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Synthesis and Diels–Alder reactions of α-fluoro- and α-trifluoromethylacrylonitriles

Valentine G. Nenajdenko [a,*], Vasiliy M. Muzalevskiy [a], Aleksey V. Shastin [b], Elizabeth S. Balenkova [a], Günter Haufe [c,*]

[a] *Moscow State University, Department of Chemistry, Leninskie Gory, Moscow 119992, Russia*
[b] *Institute of Problems of Chemical Physics, Chernogolovka, Moscow Region 142432, Russia*
[c] *Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, D-48149 Münster, Germany*

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Abstract

A novel synthetic method for the preparation of α-fluoro- and the still unknown α-trifluoromethylacrylonitriles is elaborated. The reaction of α-fluorovinylbromides and α-trifluoromethylvinylbromides with CuCN leads to the title compounds in good to high yields. While the α-fluoroacrylonitriles were isolated as mixture of *Z*/*E*-isomers, the α-trifluoromethylacrylonitriles were obtained as pure *Z*-isomers. The α-trifluoromethylacrylonitriles are shown to be excellent dienophiles for Diels–Alder reactions.

Keywords: Catalytic olefination reaction; Substitution with CuCN; α-Fluoroacrylonitriles; α-Trifluoromethylacrylonitriles; Diels–Alder reaction

1. Introduction

Fluorine-containing drugs and pesticides are an object of increasing interest in modern bioorganic chemistry due to their remarkable biological activity [1–5]. Extensive studies have been made to develop a cheap and efficient synthetic methodology for the synthesis of various organofluorine compounds [6–9]. Biologically active molecules containing a vinylic fluorine atom are of special interest, in part, because fluoroolefins are potential enzyme inhibitors [10] and can be used as an isosteric replacement for an amido group in peptides [11–13] or aminoacids [14].

Recently, we reported a novel catalytic olefination reaction (COR) of aldehydes and ketones [15–23]. It was found that *N*-unsubstituted hydrazones of carbonyl compounds can be smoothly transformed into various substituted alkenes by treatment with polyhalogenoalkanes in the presence of catalytic amounts of CuCl. It was also shown that COR can be successfully used for synthesis of different fluorocontaining alkenes. Based on COR we elaborated a novel approach to synthesis of β,β-chlorofluorostyrenes ArC(H)=C(Cl)F [20], β,β-chloro(trifluoromethyl)styrenes ArC(H)=C(Cl)CF_3, β,β-fluoro(chlorodifluoromethyl)styrenes ArC(H)=C(F)CF_2Cl [21], *gem*-difluoroalkenes [22], β,β-fluoro(bromodifluoromethyl)-styrenes ArC(H)=C(F)CF_2Br [23], β,β-bromo(trifluoromethyl)-styrenes ArC(H)=C(Br)CF_3 [24] and β,β-bromofluorostyrenes ArC(H)=C(Br)F [25].

The advantages of the proposed method over existent methods like Burton's Wittig-type conversion of benzaldehydes [26,27] are the inexpensive starting materials, convenient reaction conditions and smooth handling of the products. Also utilizing of excess of metalloorganic or organophosphorous compounds is not required. β,β-Bromo(trifluoromethyl)styrenes and β,β-bromofluorostyrenes are of special interest because of rather labile bromine–carbon bond, which opens a pathway for direct substitution reactions with different nucleophiles. As result various alkenes can be prepared.

It should be very interesting to replace bromine by a cyano group, because it could open a new route to α-fluoroacrylonitriles and the still unknown α-trifluoromethylacrylonitriles. The electron-deficient double bond of this class of compounds might be useful for both the Michael addition [28], and the Diels–Alder reaction [29]. Also the nitrile function might be

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* Corresponding author.
E-mail addresses: nen@acylium.chem.msu.ru (V.G. Nenajdenko), shastin@icp.ac.ru (A.V. Shastin), haufe@uni-muenster.de (G. Haufe).

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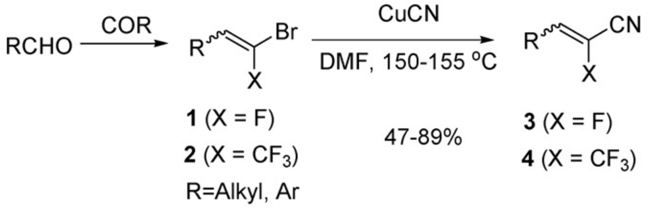


Scheme 1. Reaction of α-fluoro- and α-trifluoromethyl vinylbromides with copper(I) cyanide.

converted into an ester through the Pinner reaction [30], or into an aldehyde by reduction with diisobutylaluminum hydride (DIBALH) and hydrolysis [31,32].

Different synthetic approaches have been proposed for synthesis of 2-fluoroacrylonitriles [28,31,32–36]. The most general route is based on the Horner–Wadsworth–Emmons (HWE) reaction of a cyanofluoromethyl-substituted phosphonate with carbonyl compounds [31,32,36,37]. But usually, these reactions proceed with low stereoselectivity and require utilization of absolute solvents, organometallic and toxic organophosphorous compounds.

2. Results and discussion

2.1. Synthesis of 2-fluoro- and 2-trifluoromethylacrylonitriles

The reaction of bromoarenes with CuCN is well known and it is one of most powerful methods for preparation of aromatic nitriles [38]. It was also reported, that substitution of the bromine atom in vinylbromides is possible under the conditions of this reaction. [39]. At the beginning, we investigated the reaction of 1-(2-bromo-2-fluorovinyl)-4-chlorobenzene with CuCN in DMF at 90 to 120 °C. But at these temperatures reaction proceeded very slow. On the other hand, strong sudden tarring was observed after 5–6 h at this temperature. However, heating at 150–155 °C led to complete conversion of bromofluorostyrene giving the target nitrile in 82% yield during 3 h. It should be noted, that in the case of longer reaction times the yield dropped down because of decomposition. We also found, that these conditions are suitable for the conversion of 1-(2-bromo-2-trifluoromethylvinyl)-4-chlorobenzene to the corresponding nitrile in good yield. Using these optimized reaction conditions, we studied the synthetic scope of the method for the preparation of α-fluoroacrylonitriles and α-(trifluoromethyl)acrylonitriles. It was shown, that a wide variety of aromatic vinyl bromides containing both electron donating and electron-withdrawing substituents at the aromatic ring **1**, **2a**–**1**, **2i** can be converted to the corresponding α-fluoro- **3** and α-trifluoromethylacrylonitriles **4** (Scheme 1, Table 1).

Aliphatic α-fluoroacrylonitriles also could be obtained by this method (see **3k**). Unfortunately in case of the heptyl substituted aliphatic α-(trifluoromethyl)acrylonitrile only traces of the desired product **4k** were obtained. The stereoselectivity of the reaction of bromofluoroalkenes with CuCN was quite good and alkenes **3** were obtained as mixtures of *Z*/*E*-isomers in which the *Z*-isomers dominate. The ratio of *Z*/*E*-isomers of α-fluoroacrylonitriles **3** was almost the same like in the initial vinylbromides. In case of the 2-bromo-2-(trifluoromethyl)styrenes **2** the reaction proceeds 100 % stereoselectively and the *E*-isomers of the α-(trifluoromethyl)acrylonitriles were obtained as the sole products, although the initial styrenes **2** were used as a mixture of *Z*/*E*-isomers (Table 1).

