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Synthetic Applications of α-Fluoroalkylated Enones. 1. Use as Dienophiles in Diels−Alder Cycloadditions

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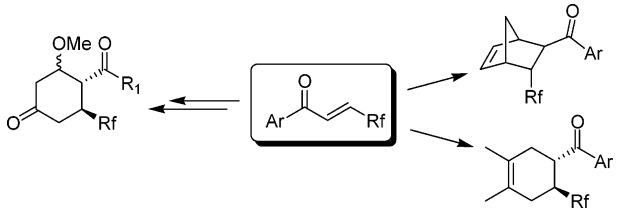

β-Fluoroalkylated enones are efficient dienophiles in Diels−Alder cycloadditions to prepare various fluorinated cylic compounds. However, the presence of the fluoroalkyl moiety modifies the reactivity and the selectivity of these cycloadditions.

Introduction

It is now well-known that the introduction of fluorine atoms or fluoroalkyl moieties into organic substrates gives rise to important physicochemical modifications of the concerned molecules.[1] Such specific properties find applications in various fields.[2]

For example, the introduction of fluorine atoms or fluoroalkyl groups into molecules constitutes a classical and systematic modification of biological properties used in medicinal chemistry for the design of new drugs.[3] More specifically, fluoroalkyl groups (particularly CF_3) cause a great interest since they generally increase the lipophilicity of the compounds and, usually, enhance their bioavailability. Consequently, more and more fluoroalkylated molecules find application in the pharmaceutical fields.[4] Moreover, cyclic compounds constitute a frequent backbone among bioactive substrates and, consequently, are important frameworks in drug design. Due to these observations, fluoroalkylated cyclic molecules should be valuable building blocks to construct medicinally relevant complex structures.

Some methods have been developed to obtain nonaromatic and nonheterocyclic fluoroalkylated compounds.[5] Among them, the Diels−Alder reaction constitutes one of the most efficient strategies.[6−9] Generally, the fluoroalkylated dienophiles are not functionalized trifluoroalkenes, often substituted on the carbon

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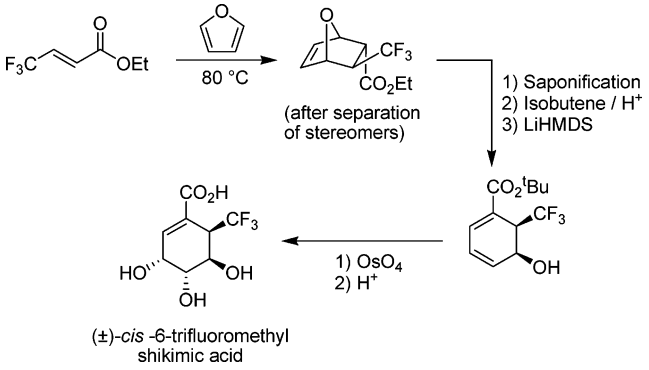
SCHEME 1. Synthesis of (±)-*cis*-6-Trifluoromethyl Shikimic Acid



bearing the CF_3 group. Concerning dienophiles bearing another functional group (usable for further reactions), the most used is the (*E*)-trifluorocrotonic ethyl ester because of its commercial availability.[7] Cycloaddition with this compound has been successfully applied in the synthesis of a trifluoromethylated analogue of shikimic acid (Scheme 1).[7b]

Nevertheless, the variety of fluoroalkylated dienophiles is relatively limited, and generally, these alkenes bear only a CF_3 moiety.

We have recently described an efficient and rapid synthesis of fluoroalkylated enones, bearing various fluoroalkyl moieties.[10] Such compounds appear to be valuable dienophiles for Diels−Alder cycloadditions.

