-substituted trifluorodiazirine have been prepared using similar protocols.[154–156]



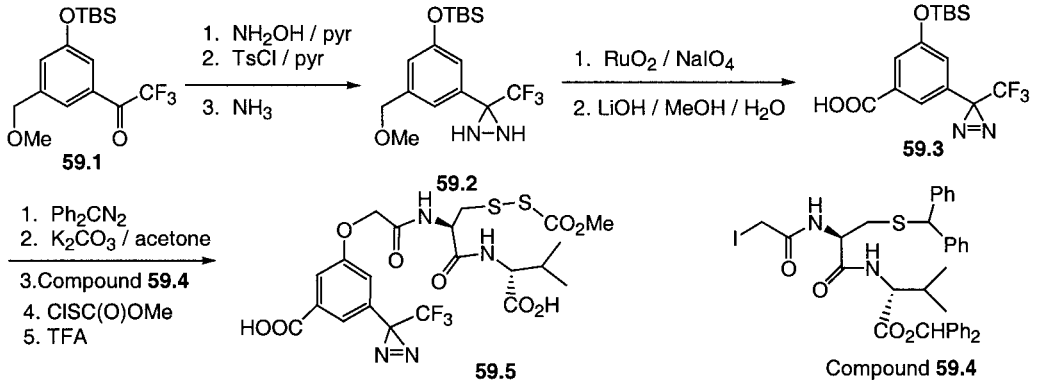
57.1 57.2 57.3 57.4 57.5 57.6 57.7 57.8

Scheme 57.



58.1 58.2 58.3 58.4 58.5 58.6

Scheme 58.

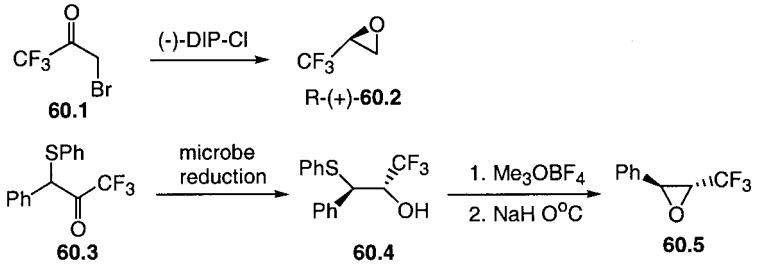


Scheme 59.

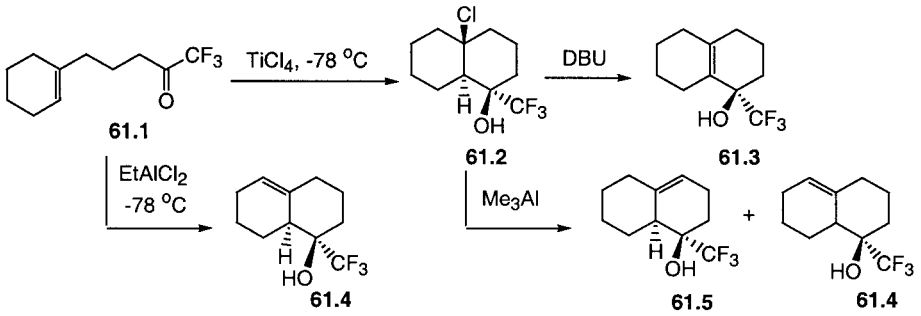
Brown and coworkers[157] have obtained (*R*)-(+)-2-trifluoromethyloxirane **60.2** from 1,1,1-trifluoro-3-bromopropan-2-one **60.1** directly by using (−)-DIP chloride [(−)-*B*-chlorodiisopinocampheylborane]. The opposite enantiomer is available from (+)-DIP chloride [(+)-*B*-chlorodiisopinocampheylborane]. The DIP chloride method for reducing α-bromoketones to give trifluoromethyloxiranes appears to be general and leads to material with high optical purity. β-Hydroxy sulfide **60.4** has also been exploited in a synthesis of (*R*)-(+)-2-trifluoromethyloxirane **60.5**.[158,159] The phenylthiomethyl ketone **60.3** was reduced with sodium borohydride and acetylated with acetic anhydride. An enzymatic resolution using lipase hydrolyses the (*R*)-ester into the (*R*)-alcohol, leaving the (*S*)-ester intact. The (*R*)-alcohol was converted into the epoxide using Meerwein salt and sodium hydroxide.[158] Resnati[159] developed a similar reaction sequence shown in Scheme 60 that used a microbial reduction on ketone **60.3** and thereby avoided the need for an enzymatic resolution.

Intramolecular Friedel–Crafts alkylation and Lewis acid induced ene cyclization of aryl and alkenyl substituted trifluoromethylated ketones have provided a convenient way to synthesize trifluoromethylated heterocycles.[160–167] Scheme 61 shows one example of a Lewis acid induced ene cyclization of an olefinic trifluoromethyl ketone **61.1** that cyclizes to give a trifluoromethyl-substituted decalin and a trifluoromethyl substituted hydrindane in high yield.[165] Depending on the choice of Lewis acid, δ-(1-cyclohexenyl) trifluoromethyl ketone **61.1** selectively leads to either 1-(trifluoromethyl)-1-hydroxy-$\Delta^{5,10}$-octalin **61.2** or to the alcohol compound **61.4**.

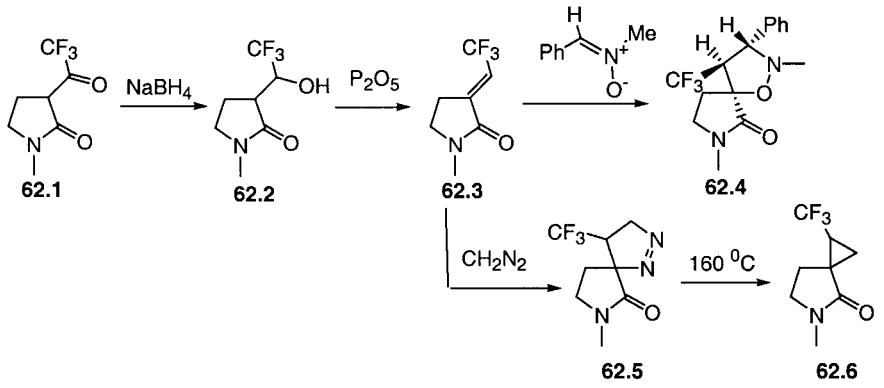
The trifluoromethyl ketones are more reactive than their corresponding methyl ketone and have a similar level of reactivity to that of aliphatic aldehydes. Thus, the cyclization of trifluoromethyl ketones normally requires milder conditions than their non-fluorinated counterparts and accordingly the chemical yields for the reactions are higher. In contrast to methyl ketones, migration of the CF_3-group is not observed in the cyclization of **61.1** in the cationic cyclization process. The complexes formed by a



Scheme 60.



Scheme 61.



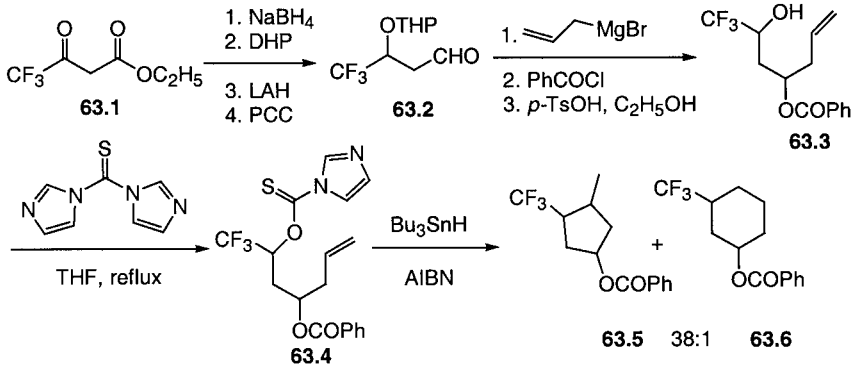
Scheme 62.

trifluoromethylated tertiary alcohol with Lewis acids are stable because the electron-withdrawing CF_3-group prevents a solvolysis or elimination reaction to occur. Thus, a large variety of Lewis acids can be used in the ene reaction with trifluoromethyl ketones (Scheme 61).