The structure of isomers was determined by NMR spectroscopy. It is well known, that coupling constants between atoms at double bond in *cis*-position are smaller than in *trans*-position. The configuration of isomers was doubtlessly determined by comparison of coupling constants $^3J_{H,F}$ between fluorine and the vinylic proton in ^{1}H NMR spectra of fluoroalkenes **3** (for values of $^3J_{H,F}$ constants see Section 4).

To determine the configuration of the α-(trifluoromethyl)acrylonitriles, the ^{13}C NMR spectrum for compound **4b** was recorded without proton decoupling and the spin–spin coupling constants between the nitrile C atom and the trifluoromethyl C atom with the proton at the double bond were measured. We found that the $^3J_{H,C}$ constant of nitrile group is 13.8 Hz and $^3J_{H,C}$ constant of trifluromethyl group is 7.4 Hz. Consequently, proton and nitrile group are in *trans*-position and compounds **4** have *E*-configuration.

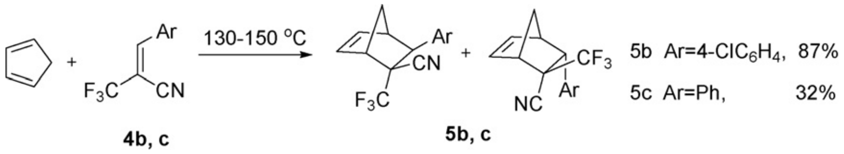
2.2. Diels–Alder reactions of 2-fluoro- and 2-trifluoromethylacrylonitriles

The Diels–Alder reaction is the most attractive approach for the synthesis of selectively fluorinated mono- or polycyclic

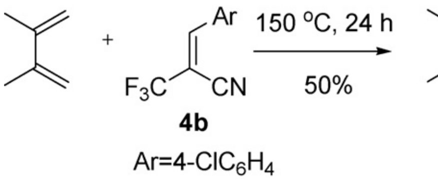
Table 1
Synthesis of nitriles **3** and **4**

	R	*E*/*Z* ratio, **1** [25]	*Z*/*E* ratio, **2** [24]	*Z*/*E* ratio, **3** (%)	Yield of **3**	Yield of **4** (%)
a	4-$NO_2C_6H_4$–	3.5		3.4	83	–[a]
b	4-ClC_6H_4–	6	7.5	4.3	82	75
c	Ph	6.2	7.0	4	70	72
d	4-$MeOC_6H_4$–	5	8.4	5.4	89	85
e	3,4-$MeOC_6H_3$–	4.5	8.2	6.3	70	70
f	4-$CO_2MeC_6H_4$–	3.5	4.8	3.2	81	58
g	2-$MeOC_6H_4$–	3.6	7.9	3.9	79	82
h	2-$NO_2C_6H_4$–	3.3	8.2	3.5	47	62
i	4-MeC_6H_4–	5.5	8.7	2.4	64	67
k	*n*-C_7H_{15}–	0.9	–	0.8	54	Traces

[a] Reaction was not carried out.



Scheme 2. Reactions of cyclopentadiene with α-trifluoromethylacrylonitriles.



Scheme 3. Reaction of nitrile **4b** with 2,3-dimethylbutadiene.

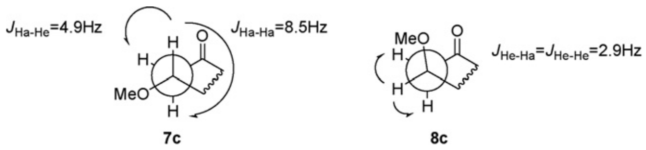


Fig. 1. Coupling constants of compounds **7c** and **8c**.

cyclohexene derivatives [40,41]. This type of reactions has been shown to be of particular interest in syntheses of fluorinated analogues of biologically active compounds such as cantharidin, endothall [42] and D-homosteroids [43]. Previously, we found that simple vinyl fluorides such as α- or β-fluorostyrenes are weak dienophiles which only react with very active dienes like diphenylisobenzofuran [44,45] or some fluorinated cyclohexa-2,4-dienones [46]. Electron-withdrawing substituents such as carbonyl functions, sulfoxide or sulfonyl groups attached to the fluorovinyl moiety increase the reactivity of the dienophiles. Therefore, 2-fluoroacroleins [47,48], α,β-unsaturated α-fluorocarboxylic acid derivatives [49–54], and unsaturated α,β-difluoroketones [55,56], β-fluoroalkylated enones [57], fluorinated furan-2(5H)-ones [58], fluorinated vinylsulfones [59,60] or an electron-poor fluorinated vinyl sulfoxide [61] were shown to be moderate or good dienophiles.

So, we decided to use prepared nitriles for Diels–Alder reactions. First, we investigated reactions of α-trifluoromethylacrylonitriles **4** with cyclopentadiene and found, that rather high temperature is needed for this reaction. The nitrile **4b** was completely converted to Diels–Alder adduct **5b** with excellent yield by heating to 130 °C without solvent for 16 h (Scheme 2).

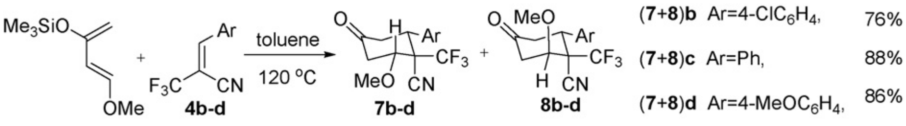
In case of the less electron-deficient nitriles **4c** and **4d** 150 °C, 24 or 72 h, respectively, were required for full consumption of the starting material. Unfortunately, the increased reaction temperature and time lead to low yields of target products. So, the adduct **5c** was obtained only in 32% yield and the adduct of nitrile **4d** with cyclopentadiene could not be isolated in pure form because of the complex mixture of unknown byproducts. Reaction proceeded non-stereoselectively with **4b**,**c** giving an 1:1 the mixture of *endo*/*exo* adducts in both cases.

Next, we tried to react α-fluoroacrylonitriles **3** with cyclopentadiene. For the most reactive nitrile **3a** with nitro group we observed almost complete consumption of starting material after heating to 150 °C for 5 h, but not any of the products could be isolated because of decomposition. Even at lower temperature the product mixture decomposed. In case of the less reactive nitrile **3b** reaction proceeded very slow yielding inseparable mixture of target compound with several products.

Furane, 1,3-cyclohexadiene, 2,3-dimethylbutadiene and Danishefsky's diene were also tested in Diels–Alder reaction under similar conditions. While the nitrile **4b** did not react with the less reactive furane and 1,3-cyclohexadiene, the reaction with 2,3-dimethylbutadiene gave the desired cyclohexene **6b** in moderate yield (Scheme 3).

