Pergamon

Tetrahedron, Vol. 52, No. 1, pp. 59-70, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00885-3

Trifluoromethylalkenes in Cycloaddition Reactions#

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Abstract: CF_3-Substituted alkenes have been described to be good partners in Diels-Alder reactions with the Danishefsky's diene and in 1,3-dipolar cycloadditions with nitrones and non-stabilized azomethine ylides. The influence of the CF_3-group on both the activation of the double bond and the stereochemistry of the cycloaddition has been evaluated. New CF_3-substituted mono- and polycyclic compounds **4** and **7**, highly functionalized isoxazolidines **18**, **19**, **22** and **23** and pyrrolidines **12**, **13** and **16** have been prepared.

The formation of quaternary carbons bearing a trifluoromethyl group and in particular of angularly CF_3-substituted compounds is of great interest for the preparation of analogues of natural compounds such as terpenes, steroids, and alkaloids. Cycloadditions are among the most widely-used reactions in organic synthesis and such reactions with trifluoromethylated ethylenic compounds is very attractive for the construction of mono- and polycyclic compounds bearing CF_3-quaternary carbons.[1,2]

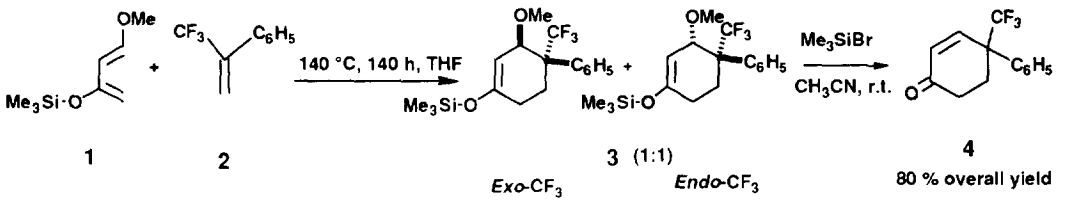
Some examples of these cycloadditions have already been described with trifluoropropene.[3,4] However, despite of the electronwithdrawing character of a CF_3 group, trifluoropropene exhibits a poor reactivity: this can be explained by the lack of π-electronwithdrawing character which is known to decrease significantly the LUMO energy level. More recently, and parallel to our investigations,[5-8] successful Diels-Alder and 1-3 dipolar cycloadditions have been reported with ethylenic compounds bearing a CF_3 group and at least one other electronwithdrawing substituent such as sulfone,[9] ester,[3a,10,11,12,13] ketone,[14] activated phenyl,[3b] and nitro group,[4b] providing elegant synthesis of alicyclic compounds, particularly in the steroid field. However none of these examples allow an evaluation of the activiting effect of a CF_3 group in cycloadditions.

Herein we report our studies on the influence of the electronic and steric effects of the CF_3 group on the course of cycloadditions with CF_3-substituted alkenes, including di- and trisubstituted alkenes bearing a CF_3 group as the only electron withdrawing substituent.

Results

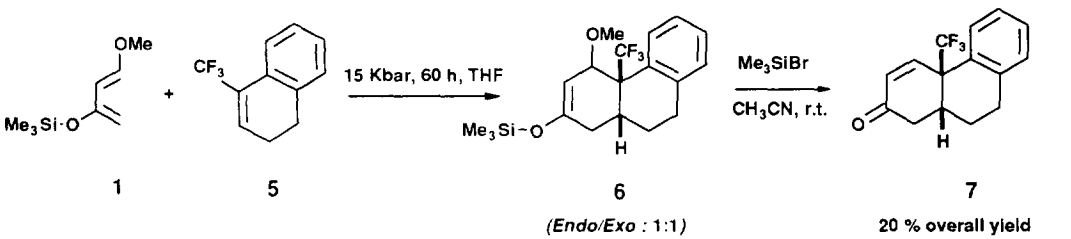
Diels-Alder Reaction

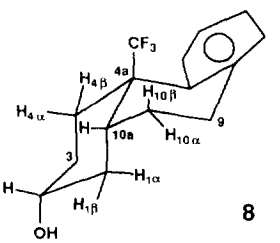
Under thermal conditions, the 1-methoxy-3-trimethylsilyloxy-butan-1,3-diene (Danishefsky's diene) **1** and α-trifluoromethylstyrene **2**[15] afforded regioselectively a 1:1 mixture of *Endo/Exo* diastereoisomeric adducts **3**. When treated with the bromotrimethylsilane in acetonitrile this mixture led to the racemic enone **4** in high yield (80 %), (Scheme 1).[16]



Scheme 1

Under the same conditions, the reaction of the sterically hindered 1-trifluoromethyl-3,4-dihydronaphthalene **5**[17] failed. However use of high pressure (15 Kbar) led to the formation of a single regioisomer **6** as a mixture of *Endo/Exo* adducts (ratio 1:1 estimated by GC analysis and ^{19}F NMR). Treatment with bromotrimethylsilane led to the 4a-trifluoromethyl-1,9,10-trihydrophenanthren-2(1H)-one **7** in 20 % overall yield (Scheme 2).[5]