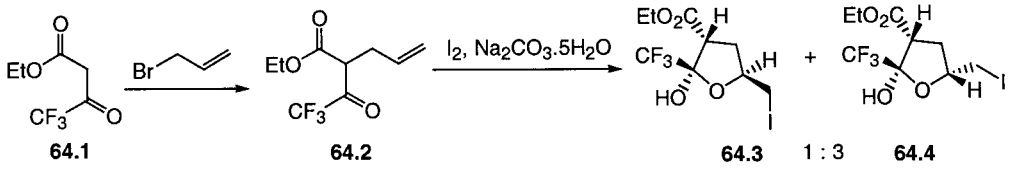
Bouillon et al.[168–173] described the use of 3-trifluoroacetyl substituted γ-lactams for the synthesis of trifluoromethylated heterocycles such as pyrazoles, pyrimidines, oxazolidines, imidazolidines. Sodium borohydride reduction of 3-trifluoroacetyl-substituted lactam **62.1** followed by dehydration gave 3-(2,2,2)-trifluoroethylidene lactam **62.3**. An 1,3-dipolar cycloaddition of compound **62.3** with *N*-methyl-α-phenylnitrone and with diazomethane gave trifluoromethylated spirocyclic isoxazolidine **62.4** and pyrazoline **62.5**, respectively. Heating pyrazoline **62.5** afforded 5-azaspiro[2,4]heptan-4-one **62.6**[173] (Scheme 62).

3.3.2. From ethyl 1,1,1-trifluoroacetoacetate. Taguchi and coworkers[174,175] used a thiocarbonylimidazole derivative in order to generate a radical α to a trifluoromethyl group which was predisposed to react with a terminal double bond in an intramolecular reaction to generate a trifluoromethyl-substituted cyclic compound. The thiocarbonylimidazole derivative **63.4** was prepared from ethyl 1,1,1-trifluoroacetoacetate **63.1**. Through a multistep reaction sequence **63.1** was transformed into the β-trifluoroaldehyde **63.2**. A reaction of aldehyde **63.2** with allylmagnesium bromide followed by benzoylation of the hydroxy group and removal of the tetrahydropyranyl (THP) protecting group gave the alcohol **63.3**. On treatment with 1,1′-thiocarbonyldiimidazole, the hydroxy group of **63.3** was converted to the thiocarbonylimidazole derivative **63.4**. The radical cyclization reaction was carried out using tributyltin hydride and AIBN in benzene which gave the CF_3-substituted cyclopentane **63.5** via a 5-*exo*-cyclization and the cyclohexane **63.6** via a 6-*endo*-cyclization in 77% yield. The product ratio of **63.5** to **63.6** is 38:1[174,175] (Scheme 63).

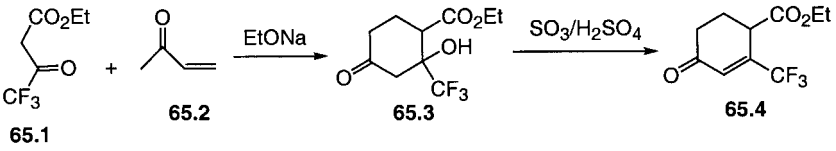
Allylation of ethyl 1,1,1-trifluoroacetoacetate **64.1** by allyl bromide gave the derivative **64.2**.[176] The iodo-etherification



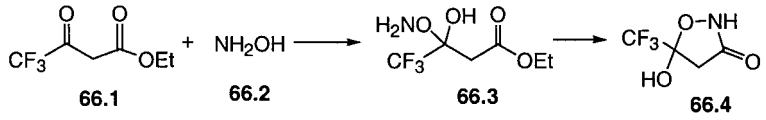
Scheme 63.



Scheme 64.



Scheme 65.



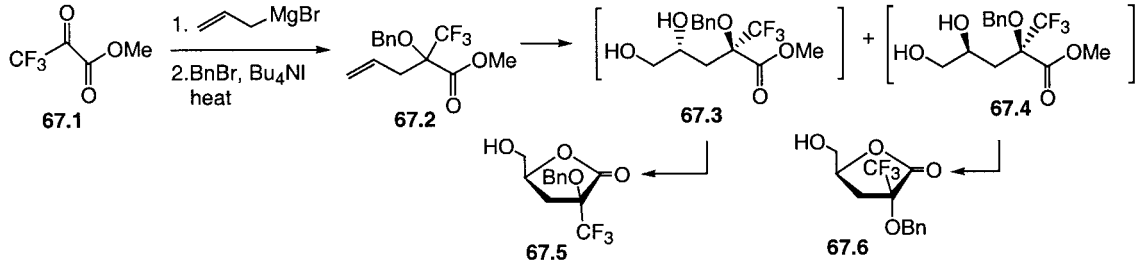
Scheme 66.

of **64.2** with iodine and sodium carbonate in dichloromethane at room temperature gave iodo-hemiketals **64.3** and **64.4** in 90% yield as a 25:75 diastereomeric mixture[177] (Scheme 64).

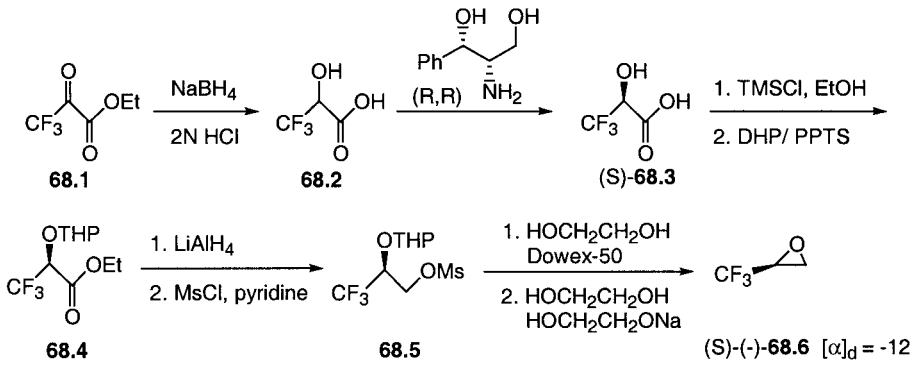
A base-catalyzed cyclization of ethyl 1,1,1-trifluoroacetoacetate **65.1** and methyl vinyl ketone **65.2** provided a mixture of two isomers of 4-carboethoxy-3-hydroxy-3-(trifluoromethyl)cyclohexanone **65.3**, which was then dehydrated with Nordhausen's acid (SO_3/H_2SO_4) to give 4-carboethoxy-3-(trifluoromethyl)-cyclohex-2-enone **65.4** in 40% yield[178] (Scheme 65).

Recently, Chambers et al.[179] described exclusive addition of the oxygen center of hydroxylamine to the ketone carbonyl of ethyl 1,1,1-trifluoroacetoacetate. Thus, addition of a basic solution of hydroxylamine **66.2** to ethyl 1,1,1-trifluoroacetoacetate and subsequent acidification to pH=3 afforded 5-hydroxy-5-(trifluoromethyl)isoxazolidin-3-one **66.4** in 56% yield. The exclusive formation of the product **66.4** was accounted for by the hard-soft acid–base theory. The trifluoromethyl group makes the ketone carbonyl group in **66.1** harder and therefore, the harder nucleophilic center is preferentially attacked by the oxygen atom of hydroxylamine in the first addition step (Scheme 66).

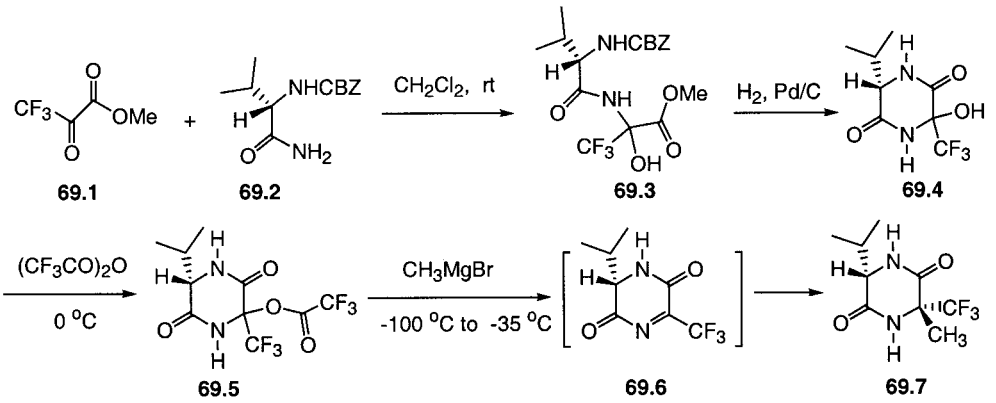
3.3.3. From trifluoromethylpyruvic acid and its ester derivatives. Reaction of allylmagnesium bromide with methyl trifluoropyruvate **67.1** followed by benzylation of the newly formed hydroxy group gave methyl 2-benzyloxy-2-trifluoromethyl-4-pentenoate **67.2**. The benzyl protection of the hydroxy group required an elevated temperature and a catalytic amount of tetrabutylammonium iodide because the electron withdrawing of the geminal trifluoromethyl group decreases nucleophilicity of the hydroxy group. Dihydroxylation of the carbon–carbon double bond of **67.2** with OsO_4 led to a diastereomeric mixture of γ-butyrolactones **67.5** and **67.6** as a 1:1 mixture[180] (Scheme 67).