Danishefsky's diene, which is well-known as a strong diene, reacted smoothly with the CF$_3$-nitriles, giving only one regioisomer of the corresponding ketones as mixtures of diasteremers **7** and **8** in approximately 2:1 ratio (Scheme 4).

The regio and stereochemistry of the products **7** and **8** was assigned ^{1}H NMR spectroscopically, particularly by the multiplicity of the protons neighboring the methoxy group or the phenyl group, respectively. For compound **7c** we observed the latter signal at 3.31 ppm as a doublet of doublets with $^{3}J_{HH}$ = 14.2 Hz and 3.4 Hz. The signal for **8c** is not resolved. Also the H atom neighboring the methoxy group is indicative. These signals appear for compound **7c** as doublet of doublets with $^{3}J_{HH}$ = 8.5 and 4.9 Hz at 3.97 ppm and for the minor isomer **8c** as a triplet with $^{3}J_{HH}$ = 2.9 Hz at 4.33 ppm (see Fig. 1). The alternative regioisomers would have more complex signals. It should be also noted, that the ^{1}H NMR spectrum of diastereomer **7c** is in good agreement with the spectrum of diastereomer with the same configuration of close analogous adduct of Danishefsky's diene with methyl (*E*)-2-cyanocinnamate [62].



Scheme 4. Reactions of Danishefsky's diene with α-trifluoromethylacrylonitriles.

3. Conclusions

We discovered a novel approach to the synthesis of α-fluoro- and α-trifluoromethylacrylonitriles by direct nucleophilic substitution of bromine with copper(I) cyanide of fluorinated bromostyrenes. These reactions proceed stereoselectively in good to high yields. In case of the α-trifluoromethylacrylonitriles the reaction proceeds 100% stereoselectively and only the isomers with *E*-configuration were obtained. It should be noted, that α-trifluoromethylacrylonitriles were synthesized for the first time. The presence of strong electron-withdrawing groups at the double bond of these molecules opens the possibility for both Michael additions, and Diels–Alder reactions. It was shown, that 2-trifluoromethylacrylonitriles do react with active dienes, like cyclopentadiene, 2,3-dimethylbutadien and Danishefsky's diene as dienophiles giving the desired cycloadducts in high yields as a mixture of diastereomers. The β-fluoroacrylonitriles **3** were shown to be not useful as dienophiles in Diels–Alder reaction with the mentioned dienes.

4. Experimental

NMR spectra were recorded on Bruker ARX 300, Bruker AMX 400 and Varian Inova 500 MHz spectrometers in $CDCl_3$ with TMS and CCl_3F as an internal standards. IR spectra were obtained with UR-20 spectrometer. Mass spectra (ESI-MS) were measured on a MicroTof Bruker Daltinics. Column and TLC chromatography was performed on silica gel Merck 60 and Merck $60F_{254}$ plates, respectively. Bromofluorostyrenes and bromotrifluorostyrenes were synthesized according to previously reported procedures [24,25]. All dienes were distilled before using.

*4.1. General procedure for the synthesis of the β-bromo-β-fluorostyrenes **1***

A solution of 2 mmol of the corresponding aldehyde in 8 ml ethanol was added dropwise to the solution of 0.11 ml (2.1 mmol) hydrazine hydrate in 4 ml of ethanol with intensive stirring. After completion of hydrazone formation (TLC monitoring) 0.2 ml (1.5 eq.) of ethylenediamine and 0.002 g (1 mol%) of CuCl were added. The reaction mixture was cooled to 0 °C and 0.3 ml (1.5 eq.) CBr_3F was added dropwise with stirring. The reaction mixture was stirred for 4–48 h at room temperature to the completion (TLC monitoring) and 50 ml 5% aq. HCl was added (in the cases of pyridine-2-carbaldehyde only water was added). The reaction products were extracted with CH_2Cl_2 (3×30 ml) and extract was dried with Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography on SiO_2 (hexane-CH_2Cl_2 mixture as eluent). The *E*- and *Z*-isomers could not be separated by column chromatography.

*4.2. General procedure for the synthesis of the β-bromo-β-trifluoromethyl styrenes **2***

A solution of aromatic aldehyde (2 mmol) in DMSO (5 ml) was added dropwise to a solution of 1 M hydrazine hydrate in DMSO (2 mmol, 2 ml) and the mixture was stirred until aldehyde disappeared (3 h, TLC monitoring). Then freshly purified CuCl 20 mg (0.2 mmol) and aqueous ammonia (0.7 ml) were added. After 10 min a solution of CBr_3CF_3 (1.93 g, 6 mmol) in DMSO (2 ml) was added dropwise, maintaining the temperature at 20 °C (water bath). The reaction mixture was stirred for 24 h and quenched with hydrochloric acid (5%) (100 ml). Reaction products were extracted with CH_2Cl_2 (3×20 ml). Extracts were dried over sodium sulfate, CH_2Cl_2 was evaporated and the residue was purified by column chromatography. *E*- and *Z*-isomers mixture of alkenes could not be separated by column chromatography.

*4.3. General procedure for the synthesis of the nitriles **3** and **4***

One-neck round bottom 25 ml flask was charged with 5 mmol of corresponding bromostyrene, 0.54 g (6 mmol) CuCN, 3 ml dry DMF and flushed with argon. Reaction mixture was heated with reflux condenser at 150–155 °C for 3–4 h (TLC control). After cooling down to room temperature 20 ml of dichloromethane and 100 ml of water were added. Formed precipitate of copper salts was filtered off and washed twice with 20 ml of dichloromethane. Organic phase was separated; water phase was extracted with 2×20 ml of dichloromethane. Joint extract was washed with water, brine and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a column with silica gel (using appropriate mixture of hexane/dichloromethane 2-1 as the eluent) to afford the corresponding nitriles. *E*- and *Z*-isomers mixture of alkenes could not be separated by column chromatography.

^1H NMR and ^{13}C NMR spectra of compounds (**3b**, **3c**, **3i**) are in agreement with published data [36].

*4.3.1. 2-Fluoro-3-(4-nitrophenyl)acrylonitrile (**3a**)*

A mixture of *Z*/*E*-isomers 3.5/1 (after purification); pale brown solid (800 mg, 83%), IR (Nujol): $\nu = 1480$ (NO_2), 1600 (C=C), 2230 (CN) cm^{-1}. *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, 1H, *CH*=*CF*, $J = 33.4$ Hz), 7.76 (d, 2H, 4-$NO_2C_6H_4$–, $J = 9.0$ Hz) 8.28 (d, 2H, 4-$NO_2C_6H_4$–, $J = 9.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.3 (d, CN, $J = 46.8$ Hz), 121.3 (d, *C*H=CF, $J = 6.5$ Hz), 124.2, 131.0 (d, $J = 8.7$ Hz), 133.1 (d, CH=*C*F, $J = 259.8$ Hz), 135.8 (d, $J = 5.9$ Hz), 148.3 (d, $J = 2.9$ Hz). *E*-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, 1H, C*H*=CF, $J = 15.4$ Hz), 7.78 (d, 2H, 4-$NO_2C_6H_4$–, $J = 8.7$ Hz), 8.27 (d, 2H, 4-$NO_2C_6H_4$–, $J = 8.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.7 (d, CN, $J = 45.9$ Hz), 124.0 (d, *C*H=CF, $J = 27.1$ Hz), 124.4, 129.4 (d, $J = 3.7$ Hz), 132.9 (d, CH=*C*F, $J = 267.9$ Hz), 134.6 (d, $J = 7.3$ Hz), 148.6. Anal. calcd. for $C_9H_5FN_2O_2$: C, 56.26; H, 2.62. Found: C, 56.40; H 2.70.