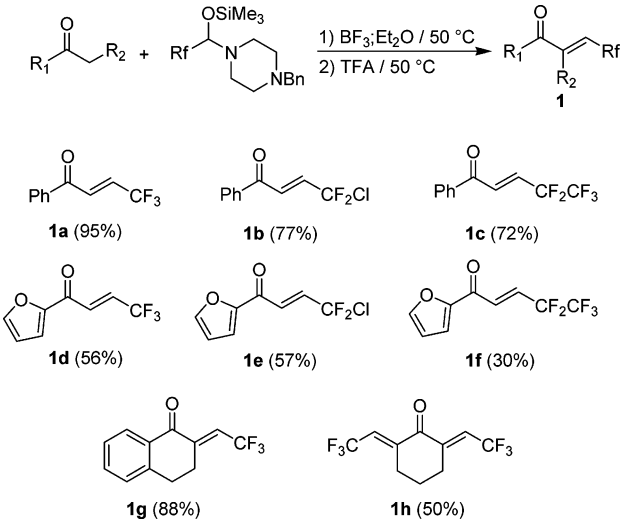
Results and Discussion

To validate our hypothesis concerning the synthetic potential of *β*-fluoroalkylated enones in Diels−Alder cycloaddditions, our study has been focused on eight enones substituted with diverse fluoroalkyl moieties, which can easily be synthesized by a one-pot, two-step procedure, as previously described (Scheme 2).[10]

To evaluate the reactivity of **1** in Diels−Alder cycloadditions, the reaction has been investigated first with cyclopentadiene (**2**), a common model for such processes (Scheme 3 and Table 1).

Compound **1a** is very reactive, and cycloaddition was observed even at 0 °C (entry 1). A complete conversion was observed at room temperature within 3 h (entry 3), but the rate was improved by heating at 80 °C (entry 4). This high reactivity can be attributed to the CF_3 moiety since the same reaction, performed with enones bearing a CH_3 (**4**) or a CCl_3 group (**5**) instead of CF_3, needed heating (90−100 °C), longer reaction times (40 h),[11] or activation with a Lewis acid.[12]

SCHEME 2. Synthesis of *β*-Fluoroalkylated Enones



SCHEME 3. Diels−Alder Cycloaddition of 1 with Cyclopentadiene

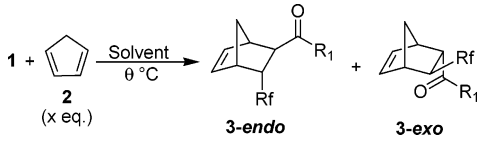


TABLE 1. Diels−Alder Reaction of 1 with Cyclopentadiene (2)

entry	1	2 (equiv)	solvent/*θ* (°C)	*t* (h)	3[a] (%) (*endo* + *exo*)	3-*endo*/ 3-*exo*[b]
1	**1a**	1	CH_2Cl_2/0	1	**3a** (55)	75/25
2	**1a**	2	CH_2Cl_2/rt	1	**3a** (88)	75/25
3	**1a**	1	CH_2Cl_2/rt	3	**3a** 95 (98)	73/27
4	**1a**	1	cyclohexane/80	1	**3a** (98)	74/26
5	**1a**	2	cyclohexane/80	1	**3a** (98)	73/27
6	**1b**	2	cyclohexane/80	3	**3b** 90 (98)	80/20
7	**1c**	2	cyclohexane/80	3	**3c** 94 (98)	76/24
8	**1d**	1	CH_2Cl_2/rt	24	**3d** (68)	76/24
9	**1d**	1	cyclohexane/80	4	**3d** (90)	75/25
10	**1d**	2	cyclohexane/80	1	**3d** 87 (98)	73/27
11	**1e**	2	cyclohexane/80	3	**3e** 73 (95)	78/22
12	**1f**	2	cyclohexane/80	3	**3f** 95 (99)	75/25
13	**1g**	2	cyclohexane/80	1	**3g** 89	100/0

[a] Isolated yield. The crude yield determined by ^{19}F NMR with an internal standard ($PhOCF_3$) is shown in parentheses. [b] Determined by ^{19}F NMR.