Scheme 67.



Scheme 68.



Scheme 69.

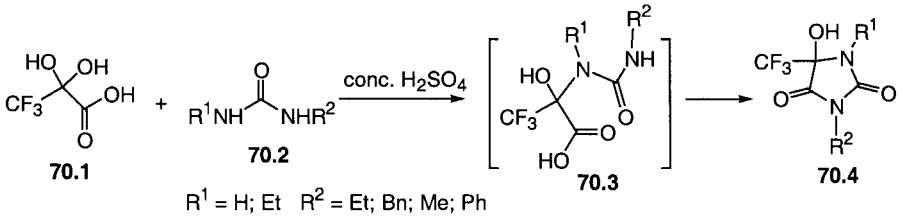
Formation of CF_3-substituted epoxides from bromohydrins is a reaction that has been known for many years.[181] Recently, advances have been made to obtain the CF_3-substitued epoxides in high enantiomeric purity. Seebach[182] used ethyl trifluoropyruvate as a precursor to both enantiomers of 2-trifluoromethyloxirane **68.6** as shown in Scheme 68. Using the resolving agent (*R,R*)-3-hydroxy-3-phenyl-2-aminopropan-1-ol, (*S*)-α-trifluoromethyl-α-hydroxyacetic acid **68.3** was obtained and was converted into the (*S*)-(−)-2-trifluoromethyloxirane **68.6**, while the (*S,S*)-3-hydroxy-3-phenyl-2-aminopropan-1-ol resolved acid was likewise converted into the (*R*)-(+)-2-trifluoromethyloxirane.

Addition of a CBZ-protected α-amino-acid amide **69.2** to methyl trifluoropyruvate gave hemiamidol **69.3**. The adduct **69.3** was converted into the corresponding 3-hydroxy-3-trifluoromethyl-2,5-diketopiperazine **69.4** after removal of the *N*-protecting group by hydrogenation. Trifluoroacetylation of **69.4** with trifluoroacetic anhydride at 0°C gave acylimide **69.5**. The diketopiperazine **69.7** was formed by the addition of methylmagnesium bromide to the imine **69.6** formed in situ via a base-catalyzed elimination. Here, the organometallic reagent acted both as a base and as a trapping reagent. Diketopiperazine **69.7** was formed with 97% d.e. stereoselectivity[183] (Scheme 69).

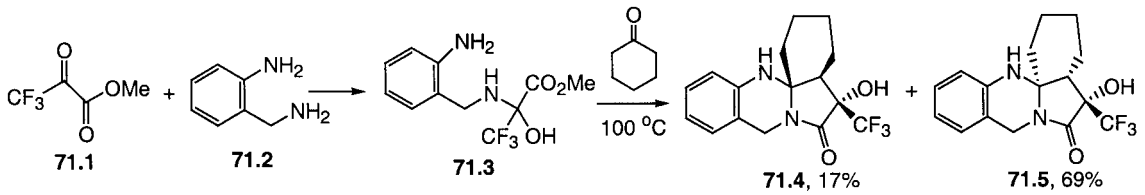
Ishikawa and coworkers[184] reported preparation of 5-hydroxy-5-trifluoromethylhydantoin derivatives from trifluoropyruvic acid hydrate with various urea derivatives in boiling dioxane and concentrated sulfuric acid. The orientation of substituents on the product is consistent with an initial attack on the most active center in trifluoropyruvic acid hydrate by the nucleophiles. Thus, the NH group in urea derivatives attacks preferentially at C-2 in **70.1** leading to the formation of the hypothetical intermediates **70.3** which then cyclize into the various hydantoins **70.4** (Scheme 70).

Addition of 2-aminobenzylamine to methyl trifluoropyruvate afforded mono-adduct **71.3** in quantitative yield.[185] The adduct **71.3** on reaction with cyclohexanone gave the heterocyclic systems **71.4** and **71.5**. The proposed mechanism for the formation of **71.4** and **71.5** involves an enamine intermediate that undergoes intramolecular nucleophilic attack at the aminol carbon bearing the CF_3-group. Breaking of the C–N bond of the aminol occurs in order to obtain products **71.4** and **71.5** (Scheme 71).

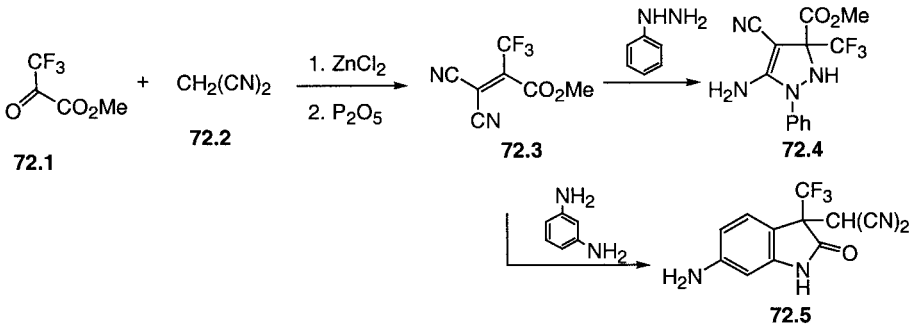
Condensation of methyl trifluoropyruvate with malononitrile gave methyl 3,3-dicycano-2-(trifluoromethyl)acrylate **72.3**.[186,187] *C*-Alkylation of *m*-phenylenediamine with



Scheme 70.



Scheme 71.



Scheme 72.

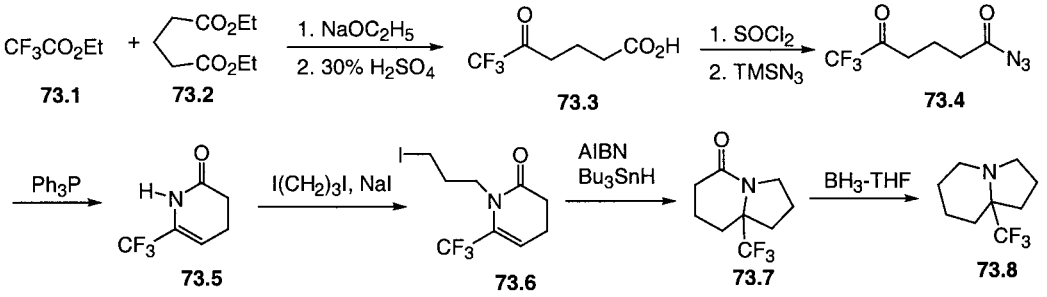
compound **72.3** and subsequent lactamization at 20°C in $CHCl_3$ afforded indoline **72.5**. Compound **72.3** reacted with phenylhydrazine to yield trifluoromethylated pyrazoline **72.4** (Scheme 72).