*4.3.2. 2-Fluoro-3-(4-chlorophenyl)acrylonitrile (**3b**)*

A mixture of *Z*/*E*-isomers 4.3/1 (after purification); pale green solid (750 mg, 82%), IR (Nujol): $\nu = 1480$ (NO_2), 1610 (C=C), 2230 (CN) cm^{-1}. *Z*-isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (d, 1H, C*H*=CF, $J = 34.1$ Hz) 7.42 (d, 2H, 4-ClC$_6$H$_4$–, J = 8.6 Hz) 7.51 (d, 2H, 4-ClC$_6$H$_4$–, J = 8.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 113.0 (d, CN, J = 46.1 Hz), 122.4 (d, *C*H=CF, J = 6.6 Hz), 128.4 (d, J = 5.9 Hz), 129.4 (CH), 131.4 (d, CH, 4-ClC$_6$H$_4$–, J = 8.1 Hz), 131.5 (d, CH=*C*F, J = 255.4 Hz), 136.8 (d, J = 3.7 Hz). *E*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.05 (d, 1H, C*H*=CF, J = 16.2 Hz), other signals are identical to *Z*-isomer; ^{13}C NMR (100 MHz, CDCl$_3$): δ 112.3 (d, CN, J = 46.8 Hz), 124.9 (d, *C*H=CF, J = 24.9 Hz), 126.6 (d, J = 6.6 Hz), 129.5 (CH), 129.7 (d, CH, 4-ClC$_6$H$_4$–, J = 2.9 Hz), 131.0 (d, CH=*C*F, J = 274.5 Hz), 136.6. Anal. calcd. for C$_9$H$_5$ClFN: C, 59.53; H, 2.78. Found: C, 59.73; H 2.60.

4.3.3. 2-Fluoro-3-phenylacrylonitrile (3c)

A mixture of *Z*/*E*-isomers 0.8/1 (after purification); colourless liquid (520 mg, 70%); IR (Nujol): ν = 1620 (C=C), 2230 (CN) cm^{-1}.

4.3.4. 2-Fluoro-3-(4-methoxyphenyl)acrylonitrile (3d)

A mixture of *Z*/*E*-isomers 5.4/1 (after purification); white solid (790 mg, 89%), IR (Nujol): ν = 1610 (C=C), 2240 (CN) cm^{-1}.

4.3.5. 2-Fluoro-3-(3,4-dimethoxyhenyl)acrylonitrile (3e)

A mixture of *Z*/*E*-isomers 6.3/1 (after purification); white solid (730 mg, 70%), IR (Nujol): ν = 1610 (C=C), 2240 (CN) cm^{-1}. *Z*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.92 (s, 3H, MeO), 3.95 (s, 3H, MeO), 6.41 (d, 1H, C*H*=CF, J = 34.8 Hz) 6.91 (d, 1H, 3,4-diMeOC$_6$H$_3$–, J = 9.0 Hz) 7.12–7.16 (m, 2H, 3,4-diMeOC$_6$H$_3$–); ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.8 (MeO), 55.9 (MeO), 111.0 (CH), 112.4 (d, J = 9.5 Hz), 113.6 (d, CN, J = 46.1 Hz), 122.9 (d, J = 5.1 Hz), 123.6 (d, J = 5.9 Hz), 124.4 (d, J = 8.1 Hz), 129.9 (d, CH=*C*F, J = 250.3 Hz), 149.0, 151.1 (d, J = 2.9 Hz). *E*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.03 (d, 1H, C*H*=CF, J = 17.0 Hz) other signals are identical to *Z*-isomer; ^{13}C NMR (100 MHz, CDCl$_3$): δ 111.2, 122.9 (d, J = 3.7 Hz), 126.2 (d, *C*H=CF, J = 24.9 Hz), other signals are identical to *Z*-isomer. Anal. calcd. for C$_{11}$H$_{10}$FNO$_2$: C, 63.76; H, 4.86. Found: C, 64.00; H 4.50.

4.3.6. Methyl 4-(2-cyano-2-fluorovinyl)benzoate (3f)

A mixture of *Z*/*E*-isomers 3.2/1 (after purification); white solid (810 mg, 81%), IR (Nujol): ν = 1610 (C=C), 1720 (CO$_2$Me), 2240 (CN) cm^{-1}. *Z*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.96 (s, 3H, CO$_2$Me), 6.52 (d, 1H, C*H*=CF, J = 33.9 Hz) 7.64 (d, 2H, 4-CO$_2$MeC$_6$H$_4$–, J = 8.3 Hz), 8.10 (d, 2H, 4-CO$_2$MeC$_6$H$_4$–, J = 8.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 52.5 (CO$_2$*Me*), 112.7 (d, CN, J = 46.1 Hz), 122.5 (d, *C*H=CF, J = 6.6 Hz), 130.1 (d, J = 8.1 Hz), 130.2, 131.6 (d, J = 2.9 Hz), 132.3 (d, CH=*C*F, J = 257.6 Hz), 133.9 (d, J = 5.6 Hz), 166.1 (*C*O$_2$Me). *E*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.11 (d, 1H, C*H*=CF, J = 16.2 Hz), 7.67 (d, 2H, 4-CO$_2$MeC$_6$H$_4$–, J = 8.3 Hz), 8.12 (d, 2H, 4-CO$_2$MeC$_6$H$_4$–, J = 8.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 112.1 (d, CN, J = 46.8 Hz), 125.0 (d, *C*H=CF, J = 24.9 Hz), 128.4 (d, J = 2.9 Hz), 130.3, 132.5 (d, J = 7.3 Hz). Anal. calcd. for C$_{11}$H$_8$FNO$_2$: C, 64.39; H, 3.93. Found: C, 64.21; H 3.81.