This difference in reactivity can be rationalized by considering the LUMO energy level of the dienophile which is lowered by the presence of an electron-withdrawing group, then favoring the $LUMO_{alkene}-HOMO_{diene}$ interaction.[6f−13] Some calculations have been realized and confirm this influence of the CF_3 moiety on the reactivity (Tables 2 and 3).

From these calculations, it appears clearly that the $LUMO_{alkene}-HOMO_{diene}$ difference is the lowest with the CF_3 substituent.

Other enones with various ketone moieties or fluoroalkyl groups also give rise to cycloadditions with good yields (entries 6−13).

To determine the configuration of the two obtained stereomers, we determined the spatial proximity of characteristic

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TABLE 2. HOMO/LUMO Energy Levels

		LUMO (eV)			HOMO (eV)
entry	method	**4**	**5**	**1a**	**2**
2	AM1[a]	−0.4529	−1.0332	−1.0966	−9.0794
4	PM3[a]	−0.5222	−1.0343	−1.1635	−9.2326

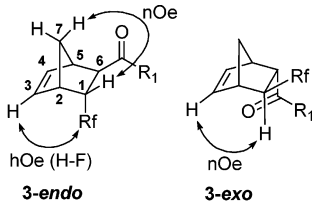
[a] Semiempirical molecular orbital calculations performed with Hyperchem 7.5.

TABLE 3. Energy Level Differences

		ΔE ($LUMO_{alkene}-HOMO_{diene2}$)		
entry	method	**4**	**5**	**1a**
2	AM1[a]	8.6265	8.0462	7.9828
4	PM3[a]	8.7104	8.1983	8.0691

[a] Semiempirical molecular orbital calculation performed with Hyperchem 7.5.

SCHEME 4. Configuration Determinations of 3



protons with each other or with fluorinated groups by using the nuclear Overhauser effect. Such characterization was realized by 2D NMR sequences, namely NOESY ($^1H/^1H$ correlation) and HOESY ($^1H/^{19}F$ correlation). Since there is only one CH_2, the protons of the bridge (H_7) are easily identified (by HSQC) and the vinylic protons (H_3) also present a specific shift. Furthermore, because of the ^3J spin coupling with fluorine atom, the vicinal proton to the fluoroakyl group (H_1) is also easy to identify. Then, a simple reading of both 2D plots allows seeing the correlation spots between H_1 and H_3 for the Rf-*exo* stereomer or between H_1 and H_7, H_1 and H_3, Rf and H_3 for the Rf-*endo* stereomer. The observed correlations are shown in Scheme 4.

These cycloadditions were stereoselective, and the major stereomer formed was that with the fluoroalkyl moiety in endo position. It must be noticed that the observed stereoselectivity is inverted compared to cycloadditions involving *trans*-1-phenylbut-3-enone (**4**)[12,13] but are in accordance with previous results observed with other fluoroalkylated alkenes.[14] The proportion between the two stereomers is relatively insensitive to the nature of R_1 or Rf substituents, and the low influence of the temperature on this ratio suggests that the **3-*endo*** product is rather a kinetic product than a thermodynamic one.

To explain such stereoselectivity, an eventual stabilizing secondary orbital interaction between the CF_3 group and the double bond has been invocated. However, the calculation of the LUMO of **1a** showed a higher orbital coefficient on the carbonyl moiety than on the fluorine atoms, suggesting a preferential secondary orbital interaction for C═O rather than for CF_3 (Figure 1).

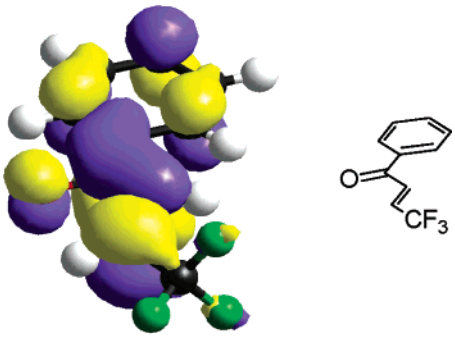
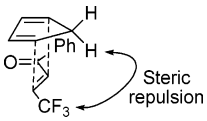
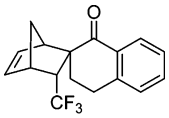