3.4. Use of trifluoroacetic acid and its derivatives

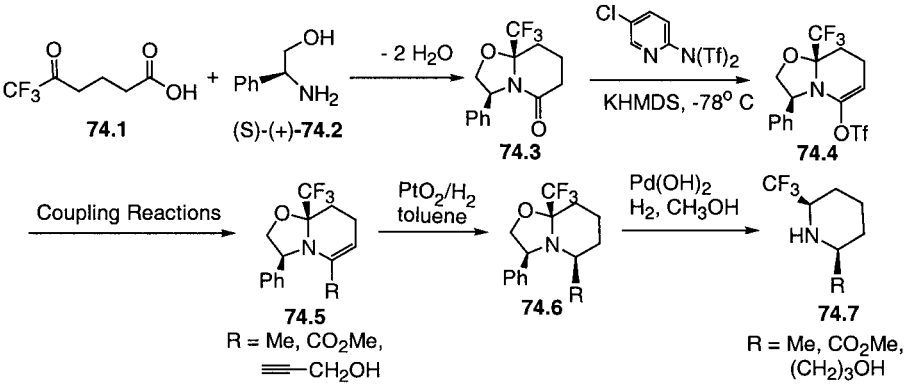
This section describes the chemistry associated with trifluoroacetic acid and its derivatives. In general terms, most trifluoroacetic derivatives require some sort of multistep sequence to incorporate the CF_3–C unit into the ring system that is being constructed. Ethyl trifluoroacetate is often a useful reagent that can be incorporated and extend a carbon chain skeleton through a Claisen condensation reaction before the final ring closure. Also noteworthy is that, unlike normal amides, trifluoroacetamides can undergo Wittig reactions with phosphorus yields readily to generate bifunctional intermediates on which further elaboration may be possible before formation of the ring. Trifluoroacetic anhydride itself is also a useful source of the CF_3-group.

3.4.1. From trifluoroacetic esters. 6,6,6-Trifluoro-5-oxohexanoic acid **73.3** was prepared by Claisen condensation of ethyl trifluoroacetate **73.1** and diethyl glutarate **73.2** with sodium ethoxide followed by decarboxylative hydrolysis in acid. The acid **73.3** was converted into its corresponding acid chloride with thionyl chloride and reaction of the acid chloride with trimethylsilyl azide formed the acid azide **73.4**. A subsequent tandem Staudinger aza-Wittig reaction of **73.4** led to the formation of cyclic enamine **73.5** in 47% yield. *N*-Halo-alkylation of **73.6** followed by a radical cyclization in a 5-*exo* manner afforded indolizidione derivative **73.7** with a trifluoromethyl group at the bridge head position adjacent to nitrogen. Reduction with borane–THF complex gave indolizidine **73.8** (Scheme 73).[11]

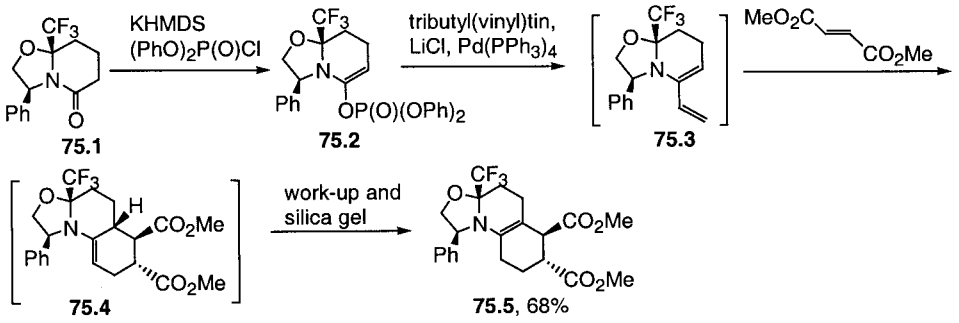
In our laboratory, an efficient synthesis of chiral, nonracemic, trifluoromethyl-substituted piperidines was recently developed from ketoacid **74.1** (prepared as in Scheme 73) via palladium-catalyzed reactions of the α-(trifluoromethanesulfonyloxy) enamine **74.4** (enamine



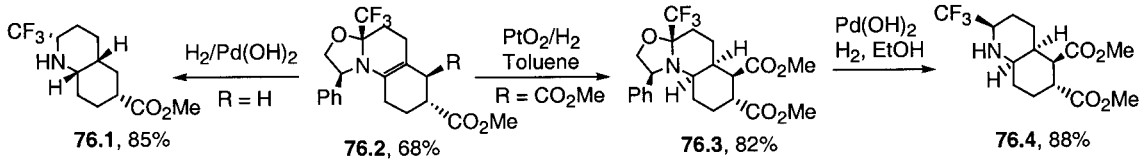
Scheme 73.



Scheme 74.



Scheme 75.



Scheme 76.

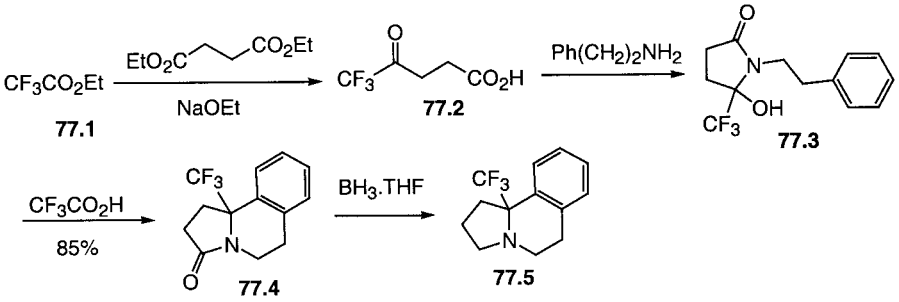
triflate).[188] Thus, reaction of the triflate **74.4** with methyl cuprate and palladium-catalyzed coupling reactions with propargyl alcohol, phenylzinc chloride and carbon monoxide/methanol gave enamines **74.5** in good to excellent yield. The enamine double bond of compounds **74.5** was selectively reduced by hydrogen (45 psi) over PtO_2 in toluene to give the oxazolidine-protected piperidine **74.6**. Hydrogenation of **74.6** over $Pd(OH)_2$ in ethanol gave piperidines **74.7** in 86% yield as single isomers (Scheme 74).

We also found that the cyclic enamine phosphate **75.2** derived from lactam **75.1** reacted with tributyl(vinyl)tin in the presence of catalytic $Pd(PPh_3)_4$ and anhydrous lithium chloride in refluxing THF for 2 h to afford diene **75.3**, which was trapped in situ by dimethyl fumarate to give adducts **75.4**. The initially formed adduct **75.4** was isomerized to adducts **75.5** by stirring with silica gel for 1 h. Adduct **75.5** was obtained as a single isomer in 65% yield (overall isolated yields based on the lactam **75.1**) (Scheme 75).

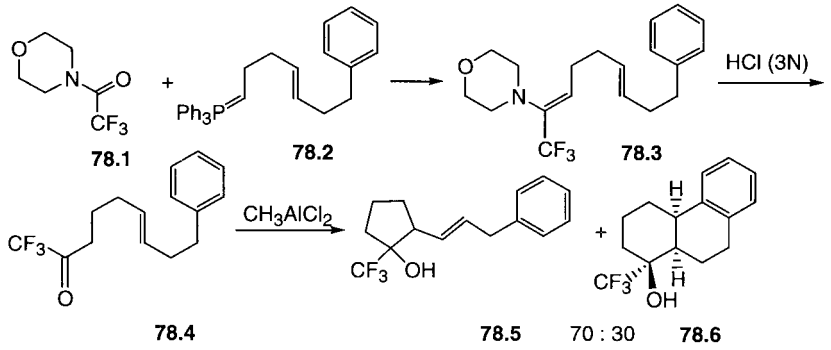
Adduct **76.2** when R=H in Scheme 76 was transformed in high yield by hydrogenation over $Pd(OH)_2$ catalyst into the decahydroquinoline **76.1** with (*S*)-configuration at the 2-position. Compound **76.4** with (*R*)-configuration at the 2-position was obtained by a two-step hydrogenation from compound **76.2** when R=CO_2Me (Scheme 76).

Ethyl trifluoroacetate has been converted by Claisen condensation into 5,5,5-trifluoro-4-oxopentanoic acid **77.2**.[189] Reaction of the γ-ketoacid **77.2** with phenethylamine gave hydroxy lactam **77.3**. Unlike non-fluorinated hemi-amidols or hydroxy-lactams, compound **77.3** was considerably stable owing to the electron-withdrawing effect of the CF_3-group. Dehydration was achieved using more harsh conditions. Thus, treatment with trifluoroacetic acid dehydrated **77.3** to indolizidinone **77.4**. Lactam **77.4** was readily converted into trifluoromethylated cyclic compounds **77.5** in high yield[190] (Scheme 77).