4.3.7. 2-Fluoro-3-(2-methoxyphenyl)acrylonitrile (3g)

A mixture of *Z*/*E*-isomers 3.9/1 (after purification); white solid (700 mg, 79%), IR (Nujol): ν = 1610 (C=C), 2240 (CN) cm^{-1}. *Z*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.89 (s, 3H, MeO), 6.94 (d, 1H, 2-MeOC$_6$H$_4$–, J = 8.3 Hz), 7.02 (t, 1H, 2-MeOC$_6$H$_4$–, J = 7.6 Hz), 7.04 (d, 1H, C*H*=CF, J = 36.6 Hz), 7.40 (dd, 1H, 2-MeOC$_6$H$_4$–, J = 1.5 Hz, J = 7.8 Hz), 7.78 (dd, 1H, 2-MeOC$_6$H$_4$–, J = 1.5 Hz, J = 7.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.7 (MeO), 110.8 (CH), 113.6 (d, CN, J = 46.1 Hz), 117.4, 121.0, 128.0, 130.8 (d, CH=*C*F, J = 237.1 Hz), 131.2 (d, J = 13.9 Hz), 132.2, 156.9. *E*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (d, 1H, C*H*=CF, J = 17.4 Hz), 7.65 (d, 1H, 2-MeOC$_6$H$_4$–, J = 7.6 Hz), other signals are identical to *Z*-isomer; ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.5 (MeO), 110.9, 119.0 (d, J = 5.9 Hz), 156.3, other signals are identical to *Z*-isomer. Anal. calcd. for C$_{10}$H$_8$FNO: C, 67.79; H, 4.55. Found: C, 67.59; H 4.45.

4.3.8. 2-Fluoro-3-(2-nitrophenyl)acrylonitrile (3h)

A mixture of *Z*/*E*-isomers 3.5/1 (after purification); yellow solid (460 mg, 47%), IR (Nujol): ν = 1480 (NO$_2$), 1600 (C=C), 2230 (CN) cm^{-1}. *Z*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.16 (d, 1H, CH=CF, J = 31.5 Hz), 7.61–7.82 (m, 3H, 2-NO$_2$C$_6$H$_4$–), 8.18 (d, 1H, 2-NO$_2$C$_6$H$_4$–, J = 8.2 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 112.1 (d, CN, J = 46.1 Hz), 118.9 (d, *C*H=CF, J = 5.9 Hz), 123.9 (d, J = 4.4 Hz), 125.3, 130.9, 131.8 (d, J = 8.8 Hz), 132.8 (d, CH=*C*F, J = 246.6 Hz), 133.7, 148.2. *E*-isomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (d, 1H, CH=CF, J = 15.7 Hz), 8.29 (d, 1H, 2-NO$_2$C$_6$H$_4$–, J = 8.6 Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 111.1 (d, CN, J = 46.8 Hz), 123.5 (d, *C*H=CF, J = 27.8 Hz), 124.3 (d, J = 8.1 Hz), 125.6, 131.2, 134.4, other signals are identical to *Z*-isomer. Anal. calcd. for C$_9$H$_5$FN$_2$O$_2$: C, 56.26; H, 2.62. Found: C, 56.06; H 2.70.

4.3.9. 2-Fluoro-3-(4-methylphenyl)acrylonitrile (3i)

A mixture of *Z*–*E*-isomers 2.4/1 (after purification); white solid (510 mg, 64%), IR (Nujol): ν = 1610 (C=C), 2230 (CN) cm^{-1}.

4.3.10. 2-Bromodec-2-enenitrile (3k)

A mixture of *Z*/*E*-isomers 0.9/1 (after purification); colourless liquid (620 mg, 54%). ^{1}H NMR (300 MHz, CDCl$_3$) for the mixture of isomers: δ 0.89 (t, 3H, J = 6.6), 1.20–1.53 (m, 10H), 2.18–2.33 (m, 2H), 5.76 (dt, 1H, CH=CF, J = 32.9 Hz, J = 7.9 Hz), 6.12 (dt, 1H, CH=CF, J = 14.2 Hz, J = 8.5 Hz); ^{19}F NMR (282 MHz, CDCl$_3$) for the mixture of isomers: δ −123.5 (d, J = 14.2), −125.4 (d, J = 32.9); ^{13}C NMR (75 MHz, CDCl$_3$) for the mixture of isomers: δ 14.1, 22.7, 24.7, 26.4, 26.5, 28.0, 28.1, 28.6, 28.7, 28.8, 28.9, 29.0, 29.1, 31.8, 111.2 (d, CN, J = 48.1 Hz,), 112.5 (d, CN, J = 47.5 Hz,), 126.9 (d, *C*H=CF, J = 14.8 Hz), 127.3 (d, *C*H=CF, J = 14.8 Hz), 132.3 (d, CH=*C*F, J = 243.0 Hz), 132.7 (d, CH=*C*F, J = 239.8 Hz); ESI-MS (*m*/*z*): calcd. for C$_{10}$H$_{16}$FNNa [M]$^+$ 192.1162, found 192.1159.

4.3.11. (2E)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylonitrile (4b)

White solid (870 mg, 75%), mp 40–41 °C; IR (Nujol): ν = 1610 (C=C), 2230 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.50 (d, 2H, 4-ClC$_6$H$_4$–, $J = 8.6$ Hz), 7.65 (s, 1H, C*H*═CCF$_3$), 7.85 (d, 2H, 4-ClC$_6$H$_4$–, $J = 8.6$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$): δ −64.23; ^{13}C NMR (100 MHz, CDCl$_3$): δ 102.1 (q, CH═*C*CF$_3$, $J = 37.3$), 112.8 (CN), 120.9 (q, CF$_3$, $J = 273.7$), 128.7, 129.8 (CH-arom), 131.5 (CH-arom), 139.6, 147.5 (q, *C*H═CCF$_3$, $J = 4.4$). Anal. calcd. for C$_{10}$H$_5$ClF$_3$N: C, 51.86; H, 2.18. Found: C, 52.02.; H 2.30; ESI-MS (*m/z*): calcd. for C$_{10}$H$_5$ClF$_3$NNa [M]$^+$ 253.9960, found 253.9955.

4.3.12. (2E)-3-phenyl-2-(trifluoromethyl)acrylonitrile (4c)

White solid (710 mg, 72%), mp 43–44 °C; IR (Nujol): $\nu = 1620$ (C═C), 2230 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53 (t, 2H, Ph, $J = 7.4$ Hz), 7.60 (t, 1H, Ph, $J = 7.4$ Hz), 7.70 (s, 1H, C*H*═CCF$_3$), 7.91 (d, 2H, Ph, $J = 7.4$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$): δ −64.17; ^{13}C NMR (100 MHz, CDCl$_3$): δ 101.5 (q, CH═*C*CF$_3$, $J = 36.6$), 113.1 (CN), 121.2 (q, CF$_3$, $J = 273.0$), 129.4 (2CH-arom), 130.3 (2CH-arom), 133.3 (CH-arom), 149.0 (*C*H═CCF$_3$, $J = 4.4$); ESI-MS (*m/z*): calcd. for C$_{10}$H$_6$ClF$_3$NNa [M]$^+$ 220.0350, found 220.0345. Anal. calcd. for C$_{10}$H$_6$ClF$_3$N: C, 60.92; H, 3.07. Found: C, 60.82; H 3.10.