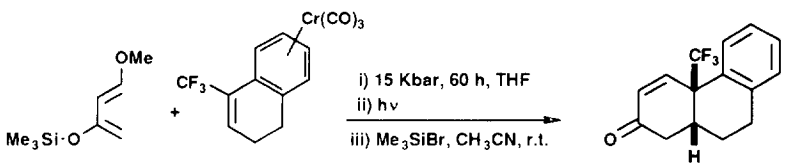


Scheme 2

The structure of the phenanthrenone was determined from NMR data of the corresponding octahydrophenanthrenol **8** obtained through two successive reductions (H_2, Pd/C and then $NaBH_4$). Its ^1H

constant with H-10 indicates an A/B *cis* junction, which has been confirmed by heteroNOESY F/H experiments.

In order to improve the yield of **7**, we investigated the cycloaddition reaction of the chromium tricarbonyl complex **9** with the Danishefsky's diene under high pressure. The use of the chromium complex dramatically increased the yield of the cycloaddition and slightly changed the stereoselectivity (70:30 mixture, ^{19}F NMR determination). Decomplexation under sunlight and treatment by bromotrimethylsilane led to 10a-CF_3-phenanthrone **7** in a 65 % overall yield[6] (Scheme 3).



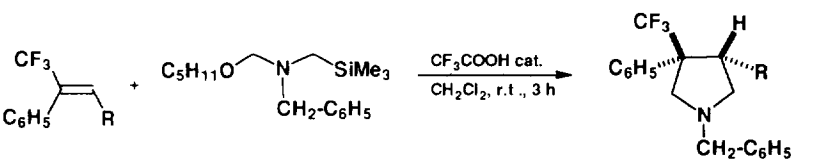
1 **9** **7**

65 % overall yield

Scheme 3

1,3-Dipolar cycloaddition reactions

Non-stabilised azomethine ylide as dipole - The reaction of trifluoropropene with a stabilised azomethine ylide, generated by the ring opening of an aziridine, has been described to lead to a mixture of regio- and stereoadducts in less than 10 %.[4a] This poor yield may be due to the thermal unstability of both reactants under thermal conditions or to their poor reactivity. We have investigated the cycloaddition reactions with non-stabilised azomethine ylides as dipoles.[7] These dipoles can be generated from an organosilylated compound under acidic catalysis and react at room temperature, with electron deficient dipolarophiles.[18] The reaction between the ylide, generated from the N-(trimethylsilylmethyl)-N-(pentoxymethyl)-benzylamine **11**, with trifluoromethylstyrene **2** or ethyl β-trifluoromethylcinnamate **10** afforded, after 3 h at room temperature, the pyrrolidines **12** and **13** in 80 % and 70 % yield respectively (Scheme 4). No reaction with the 1-trifluoromethyl-3,4-dihydronaphthalene **5** occurred.



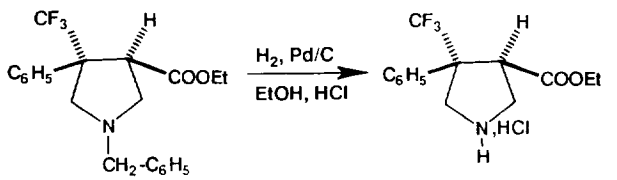
2 R = H
10 R = COOEt

11

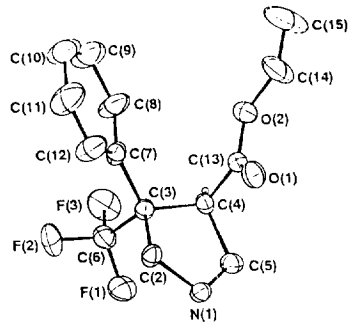
12 R = H (80 %)
13 R = COOEt (70 %)

Scheme 4

The determination of the relative configuration of substituents in pyrrolidine **13** could not be assigned from NMR experiments, but through the X ray diffraction of the chlorohydrate **14** (Scheme 5).[32]