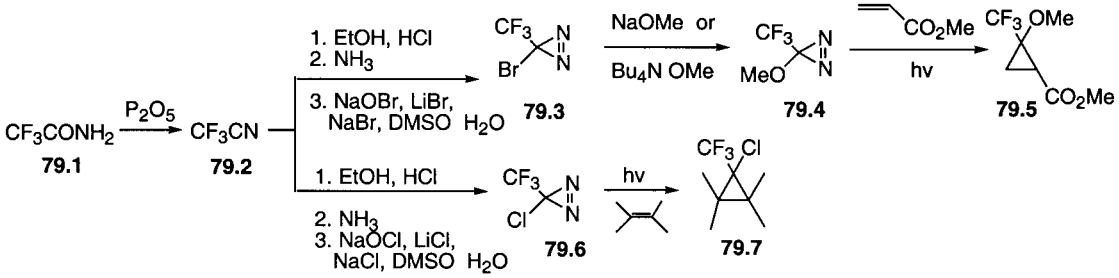
3.4.2. From trifluoroacetamide and related reagents. The electron-withdrawing trifluoromethyl group increases the electrophilicity of the amide carbonyl, thus allowing Wittig reactions to occur at the amido carbonyl group. Bonnet-Delpon and coworkers[191–193] described a Wittig reaction of *N*-trifluoroacetylmorpholine **78.1** followed by hydrolysis that afforded on work up trifluoromethyl ketone **78.4**. A sequential carbonyl ene cyclization of trifluoromethyl ketone was catalyzed by aluminum Lewis acids. Thus, the Me_2AlCl or $MeAlCl_2$-induced cyclization of ketone **78.4** provided a mixture of cyclic products **78.5** and **78.6** in 40% yield[193] (Scheme 78).



Scheme 77.



Scheme 78.

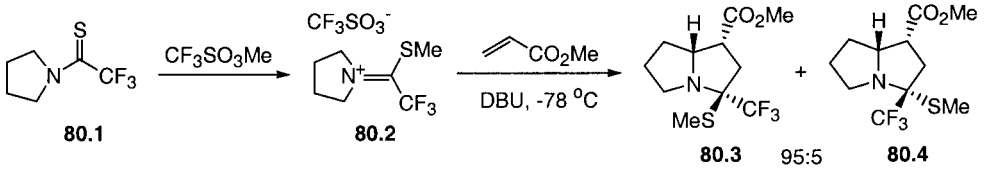


Scheme 79.

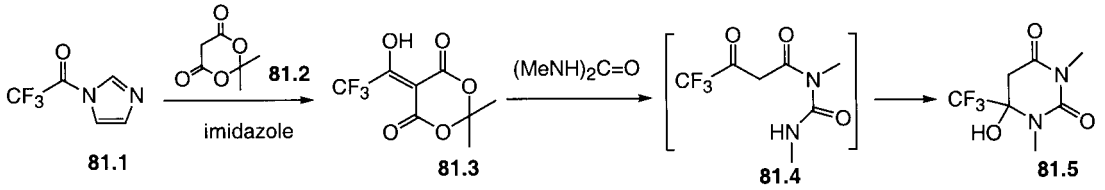
Moss et al.[194] generated trifluoromethyl substituted cyclopropyl ether **79.5** from trifluoroacetamide. Dehydration of the trifluoroacetamide **79.1** to trifluoroactonitrile **79.2**. Subsequent amidine hydrochloride formation followed by a Graham oxidation[195] using sodium hypobromite in aqueous DMSO in the presence of lithium bromide and sodium bromide gave the bromo-diazirine **79.3**. The bromide was displaced with methoxide. Irradiation of the diazirine **79.4** in the presence of methyl acrylate led to the cyclopropyl ether **79.5**. In a similar transformation sequence, trifluoroacetonitrile **79.2** was converted into the chlorodiazirine **79.6** and irradiation of chlorotrifluoromethyl diazirine **79.6** gave chloro-trifluoromethylcyclopropane **79.7**[196] (Scheme 79).

Thioamide **80.1** derived from *N*-trifluoroacetylpyrrolidine and phosphorus pentasulfide was converted into a trifluoromethyl thiomethyl-iminium salt **80.2**. A deprotonation reaction at −78°C with DBU followed by a cycloaddition reaction with methyl acrylate gave pyrrolizidines **80.3** and **80.4** with high diastereoselectivity. This high selectivity can be rationalized both by a mainly *syn*-CF_3 dipole formation and *endo* approach of the dipolarophile and by $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction leading to one major regioisomer[197] (Scheme 80).

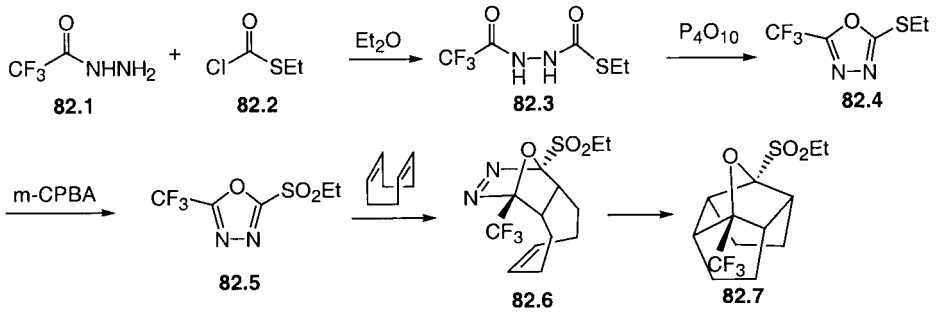
Reaction of *N*-trifluoroacetylimidazole **81.1** with Meldrum's acid **81.2** in the presence of imidazole at room temperature afforded **81.3** in 71% yield.[198] Thermolysis of **81.3** leads to trifluoromethylacetyl ketene generation in situ and reaction of this putative ketene with 1,3-dimethylurea gave the dihydrouracil derivative **81.5** in 90% yield



Scheme 80.



Scheme 81.



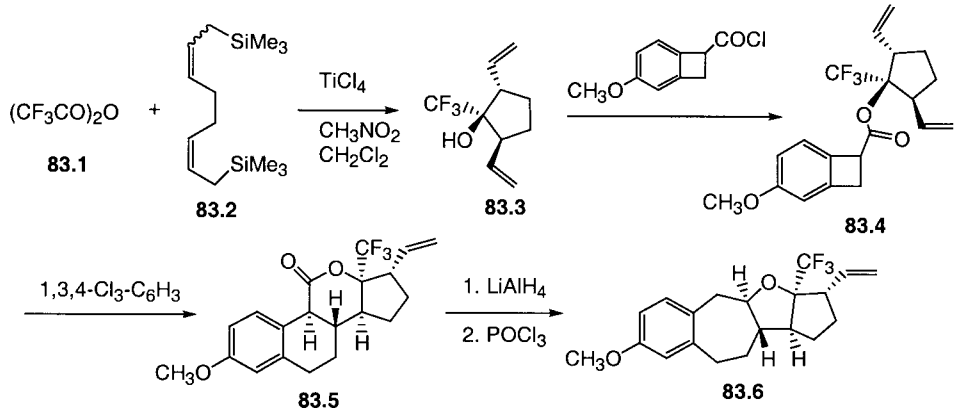
Scheme 82.

presumably via the intermediate of trifluoroacetoacetamide derivative **81.4**. 1,3-Dimethylthiourea may be used instead of 1,3-dimethylurea in this reaction (Scheme 81).

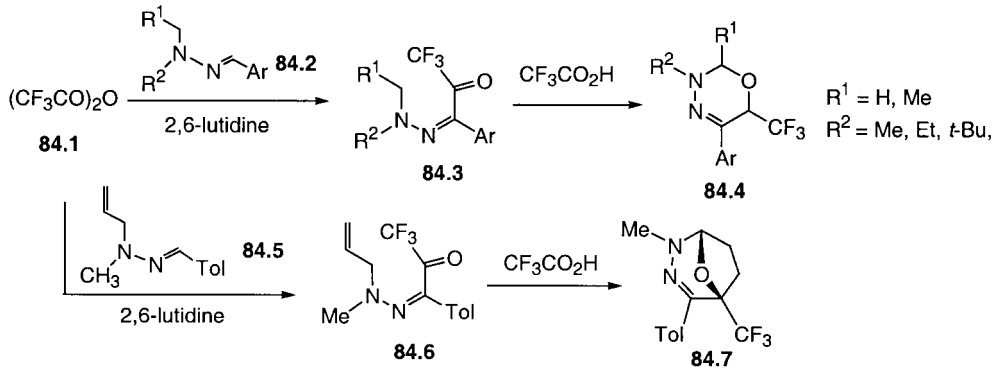
2-Ethanesulfonyl-5-trifluoromethyl-1,3,4-oxadiazole **82.5** was prepared from trifluoroacetic acid hydrazide **82.1** in a three step sequence.[199] Reaction of compound **82.5** with 1,5-cyclooctadiene gave the cage compound **82.7** in a stereospecific three-step reaction sequence: a [4+2] cycloaddition, a [3+2] cycloreversion and a final [3+2] cycloaddition (Scheme 82).