4.3.13. (2E)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylonitrile (4d)

Colourless liquid (970 mg, 85%); IR (Nujol): $\nu = 1600$ (C═C), 2220 (CN) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.90 (s, 3H, MeO), 7.01 (d, 2H, 4-MeOC$_6$H$_4$–, $J = 9.0$ Hz), 7.57 (s, 1H, C*H*═CCF$_3$), 7.90 (d, 2H, 4-MeOC$_6$H$_4$–, $J = 9.0$ Hz); ^{19}F NMR (282 MHz, CDCl$_3$): δ −63.61; ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.6 (MeO), 97.7 (q, CH═*C*CF$_3$, $J = 36.6$), 113.8 (CN), 114.8 (CH-arom), 121.6 (q, CF$_3$, $J = 273.0$), 123.0, 132.8 (CH-arom), 148.2 (*C*H═CCF$_3$, $J = 4.4$), 163.7; ESI-MS (*m/z*): calcd. for C$_{11}$H$_8$ClF$_3$NONa [M]$^+$ 250.0456, found 250.0439. Anal. calcd. for H, C$_{11}$H$_8$ClF$_3$NO: C, 58.15; H, 3.55. Found: C, 58.20; H 3.40.

4.3.14. (2E)-3-(3,4-dimethoxyphenyl)-2-(trifluoromethyl)acrylonitrile (4e)

White solid (900 mg, 70%), mp 37–38 °C; IR (Nujol): $\nu = 1600$ (C═C), 2220 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.95 (s, 3H, MeO), 3.97 (s, 3H, MeO), 6.95 (d, 1H, 3,4-diMeOC$_6$H$_3$–, $J = 8.5$ Hz), 7.38 (dd, 1H, 3,4-diMeOC$_6$H$_3$–, $J = 8.5$ Hz, $J = 2.0$ Hz), 7.56 (s, 1H, C*H*═CCF$_3$), CCF$_3$), 7.68 (d, 1H, 3,4-diMeOC$_6$H$_3$–, $J = 2.0$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 56.0 (MeO), 56.1 (MeO), 97.9 (q, CH═*C*CF$_3$, $J = 36.6$), 111.0 (2CH-arom), 113.9 (CN), 121.7 (q, CF$_3$, $J = 273.0$), 123.3, 126.8 (CH-arom), 148.5 (*C*H═CCF$_3$, $J = 4.4$), 149.4, 153.5. Anal. calcd. for C$_{12}$H$_{10}$F$_3$NO$_2$: C, 56.04; H, 3.92. Found: C, 56.20; H 3.80.

4.3.15. Methyl 4-((1E)-2-cyano-3,3,3-trifluoroprop-1-enyl)benzoate (4f)

White solid (740 mg, 58%), mp 56–57 °C; IR (Nujol): $\nu = 1610$ (C═C), 2230 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.93 (s, 3H, Me), 7.70 (s, 1H, C*H*═CCF$_3$), 7.91 (d, 2H, arom, $J = 8.2$ Hz), 8.12 (d, 2H, arom, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 52.5 (Me), 103.9 (q, CH═*C*CF$_3$, $J = 36.6$), 112.6 (CN), 120.8 (q, CF$_3$, $J = 273.7$), 130.1 (CH-arom), 130.3 (CH-arom), 132.1, 134.0, 147.7 (q, *C*H═CCF$_3$, $J = 4.4$), 165.7 (*C*O$_2$Me). Anal. calcd. for C$_{12}$H$_8$F$_3$NO$_2$: C, 56.48; H, 3.16. Found: C, 56.62; H 3.29.

4.3.16. (2E)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylonitrile (4g)

Colourless oil (930 mg, 82%); IR (Nujol): $\nu = 1610$ (C═C), 2230 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.93 (s, 3H, MeO), 7.00 (d, 1H, arom, $J = 7.9$ Hz), 7.08 (t, 1H, arom, $J = 7.9$ Hz), 7.55 (t, 1H, arom, $J = 7.9$ Hz), 8.18 (d, 1H, arom, $J = 7.9$ Hz), 8.21 (s, 1H, C*H*═CCF$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 55.8 (MeO), 100.7 (q, CH═*C*CF$_3$, $J = 36.6$), 111.3 (CH-arom), 113.5 (CN), 119.4, 121.0 (CH-arom), 121.5 (q, CF$_3$, $J = 275.2$), 128.8 (CH-arom), 135.0 (CH-arom), 143.9 (q, *C*H═CCF$_3$, $J = 4.4$), 158.8. Anal. calcd. for C$_{11}$H$_8$ClF$_3$NO: C, 58.15; H, 3.55. Found: C, 58.26; H 3.47.

4.3.17. (2E)-3-(2-nitrophenyl)-2-(trifluoromethyl)acrylonitrile (4h)

Yellow solid (750 mg, 62%), mp 88–89 °C; IR (Nujol): $\nu = 1600$ (C═C), 2225 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.74–7.91 (m, 3H, arom), 8.30–8.37 (m, 1H, arom), 8.33 (s, 1H, C*H*═CCF$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 106.7 (q, CH═*C*CF$_3$, $J = 36.6$), 111.6 (CN), 120.3 (q, CF$_3$, $J = 275.2$), 125.7 (CH-arom), 126.9, 130.6 (CH-arom), 132.6 (CH-arom), 134.9 (CH-arom), 147.0, 148.3 (q, *C*H═CCF$_3$, $J = 4.4$). Anal. calcd. for C$_{10}$H$_5$F$_3$N$_2$O$_2$: C, 49.60; H, 2.08. Found: C, 49.72; H 2.19.

4.3.18. (2E)-3-(4-methylphenyl)-2-(trifluoromethyl)acrylonitrile (4i)

White solid (710 mg, 67%), mp 32–33 °C; IR (Nujol): $\nu = 1620$ (C═C), 2230 (CN) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.45 (s, 3H, Me), 7.32 (d, 2H, 4-MeC$_6$H$_4$–, $J = 8.2$ Hz), 7.63 (s, 1H, C*H*═CCF$_3$), 7.81 (d, 2H, 4-MeC$_6$H$_4$–, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$): δ 21.8 (Me), 102.2 (q, CH═*C*CF$_3$, $J = 36.6$), 113.4 (CN), 121.3 (q, CF$_3$, $J = 272.2$), 127.7, 130.1 (CH-arom), 130.5 (CH-arom), 144.5, 148.8 (q, *C*H═CCF$_3$, $J = 3.0$). Anal. calcd. for C$_{11}$H$_8$F$_3$N: C, 62.56; H, 3.82. Found: C, 62.61; H 3.94.

4.4. General procedure for cycloaddition reactions of the nitriles 3 and 4 with dienes

One millimole of the corresponding α-trifluoromethylacrylonitrile and 1.5 ml of diene were heated in sealed glass tube with a Young-tap. The excess of dienes was evaporated at reduced pressure and the residue was purified by column chromatography with silica gel (using mixture of cyclohexane/ethyl acetate 20-1 as the eluent).