FIGURE 1. Representation of LUMO of **1a**.[15]

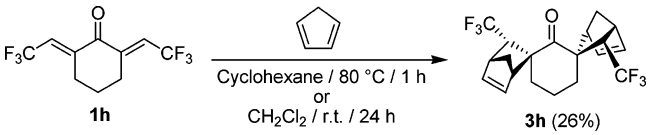
SCHEME 5. Steric Repulsion in 1a



SCHEME 6. Lone 3g Stereomer



SCHEME 7. Cycloaddition Adduct from 1h



As recently suggest by Salvaltella et al.,[16] it seems more reasonable to invoke a steric repulsion between the CF_3 group and the methylene moiety of **2** (Scheme 5), since it is well-admitted now that the steric demand of the CF_3 moiety is closer to that of an isopropyl group than to a methyl one.[17]

In the case of spiro compound **3g**, resulting from **1g**, the reaction needed heating to achieve complete conversion, certainly because of the more hindered nature of enone **1g**. However, the cycloaddition is 100% stereoselective leading exclusively to the *endo*-stereomer (Scheme 6).

When the Diels−Alder cycloaddition was realized with the bis-trifluoromethylated enone **1h**, the reaction gave a complex mixture, both at room temperature and in refluxing cyclohexane. Nevertheless, in both cases, compound **3h** has been isolated from this mixture (Scheme 7). Its structure has been determined by X-ray crystallography (see the Supporting Information).[18]

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(18) CCDC 286977 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.; fax: (int) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

SCHEME 8. Diels−Alder Cycloaddition of 1 with 6

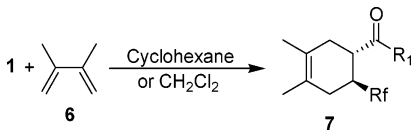

TABLE 4. Diels−Alder Cycloaddition of 1 with 6

entry	1	solvent/*T* (°C)	*t* (h)	7[a] (%)
1	**1a**	CH_2Cl_2/0	24	**7a** (0)
2	**1a**	CH_2Cl_2/50[b]	24	**7a** (78)
3	**1a**	cyclohexane/80	3	**7a** 92
4	**1b**	cyclohexane/80	20	**7b** 86 (90)
5	**1c**	cyclohexane/80	20	**7c** 84 (91)
6	**1d**	CH_2Cl_2/50[b]	24	**7d** (80)
7	**1d**	cyclohexane/80	20	**7d** 87 (90)
8	**1e**	cyclohexane/80	20	**7e** 94 (98)
9	**1f**	cyclohexane/80	20	**7f** 87 (94)
10	**1g**	cyclohexane/80	120	**7g** (25)
11	**1g**	cyclohexane/120[b]	7	**7g** (48)
12	**1g**	cyclohexane/120[b]	24	**7g** 90 (95)

[a] Isolated yield. The crude yield determined by ^{19}F NMR with an internal standard ($PhOCF_3$) is shown in parentheses. [b] Sealed tube.

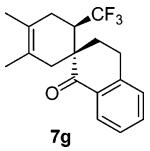

FIGURE 2. Spiro compound **7g**.

To extend the present study on the reactivity of enones **1a−g** in Diels−Alder cycloadditions, 2,3-dimethylbutadiene has been investigated as another diene (Scheme 8 and Table 4).

In contrast to the previous set of reactions, heating was always required to achieve good yields. With the exception of **1a**, which is very reactive (entry 3), the optimal conditions were heating to 80 °C for 20 h.

The difference between the two reactions certainly came from the structure of diene since the *s-cis* conformation is fixed in **2** whereas the *s-trans* conformation is favored for **6,** and some energy was required to adopt the conformation needed for cycloaddition.

The more hindered structure of **1g** requires heating at 120 °C in a sealed tube to get the spiro compound **7g** in moderate yield (Figure 2).