3.4.3. From trifluoroacetic anhydride. Santelli and coworkers[200,201] reported addition reaction of 1,8-bis(trimethylsilyl)-2,6-octadiene **83.2** to trifluoroacetic anhydride to give *dl*-1-trifluoromethyl-2,5-divinylcyclopentan-1-ol (**83.3**). Scheme 83 shows the preparation of a B(9α)-homo-*C*-norsteroid **83.6** from the alcohol **83.3**. Esterification of compound **83.3** with 4′-methyoxybenzocyclobutene-1-carboxylic acid chloride and subsequent heating gave (+/−)-3-methoxy-12-oxa-18,18,18-trifluoromethyl-17-vinylestra-1,3,5(10)trien-11-one (**83.5**). Lactone **83.5** was reduced with lithium aluminum hydride into the diol and on treatment with phosphorus oxychloride compound **83.6** was obtained.

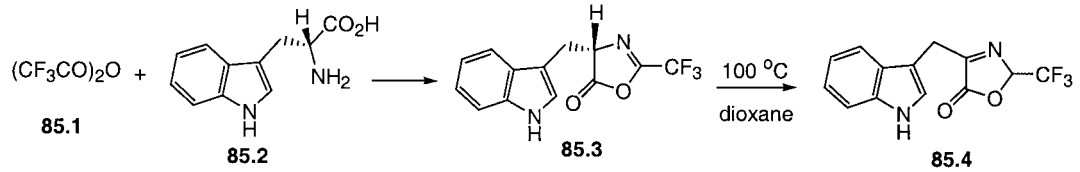
Reaction of arene carboxaldehyde *N*-methyl-*N*-alkyl hydrazones with trifluoroacetic anhydride afforded trifluoroacetyl hydrazones **84.3**. Treatment of hydrazones **84.3** with trifluoroacetic acid at room temperature gave 6-trifluoromethyl-3,6-dihydro-2*H*-1,3,4-oxadiazine **84.4**.[202–204] There was an exception. Treatment of the *N*-allyl substituted



Scheme 83.



Scheme 84.



Scheme 85.

hydrazone **84.5** with trifluoroacetic acid gave a bicyclic oxadiazine derivative **84.7**[205] (Scheme 84).

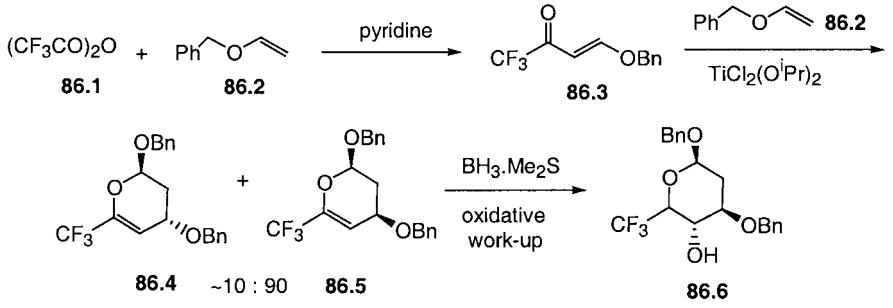
Steglich and coworkers[206–208] have reported the reaction of α-amino acids with trifluoroacetic anhydride to give 2-trifluoromethyl-5(4*H*)-oxazolones. The first-formed 2-trifluoromethyl-5(4*H*)-oxazolones are readily isomerized at 100°C to 2-trifluoromethyl-5(2*H*)oxazolones. In a more recent reinvestigation of the reaction, Bergmann and Lidgren[209] reported that the transformation of tryptophan by trifluoroacetic anhydride into the crystalline 2-trifluoromethyl-5(4*H*)-oxazolone (**85.3**) occurred without racemization. Dissolution of optically active **85.3** in acetonitrile gave racemic tryptophan compound **85.3**, whereas treatment of **85.3** with hot aqueous dioxane for a few minutes gave achiral oxazolone **85.4** in 80% yield (Scheme 85).

Reaction of trifluoroacetic anhydride with benzyl vinyl ether **86.2** afforded the heterodiene **86.3**. The thermally activated cycloaddition of the heterodiene **86.3** with enol ether **86.2** gave an approximately 1:1 mixture of *endo* and *exo* cycloadducts in good yield[210] while a titanium-derived Lewis acids promoted cycloaddition of heterodiene **86.3** and enol ether **86.2** showing high *endo* diastereoselectivity. The cycloadduct is useful for the synthesis of sugar derivatives. For example treatment of cycloadduct **86.5** with borane-dimethyl sulfide followed by an oxidative workup gave the protected β-glycoside derivative **86.6** in 72% yield[211] (Scheme 86).

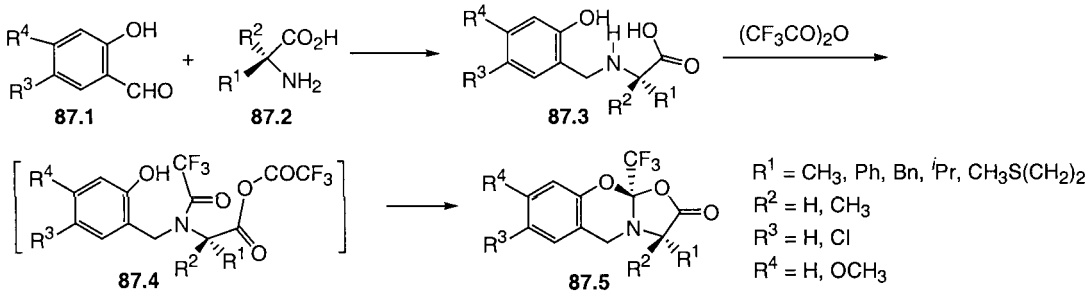
A diastereospecific double ring closure of *N*-(2-hydroxybenzyl)-α-amino acids (**87.3**) has been reported to react with trifluoroacetic anhydride and leads to the formation of 10a-trifluoromethyl-2,3,4,10a-tetrahydro-[1,3]oxazolo[2,3-*b*][1,3]benzoxazin-2(5*H*)-ones (**87.5**) in 66–81% yield.[212] Thus, when an optically active amino acid was used as the starting material, a single diastereomer **87.5** was obtained (Scheme 87).

3.5. Use of miscellaneous trifluoromethyl carrier reagents

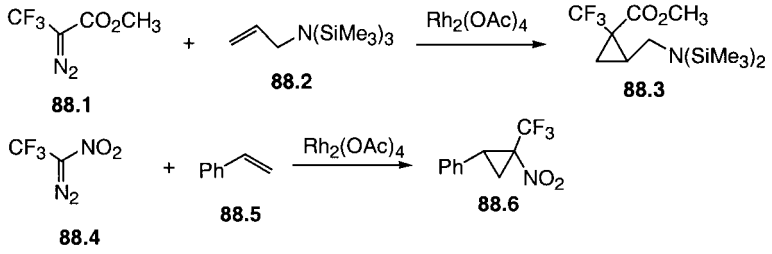
Cyclopropanation of olefins using carbenoids has been known for some time. Early work by Seyferth[213–215] showed that trifluoro-substituted cyclopropanes may be prepared from olefins by thermolysis of appropriate organomercurial compounds to form a trifluoromethyl substituted carbenoid intermediate. More recently, rhodium(II) acetate mediated reaction of trifluoromethyl substituted diazo compounds has provided an easy way to trifluoromethylated carbenoids that react with olefins to give cyclopropyl systems. Two examples using rhodium are shown below, the first is for a



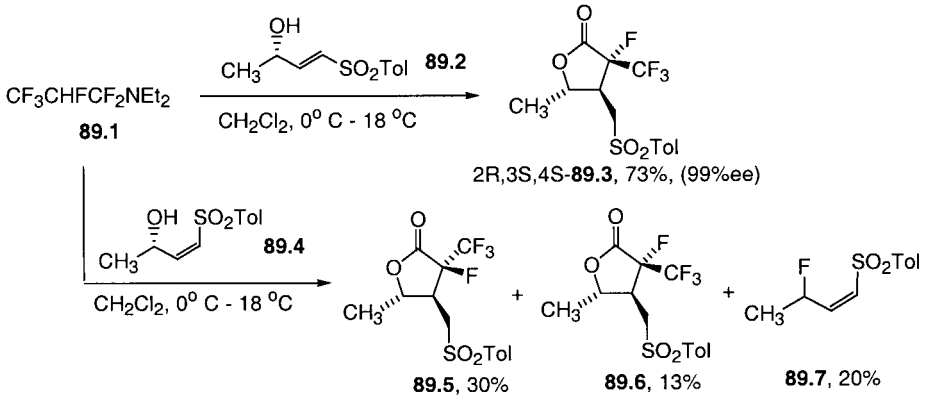
Scheme 86.