4.4.1. 3-(4-Chlorophenyl)-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (5b)

3-(4-Chlorophenyl)-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (**5b**) was obtained from **4b** by heating with cyclopentadiene at 130 °C during 16 h. Colourles solid (253 mg, 87%); ^{1}H NMR (300 MHz, CDCl$_3$) for the mixture of diastereomers: δ 1.73 (bd, 1H, –CH$_2$–, J = 9.8 Hz), 1.96 (bd, 2H, –CH$_2$–, J = 9.8 Hz), 2.33 (bd, 1H, –CH$_2$–, J = 9.8 Hz), 3.13 (d, 1H, –CH-Ar, J = 1.9 Hz), 3.24 (bs, 1H, –CH–), 3.30 (bs, 1H, –CH–), 3.49 (bs, 1H, –CH–), 3.56 (bs, 1H, –CH–), 3.70 (d, 1H, –CH-Ar, J = 2.9 Hz), 6.16 (pent, 1H, –CH=, J = 2.7 Hz), 6.53–6.60 (m, 2H, –CH=), 6.71 (dd, 1H, –CH=, J = 5.7 Hz, J = 3.0 Hz), 7.20–7.39 (m, 8H, arom); ^{19}F NMR (282 MHz, CDCl$_3$) for the mixture of diastereomers: δ −66.74, −68.61; ^{13}C NMR (75 MHz, CDCl$_3$) for the mixture of diastereomers: δ 48.4, 48.5, 49.6, 49.1, 50.3, 51.1, 51.8, 52.3, 56.1 (d, J = 25.4 Hz), 56.6 (d, J = 28.0 Hz); 116.4 (CN), 117.4 (CN), 124.8 (q, CF$_3$, J = 282.3 Hz), 125.2 (q, CF$_3$, J = 282.3 Hz); 129.1 (CH), 129.5 (CH), 130.1 (CH), 130.9 (CH), 132.0, 134.4, 134.5, 135.6 (arom); 133.2, 136.9, 139.5, 141.2 (–*C*H=*C*H–); ESI-MS (*m*/*z*): calcd. for $C_{15}H_{11}ClF_3NNa$ [M]$^+$ 320.0430, found 320.0424.

4.4.2. *3-Phenyl-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (**5c**)*

3-Phenyl-2-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (**5c**) was obtained from **4c** by heating with cyclopentadiene at 150 °C during 24 h. Colourles solid (85 mg, 32%); ^{1}H NMR (500 MHz, CDCl$_3$) for the mixture of diastereomers: δ 1.71 (bd, 1H, –CH$_2$–, J = 9.7 Hz), 1.94 (bd, 2H, –CH$_2$–, J = 9.7 Hz), 2.39 (bd, 1H, –CH$_2$–, J = 9.7 Hz), 3.16 (d, 1H, –CH-Ar, J = 2.1 Hz), 3.27 (bs, 1H, –CH–), 3.31 (bs, 1H, –CH–), 3.47 (bs, 1H, –CH–), 3.54 (bs, 1H, –CH–), 3.74 (d, 1H, –CH-Ar, J = 2.8 Hz), 6.14 (pent, 1H, –CH=, J = 2.7 Hz), 6.52–6.56 (m, 2H, –CH=), 6.73 (dd, 1H, –CH=, J = 5.5 Hz, J = 3.2 Hz), 7.25–7.45 (m, 10H, arom); ^{19}F NMR (470 MHz, CDCl$_3$) for the mixture of diastereomers: δ −66.98, −68.88; ^{13}C NMR (125 MHz, CDCl$_3$) for the mixture of diastereomers: δ 47.9, 48.0, 48.1, 48.7, 49.9, 51.1, 51.3, 52.5, 55.6 (d, J = 26.4 Hz), 56.1 (d, J = 27.0 Hz); 116.0 (CN), 117.1 (CN), 124.4 (q, CF$_3$, J = 282.2 Hz), 124.8 (q, CF$_3$, J = 282.2 Hz); 127.9 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.8 (CH), 129.0 (CH), 136.6, 137.8 (arom); 132.6, 136.0, 139.4, 140.9 (–*C*H=*C*H–); ESI-MS (*m*/*z*): calcd. for $C_{15}H_{12}F_3NNa$ [M]$^+$ 286.0820, found 286.0814.

4.4.3. *6-(4-Chlorophenyl)-3,4-dimethyl-1-(trifluoromethyl)cyclohex-3-ene-1-carbonitrile (**5b**)*

6-(4-Chlorophenyl)-3,4-dimethyl-1-(trifluoromethyl)cyclohex-3-ene-1-carbonitrile (**5b**) was obtained from **4b** by heating with 2,3-dimethylbutadiene at 150 °C during 24 h. Colourles solid (105 mg, 50%), mp 50–52 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.71 (bs, 3H, Me), 1.73 (bs, 3H, Me), 2.25 (dd, 1H, –CH$_2$–, J = 17.4 Hz, J = 5.0 Hz), 2.54 (bd, 1H, –CH$_2$–, J = 16.7 Hz), 2.63–2.76 (m, 2H, –CH$_2$–), 3.11 (dd, 1H, –CHAr, J = 12.0 Hz, J = 5.0 Hz), 7.28–7.35 (m, 4H, arom); ^{19}F NMR (470 MHz, CDCl$_3$): δ and 70.51; ^{13}C NMR (125 MHz, CDCl$_3$): δ 18.3 (Me), 18.4 (Me), 37.3 (q, –CH–, J = 1.5 Hz), 37.5 (–CH$_2$–), 42.7 (–CH$_2$–), 48.2 (q, CF$_3$, J = 26.4 Hz), 116.1 (q, CN, J = 1.5 Hz), 120.1 (–C(Me)=), 123.9 (q, CF$_3$, J = 284.2 Hz), 126.6 (–C(Me)=), 128.8 (CH-arom), 129.9 (CH-arom), 133.9 (arom), 137.0 (arom); ESI-MS (*m*/*z*): calcd. for $C_{16}H_{15}ClF_3NNa$ [M]$^+$ 336.0743, found 336.0737. Anal. calcd. for $C_{16}H_{15}ClF_3N$: C, 61.25; H, 4.82; N, 4.46. Found: C, 61.20; H 4.75; N, 4.46.

4.5. *General procedure for reactions of the nitriles **3** and **4** with Danishefsky's diene*

One millimole of α-trifluoromethylacrylonitrile and 1.2 mmol of Danishefsky's diene in 1 ml of dry toluene were heated in sealed glass tube with a Young-tap at 120°. Toluene was evaporated at reduced pressure and the residue was purified by column chromatography with silica gel (using mixture of cyclohexane/ethyl acetate 1-1 as the eluent).