To synthesize more functionalized molecules, useful for further applications, Danishefsky's diene[19] (**8**) has been opposed to the fluoroalkyl enones **1** (Scheme 9 and Table 5).

It can be noticed that, in some cases, the reaction required heating in a sealed tube and 2 equiv of **8** but, nevertheless, led to the expected products in good yields.

The hydrolysis of the cycloadduct **9** under the conditions reported by Danishefsky[20] did not give rise to the same results. Indeed, instead of obtaining cyclohexenones **11**, compounds **10**, with a remaining methoxy group, were preferably formed; only a small amount of **11** was detected.

The same phenomenon has been already observed in the cycloaddition of trifluoromethylalkenes[6f] and in the hetero-Diels−Alder reactions of fluoroalkyl aldehydes with

SCHEME 9. Diels−Alder Cycloaddition of 1 with 8 and Hydrolysis of the Product 9

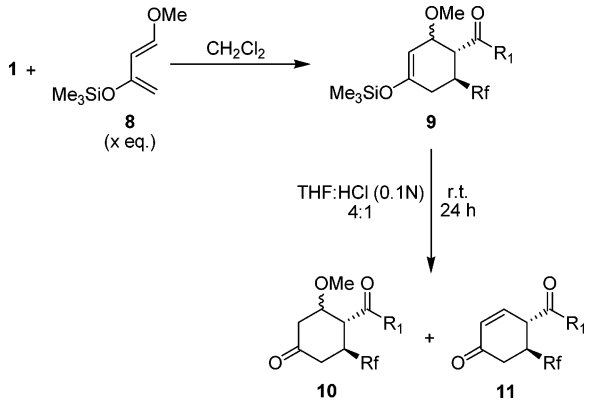

TABLE 5. Diels−Alder Cycloaddition of 1 with 8

entry	1	8 (equiv)	*T* (°C)	*t* (h)	yield of 9[a] (%) (de)	yield 10[b] (%) (de)	11[c] (%)
1	**1a**	1	rt	17	**9a** 73 (26)	**10a** 66 (21)	**11a** (3)
2	**1b**	2	50	19	**9b** 91 (22)	**10b** 86 (23)	**11b** (6)
3	**1c**	1	50	72	**9c** 35 (20)		
4	**1c**	2	50	17	**9c** 70 (21)	**10c** 65 (20)	**11b** (13)
5	**1d**	1	rt	17	**9d** 86 (20)	**10d** 60 (20)	**11d** (3)
6	**1e**	1	50	72	**9e** 40 (25)		
7	**1e**	2	50	17	**9e** 90 (20)	**10e** 86 (20)	**11e** (10)
8	**1f**	2	50	19	**9f** 84 (11)	**10f** 72 (10)	**11f** (11)
9	**1g**	1	rt	72	**9g** 5		
10	**1g**	2	50	25	**9g** 75 (50)	**10g** 65 (74)	**11g** (15)

[a] Crude yield determined by ^{19}F NMR with an internal standard ($PhOCF_3$). [b] Isolated yield. [c] Crude yield determined by ^{19}F NMR with an internal standard ($PhOCF_3$).

Danishefsky's diene. This phenomenon might be explained by the high electron-withdrawing inductive effect of the fluoroalkyl moiety, which precludes the elimination of methanol.[21]

These cycloadditions were also highly regioselective and delivered a single regioisomer (the structures of which have been determined by COSY, HSQC, and HMBC experiments). This regioselectivity was identical to that observed in non-fluorinated series.[19] This led us to suppose that the fluoroalkyl moieties do not influence the relative comparison of the orbital coefficients, as shown by semiempirical calculations which are in accordance with the observed regioselectivity (Figure 3).

Since Danishefsky's diene is well-known to give rise to excellent regioselectivities, another diene (isoprene) has been put in reaction with **1a** in order to have a more accurate opinion concerning the influence of the fluorinated group onto the regioselectivity (Scheme 10).