Scheme 87.



Scheme 88.



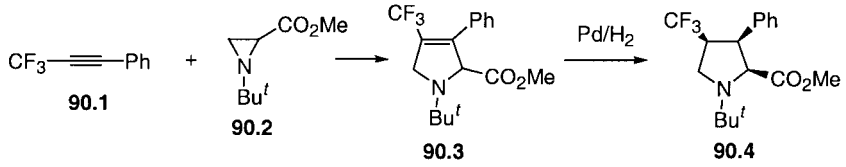
Scheme 89.

bis-silylated allylamine[216] and the second for styrene[217] (Scheme 88).

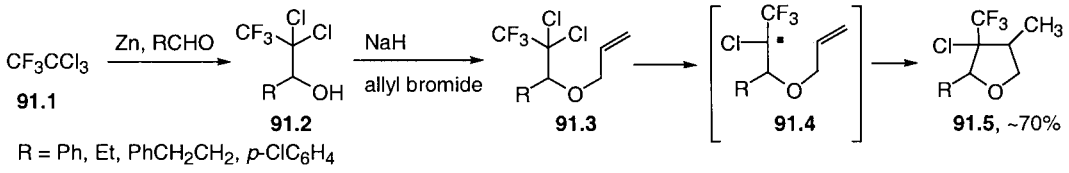
(*E*)-3-Hydroxy-1-alkenyl *p*-tolyl sulfone **89.2** was reacted with a hexafluoropropene-diethylamine adduct [or perfluoropropene-diethylamine adduct (PPDA)] **89.1** to afford α-fluoro-α-trifluoromethyl-β-[(*p*-toluenesulfonyl)-methyl]-γ-lactone (**89.3**) as a single diastereomer. However, reaction of (*Z*)-3-hydroxy-1-alkenyl *p*-tolyl sulfone **89.4** with PPDA gave a mixture of γ-lactone **89.5** in 30% yield and **89.6** in 13% yield along with the fluorinated product **89.7** shown in Scheme 89.[218,219] In the reaction of the (*E*)-isomer **89.2**, formation of the lactone **89.3** requires that a hydrogen be γ to the sulfonyl group since reaction of (*E*)-3-hydroxy-3-methyl-1-butenyl *p*-tolyl sulfone failed to give any lactone product.

1-Aryl-3,3,3-trifluoro-1-propynes have been shown to undergo cycloaddition reactions easily with dipoles such as nitrile oxides and azides to give aryl trifluoromethyl substituted isoxazoles and 1,2,3-triazoles.[220,221] A thermal ring opening of methyl 1-*tert*-butylaziridine-2-carboxylate **90.2** with 1-phenyl-3,3,3-trifluoro-1-propyne has also been reported. Addition of the assumed azomethine ylid to the CF_3-substituted acetylene **90.1** gave two regioisomeric pyrrolines[222] one of which, the major product **90.3**, was isolated and hydrogenated to give racemic pyrrolidine **90.4** (Scheme 90).

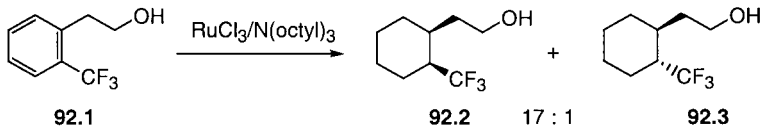
An α-trifluoromethyl carbon radical **91.4**, that was generated using a tributyltin radical, added intramolecularly to a terminal carbon–carbon double bond to afford the CF_3-substituted tetrahydrofurans **91.5**.[223–225] The starting



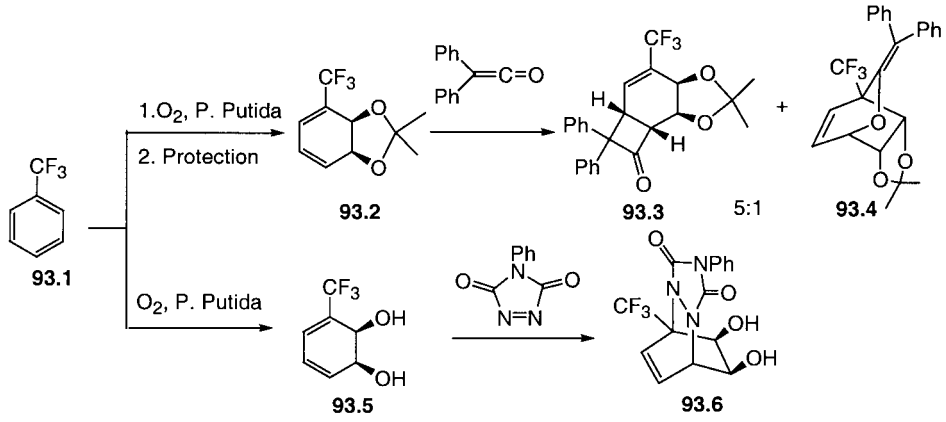
Scheme 90.



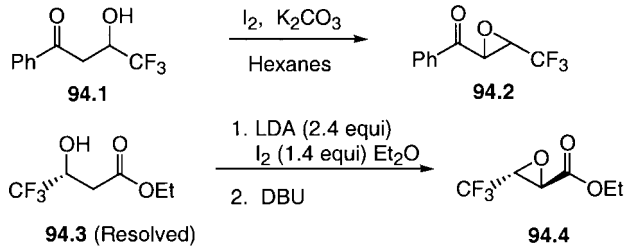
Scheme 91.



Scheme 92.



Scheme 93.



Scheme 94.

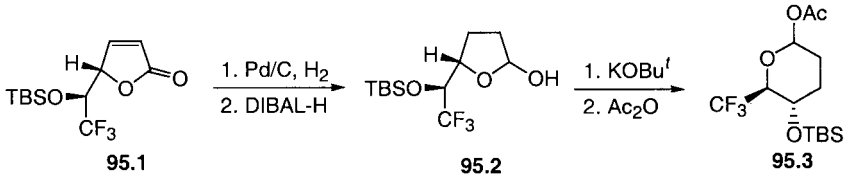
materials **91.3** were prepared by reaction of allyl bromide with 2-trifluoromethyl-2,2-dichloroethyl alcohols. The latter alcohols came from the reaction of 1,1,1-trifluoro-2,2,2-trichloroethane **91.1** with aldehydes in the presence of zinc[226] (Scheme 91).

Hydrogenation of substituted benzene-derived aromatic compounds provides access to numerous cyclohexyl derivatives whose syntheses by direct cyclization methods often prove difficult. Trifluoromethylated saturated cycles can also be produced by hydrogenation. For example, Lemaire and coworkers[227] described a colloidal ruthenium-catalyzed hydrogenation of 2-(2-trifluoromethylphenyl)ethanol **92.1** to the corresponding 2-(2-trifluoromethylcyclohexyl)ethanols **92.2** and **92.3** in 77% yield as a 17:1 *cis/trans* mixture (Scheme 92).