4.5.1. *2-Methoxy-6-(4-chlorophenyl)-4-oxo-1-(trifluoromethyl)cyclohexanecarbonitrile (**7** + **8b**)*

2-Methoxy-6-(4-chlorophenyl)-4-oxo-1-(trifluoromethyl)-cyclohexanecarbonitrile (**7** + **8b**) was obtained from **4b** by heating with Danishefsky's diene at 120 °C during 48 h. Colourles oil (250 mg, 76%); major diastereomer **7b**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.52 (dd, 1H, J = 15.9 Hz, J = 3.0 Hz, CH$_2$), 2.86–3.17 (m, 3H, CH$_2$), 3.33 (dd, 1H, J = 14.2 Hz, J = 3.4 Hz, C*H*-Ar), 3.50 (s, 3H, MeO), 3.98 (dd, 1H, J = 8.1 Hz, J = 4.9 Hz, C*H*-MeO), 7.30–7.40 (m, 4H, arom); ^{19}F NMR (282 MHz, CDCl$_3$): δ −67.3; ^{13}C NMR (75 MHz, CDCl$_3$): δ 41.4 (*C*H-Ar), 42.6 (CH$_2$), 44.1 (CH$_2$), 54.8 (q, J = 24.4 Hz, *C*-CF$_3$), 58.5 (MeO), 77.1 (*C*H-MeO), 113.1 (CN), 123.5 (q, J = 287.2 Hz, CF$_3$,); 129.2, 129.6, 134.7, 135.0 (arom); 202.3 (C=O); minor diastereomer **8b**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.60 (bd, 1H, J = 15.4 Hz, CH$_2$), 3.45 (s, 3H, MeO), 4.34 (t, 1H, 2.9 Hz, C*H*-MeO), other signals are identical to major diastereomer; ^{19}F NMR (282 MHz, CDCl$_3$): δ −64.4; ^{13}C NMR (75 MHz, CDCl$_3$): δ 39.9 (*C*H-Ar), 41.4 (CH$_2$), 44.5 (CH$_2$), 53.3 (q, J = 25.6 Hz, *C*-CF$_3$), 57.9 (MeO), 78.6 (*C*H-MeO), 114.6 (CN), 123.0 (q, J = 286.0 Hz, CF$_3$,), 202.9 (C=O), other signals are identical to major diastereomer; ESI-MS (*m*/*z*): calcd. for $C_{15}H_{13}ClF_3NO_2Na$ [M]$^+$ 354.0483, found 354.0485.

4.5.2. *2-Methoxy-6-phenyl-4-oxo-1-(trifluoromethyl)cyclohexanecarbonitrile (**7** + **8c**)*

Methoxy-6-phenyl-4-oxo-1-(trifluoromethyl)cyclohexane-carbonitrile (**7** + **8c**) was obtained from **4c** by heating with Danishefsky's diene at 120 °C during 72 h. Colourles oil (252 mg, 88%); major diastereomer **7c**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.56 (dd, 1H, J = 15.9 Hz, J = 3.0 Hz, CH$_2$), 2.82–3.21 (m, 3H, CH$_2$), 3.31 (dd, 1H, J = 14.2 Hz, J = 3.4 Hz, C*H*-Ar), 3.51 (s, 3H, MeO), 3.97 (dd, 1H, J = 8.5 Hz, J = 4.9 Hz, C*H*-MeO), 7.35–7.41 (bs, 5H, arom); ^{19}F NMR (282 MHz, CDCl$_3$): δ −66.6; ^{13}C NMR (75 MHz, CDCl$_3$): δ 40.7 (*C*H-Ar), 41.5 (CH$_2$), 43.1 (CH$_2$), 53.6 (q, J = 24.4 Hz, *C*-CF$_3$), 57.2 (MeO), 76.3 (*C*H-MeO), 112.0 (CN), 122.3 (q, J = 286.6 Hz, CF$_3$,); 126.9, 127.5, 127.6, 135.2 (arom); 201.4 (C=O); minor diastereomer **8c**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.59–2.68 (bd, 1H, J = 15.4 Hz, CH$_2$), 3.46 (s, 3H, MeO), 4.33 (t, 1H, 2.9 Hz, C*H*-MeO), other signals are identical to major diastereomer;

^{19}F NMR (282 MHz, CDCl$_3$): δ -64.4; ^{13}C NMR (75 MHz, CDCl$_3$): δ 39.3 (*C*H-Ar), 40.1 (CH$_2$), 43.4 (CH$_2$), 52.2 (q, *J* = 25.6 Hz, *C*-CF$_3$), 56.5 (MeO), 77.4 (*C*H-MeO), 113.5 (CN), 121.8 (q, *J* = 286.0 Hz, CF$_3$,); 134.8 (arom); 202.1 (C═O), other signals are identical to major diastereomer; ESI-MS (*m/z*): calcd. for $C_{15}H_{14}F_3NO_2Na$ [M]$^+$ 320.0868, found 320.0874. Anal. calcd. for $C_{15}H_{14}F_3NO_2$: C, 60.60; H, 4.75; N, 4.71. Found: C, 60.28; H 4.65; N, 4.53.

4.5.3. 2-Methoxy-6-(4-methoxyphenyl)-4-oxo-1-(trifluoromethyl)cyclohexanecarbonitrile (7 + 8d)

2-Methoxy-6-(4-methoxyphenyl)-4-oxo-1-(trifluoromethyl)cyclohexanecarbonitrile (**7** + **8d**) was obtained from **4d** by heating with Danishefsky's diene at 120 °C during 136 h. Colourles oil (280 mg, 86%); major diastereomer **7d**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.53 (dd, 1H, *J* = 15.9 Hz, *J* = 3.0 Hz, CH$_2$), 2.82–3.17 (m, 3H, CH$_2$), 3.29 (dd, 1H, *J* = 14.1 Hz, *J* = 3.3 Hz, C*H*-Ar), 3.50 (s, 3H, MeO), 3.81 (s, 3H, MeO-Ar), 3.96 (dd, 1H, *J* = 8.3 Hz, *J* = 4.9 Hz, C*H*-MeO), 6.90 (d, 2H, *J* = 8.8 Hz, Ar), 7.29 (d, 2H, *J* = 8.8 Hz, Ar); ^{19}F NMR (282 MHz, CDCl$_3$): δ -66.6; ^{13}C NMR (75 MHz, CDCl$_3$): δ 41.4 (*C*H-Ar), 44.5 (2CH$_2$), 53.6 (q, *J* = 25.0 Hz, *C*-CF$_3$), 55.3 (MeO-Ar), 58.5 (MeO), 77.5 (*C*H-MeO), 113.3 (CN), 124.3 (q, *J* = 286.6 Hz, CF$_3$,); 114.3, 128.4, 129.3, 159.7 (arom); 203.0 (C═O); minor diastereomer **8d**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.60 (bd, 1H, *J* = 15.6 Hz, CH$_2$), 3.45 (s, 3H, MeO), 4.33 (t, 1H, 3.0 Hz, C*H*-MeO), 7.01 (d, 2H, *J* = 8.9 Hz, Ar), other signals are identical to major diastereomer; ^{19}F NMR (282 MHz, CDCl$_3$): δ -64.4; ^{13}C NMR (75 MHz, CDCl$_3$): δ 40.0 (*C*H-Ar), 42.7 (CH$_2$), 45.0 (CH$_2$), 57.8 (MeO), 78.7 (*C*H-MeO), 114.6 (CN), 123.4 (q, *J* = 286.0 Hz, CF$_3$,), 203.6 (C═O), other signals are identical to major diastereomer; ESI-MS (*m/z*): calcd. for $C_{16}H_{16}F_3NO_3Na$ [M]$^+$ 350.0974, found 350.0980.

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