The observed regioselectivity is very modest (a 60:40 ratio). The same disappointing selectivity has been also observed with nonfluorinated series,[22] confirming our previous opinion about the very low influence of the fluoroalkyl group on regioselectivity.

In conclusion, *β*-fluoroalkylated enones constitute efficient dienophiles for Diels−Alder cycloadditions. The presence of the fluorinated moiety both increased the reactivity of these compounds and implied modification of the stereoselectivity. Nevertheless, the high reactivity in Diels−Alder reactions opens

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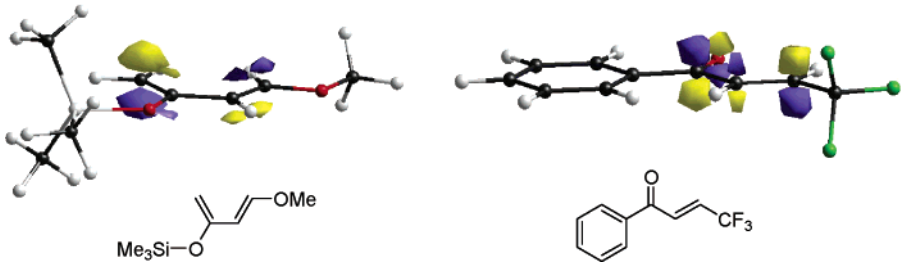
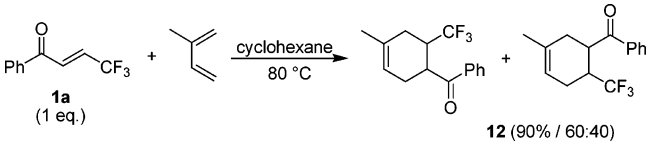


FIGURE 3. Representation of orbital coefficients of **8** and **1**.[15]

SCHEME 10. Diels−Alder Cycloaddition of 1a with Isoprene



potential synthetic applications to synthesize various fluorinated molecules, bearing a large variety of fluorinated moieties. Other reactivity studies and synthetic applications of compounds **1** are being conducted in our laboratories and will be published in due course.

Experimental Section

Diels−Alder Cycloadditions of 1a with Cyclopentadiene and 2,3-Dimethylbutadiene. A solution of β-trifluoromethylated enone **1a** (1 mmol) and diene (2 mmol) in cyclohexane (1 mL) was stirred at 80 °C for the time indicated in Tables 1 and 4. The solvent was then evaporated in vacuo and the crude product purified by flash chromatography.

***trans*-Phenyl[3-*endo*-(trifluoromethyl)bicyclo[2.2.1]hept-5-en-2-yl]methanone (3a-*endo*).** ^{1}H NMR: δ = 7.96 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 6.43 (m, 1H), 6.26 (m, 1H), 4.09 (ddq, J = 5, J = 3, J = 11, 1H), 3.33 (dd, J = 5, J = 1, 1H), 3.22 (bs, 1H), 3.04 (bl, 1H), 1.70 (d, J = 9, 1H),1.45 (d, J = 9, 1H). ^{13}C NMR: δ = 198.2, 136.4, 136.2, 129.3, 129.2; 129.0; 128.0 (q, J = 280), 49.6; 49.4, 47.2, 45.3 (q, J = 30), 43.7 (q, J = 2). ^{19}F NMR: δ = −66.15 (d, J = 11). Anal. Calcd for $C_{15}H_{13}F_3O$: C, 67.66; H, 4.92. Found: C, 67.52; H, 5.10.

***trans*-Phenyl[3-*exo*-(trifluoromethyl)bicyclo[2.2.1]hept-5-en-2-yl]methanone (3a-*exo*).** ^{1}H NMR: δ = 7,96 (m, 2H); 7,58 (m, 1H); 7,47 (m, 2H); 6,37 (m, 1H); 5,80 (m, 1H); 3,96 (dd, J = 5, J = 3, 1H); 3,33 (bl, 1H); 3,15 (bl, 1H); 2,96 (ddq, J = 5, J = 1, J = 10, 1H); 1,94 (d, J = 9, 1H); 1,56 (d, J = 9, 1H). ^{19}F NMR: δ = −67,17 (d, J = 10). Anal. Calcd for $C_{15}H_{13}F_3O$: C, 67.66; H, 4.92. Found: C,67.81; H, 4.99.