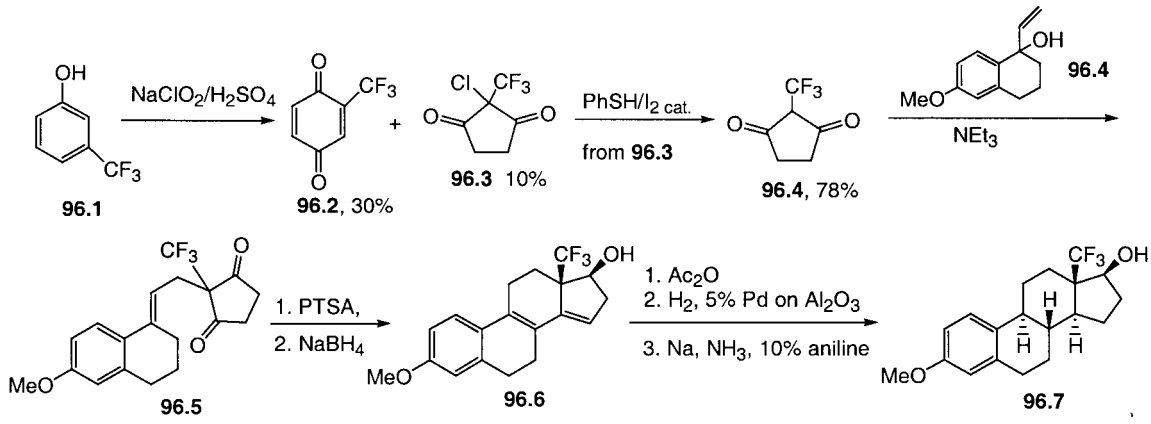
Microbial oxidation of trifluoromethylated benzene has been shown to give rise to optically pure 1,3-cyclohexadiene-5,6-diols. Reaction of the cyclohexadiene **93.2** with diphenylketene gave a [2+2] cycloaddition adduct as the major product,[228] while the reaction of *cis*-diol **93.5** with 4-phenyl-1,2,4-triazoline-3,5-dione at ambient temperatures has been reported to give a [4+2] cycloadduct **93.6** in 75% yield (Scheme 93).[228–230]

CF_3-substituted epoxides have been derived from β-hydroxy esters and ketones. As shown in Scheme 94 base treatment of the β-hydroxy ketone **94.1** followed by iodine leads to a mixture of epoxides.[231] Using a resolved β-hydroxy ester **94.3**, Seebach[232] was able to generate the *trans*-epoxide. Here, the first-formed lithium alcoholate chelates with the carbonyl group and subsequent iodination occurs from the less-hindered face. Epoxide formation using DBU appears to be mild enough not to racemize the chirality center at C-2.

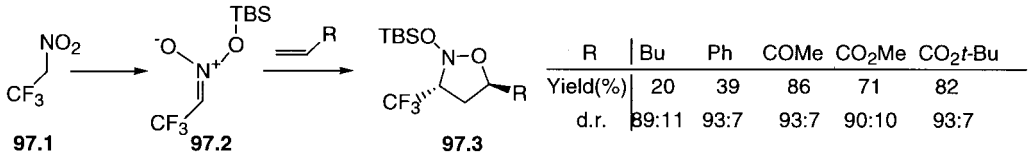
Butenolide **95.1** has been prepared from furan and ethyl trifluoroacetate in a multi-step synthesis that involved an enzymatic optical resolution.[233] Kitazume and coworkers[234,235] reported that potassium *t*-butoxide promoted a 1,2-silyl migration of the TBS group on the furanoside **95.2** to afford 6-deoxy-6,6,6-trifluoromethyl pyranoside **95.3** as the major product after acetylation. The existence of the electron-withdrawing CF_3-group is



Scheme 95.

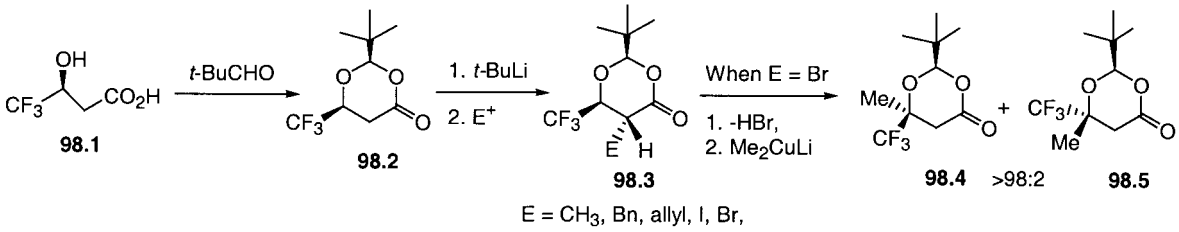


Scheme 96.



R	Bu	Ph	COMe	CO_2Me	CO_2t-Bu
Yield(%)	20	39	86	71	82
d.r.	89:11	93:7	93:7	90:10	93:7

Scheme 97.



Scheme 98.

key to attaining the 95:5 selectivity of the pyranoside form over that of the furanoside (Scheme 95).

Blazejewski [108,109] reported that a chlorous acid oxidation on 3-trifluoromethylphenol **96.1** gave 2-trifluoromethyl-1,4-benzoquinone **96.2** in 30% yield and 2-chloro-2-trifluoromethyl-1,3-cyclopentadione **96.3** in 10% yield. A reduction reaction on 2-chloro-1,3-cyclopentadione **96.3** removed the chlorine atom and gave 1,3-cyclopentadione **96.4** which was used for synthesis of various trifluoromethylated steroidal compounds such as **96.7**[236–241] (Scheme 96).

Trifluoromethylated silyl nitronate **97.2** is readily prepared by silylation of the corresponding nitroalkane **97.1**.[242] Seebach et al. studied the 1,3-dipolar cycloaddition reaction of **97.2** with olefins to give *N*-(silyloxy)isoxazolidines **97.3** with a relative configuration of 2,3-*cis* and 3,5-*trans*. The major course of the reaction was determined to be *exo*-approach of the dipolarophiles toward the (*Z*)-silyl nitronate (Scheme 97).

Seebach and coworkers[243–246] have extensively studied the chemistry of 1,3-dioxanes **98.2**. The 1,3-dioxanes **98.2** are obtained from enantiomerically pure (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid **98.1**, available by a big scale classical resolution, with pivaldehyde and acid catalysis. The lithium enolate derived from the *cis* 1,3-dioxane **98.2** was reacted with electrophiles such as alkyl halides, aldehydes or bromine. A preference for the formation of the *trans*, *trans*-2,5,6-trisubstituted-1,3-dioxanes is normally seen. Conditions have been developed that lead to elimination of hydrogen bromide from 5-bromo-substituted 1,3-dioxane derivative **98.3**. The expected α,β-unsaturated systems undergo Michael addition reactions with organocuprates to produce 6,6-disubstituted 1,3-dioxanes with a CF_3-group situated at C-6 (Scheme 98).

4. Summary

Synthesis of mono-trifluoromethylated saturated cycles has emerged as an important research area that has previously received little attention in reviews. This review illustrates a variety of reagents available for direct trifluoromethylation of non-fluorinated cycles, and various CF_3-containing synthetic building blocks that may be incorporated into the cyclic compounds. Direct trifluoromethylation has been dominated by the use of TFMTMS on cyclic ketones and lactones because of its simplicity. The more widely applicable approach is that of converting readily available

simple trifluoromethylated compounds into a variety of cycles. Here, the Diels–Alder reactions and 1,3-dipolar cycloadditions of the trifluoromethylated alkenes are of significant value. Many mono-trifluoromethylated saturated cycles are accessible from trifluoromethylated carbonyl compounds by a number of multiple-step synthetic routes. It is hoped that this Report will help guide synthetic chemists who are not organo-fluorine specialists to develop synthetic routes to trifluoromethylsubstituted saturated cycles.

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Biographical Sketch

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Jinlong Jiang, born in 1962 in China, received his BSc (1982) and MSc (1985) in chemistry from Hangzhou University. He worked on his MSc thesis under the supervision of Prof. Yongmin Zhang in the area of organo-transitionmetallic chemistry. From 1985 to 1988, he was a lecturer teaching physical organic chemistry for undergraduate students at the same university. In 1993, he received his Ph.D in synthetic organic chemistry and heterocyclic chemistry from the University of Florida, USA, under the supervision of Prof. Alan R. Katritzky. After 2 years of postdoctoral research in the same group, he joined Merck & Co. Inc. as a senior research chemist. His current research interests include medicinal chemistry and organic synthesis. He has authored and co-authored 31 research and review publications in organic chemistry.