***trans*-[3,4-Dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl]-(phenyl)methanone (7a).** White solid. Mp = 79 °C. ^{1}H NMR: δ = 7.97 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 3.77 (dt, J = 6, J = 10, 1H), 2.99 (m, 1H), 2.25 (m, 4H), 1.71 (s, 3H), 1.62 (s, 3H). ^{13}C NMR: δ = 202.3, 137.0, 133.7, 129.1, 128.7, 128.0 (q, J = 280), 124.5, 123.1, 40.9 (q, J = 26), 40.6, 35.8, 30.2 (q, J = 3), 19.0, 18.9. ^{19}F NMR: δ = −70.42 (d, J = 8). Anal. Calcd for $C_{16}H_{17}F_3O$: C, 68.07; H, 6.07. Found: C, 68.15; H, 5.93.

Diels−Alder Cycloadditions of 1a with Danishefsky's Diene. A solution of β-trifluoromethylated enone **1a** (1 mmol) and Danishefsky's diene (2 mmol) in CH_2Cl_2 (1 mL) was stirred at 50 °C in a sealed tube for the time indicated in Table 5. After the mixture was cooled to rt, a 4:1 mixture of THF/aqueous HCl 0.1 N (4 mL) was added, and the crude mixture was vigorously stirred for 10 h. Then, the mixture was poured into an aqueous solution of $NaHCO_3$ (6%) and extracted three times with CH_2Cl_2. After drying over Na_2SO_4, the solvent was evaporated in vacuo and the crude product purified by flash chromatography.

4-Benzoyl-3-methoxy-5-(trifluoromethyl)cyclohexanone (10a). First Diastereomer. ^{1}H NMR: δ = 8.03 (m, 2H), 7.63 (m, 1H), 7.52 (m, 2H), 4.09 (dd, J = 10.0, J = 5.5, 1H), 3.80 (m, 1H), 3.39 (m, 1H), 3.25 (s, 3H), 2.55−2.82 (br, 4H). ^{13}C NMR: δ = 204.6, 199.6, 136.7, 134.2, 129.3, 128.9, 126.8 (q, J = 279.6), 78.4, 57.4 (q, J = 1.8), 46.9 (q, J = 1.7), 43.0, 39.3 (q, J = 27.8), 37.3 (q, J = 2.2). ^{19}F NMR: δ = −71.89 (d, J = 8.0). Anal. Calcd for $C_{15}H_{15}F_3O_3$: C, 60.00; H, 5.04. Found: C, 60.16; H, 4.98. Second Diastereomer. ^{1}H NMR: δ = 7.96 (m, 2H), 7.65 (m, 1H), 7.54 (m, 2H), 4.12 (m, 1H), 4.02 (dd, J = 6.8, J = 3.8, 1H), 3.84 (m, 1H), 3.11 (s, 3H), 2.91 (m, 2H), 2.59 (m, 2H). ^{13}C NMR: δ = 205.5, 196.6, 136.6, 133.9, 129.4, 128.5, 127.7 (q, J = 279.6), 76.9, 57.6 (q, J = 2.0), 45.3 (q, J = 1.6), 42,2, 37.1 (q, J = 27.5), 36.8 (q, J = 2.4). ^{19}F NMR: δ = −71.84 (d, J = 10.3). Anal. Calcd for $C_{15}H_{15}F_3O_3$: C, 60.00; H, 5.04. Found: C, 60.19; H, 5.32.

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Supporting Information Available: Typical procedures and characterization data of all compounds; X-ray crystallographic data for compound **3h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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