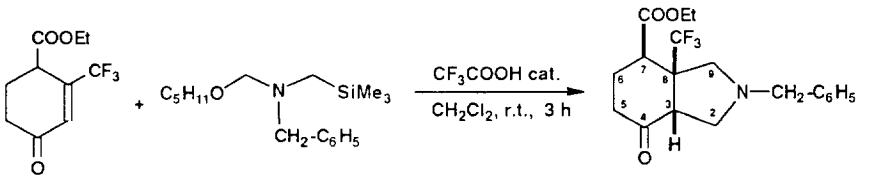
13 14



ORTEP diagram of **14**

Scheme 5

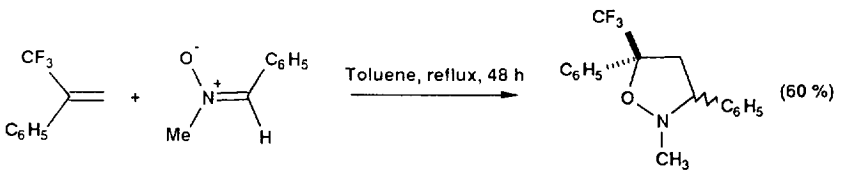
The 4-carbethoxy-3-trifluoromethylcyclohex-2-ene-1-one **15**, fluorinated analogue of the Hagemann's ester,[19] led to the perhydroisoindolone **16** in moderate yield (48 %) after 3 h at room temperature (Scheme 6). From heteroNOE F/H experiments, enhancement of the junction proton H-3 signal is observed indicating a spatial proximity and thus a *cis* relationship between the CF_3 group and the proton H-3. In the ^1H NMR spectrum, the H-7 signal exhibits a large (9 Hz) and a small (4 Hz) coupling constant with H-6 indicating its axial position. This H-7 proton exhibits a $^4J_{HF}$ coupling constant that indicates either a *trans* diaxial position towards CF_3 (^4J *W* coupling constant), or a spatial proximity (through space coupling constant). The absence of heteroNOE rules out this proximity and demonstrates the *trans*-relationship between H-7 and CF_3.



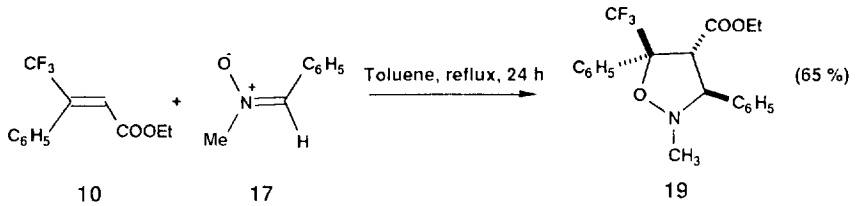
15 11 16 (48 %)

Scheme 6

b. Nitrone as dipole - We have investigated reactions between the readily available stable nitrone, N-(benzylidene)-methylamine-N-oxide **17**.[8] The reaction was successful with a-trifluoromethyl styrene **2** and ethyl b-trifluoromethylcinnamate **10**,[20] affording a diastereoisomeric mixture of trifluoromethyl isoxazolidines **18** in a 60% yield from **2**, and a single diastereoisomer **19** (65 %) from **10** (Scheme 7). The reaction failed with the more sterically demanding 1-trifluoromethyl-3,4-dihydronaphthalene **5**.

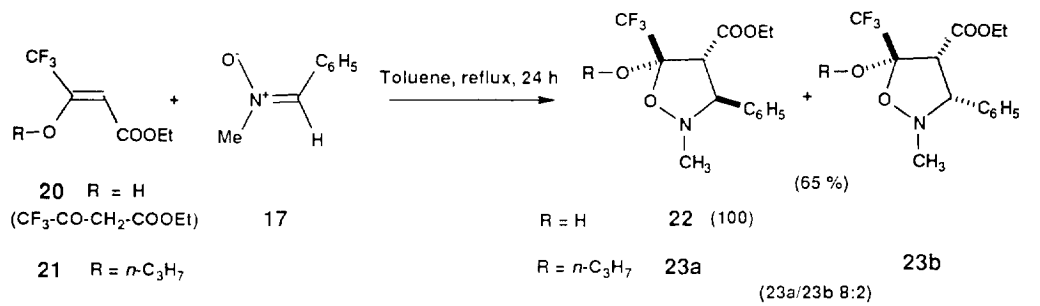


2 17 18 (mixture 1:1)



Scheme 7

These results prompted us to investigate the reactivity of ethyl trifluoroacetoacetate (ETFAA) **20** which could act as a dipolarophile in its enolic form. The reaction with nitrone **17** led regio- and stereoselectively to the isoxazolidine **22** (65 %) (Scheme 8). The corresponding enol ether **21**[21] displayed a similar reactivity but led to a mixture of two diastereoisomers **23a** and **23b** (8:2 ratio) in a 65% yield.



Scheme 8

The stereochemistry of the adducts was determined by heteroNOE experiments. When irradiating the CF_3 group an enhancement of the H-4 proton signal in the isoxazolidines **22**, **23a** and **23b** was observed (about 8-10%) indicating a spatial proximity of the CF_3 group and the H-4 proton and thus a *trans* relationship between the CF_3 and the CO_2Et groups. In the ^1H NMR spectrum, the high value (10 Hz) of the coupling constant between H-3 and H-4, indicates their *trans* relationship in **22** and **23a**, while $J_{H\text{-}3,H\text{-}4}$ is only 7 Hz in **23b**. This stereochemistry has been confirmed by X-ray diffraction of the isoxazolidine **22** (Figure 1).

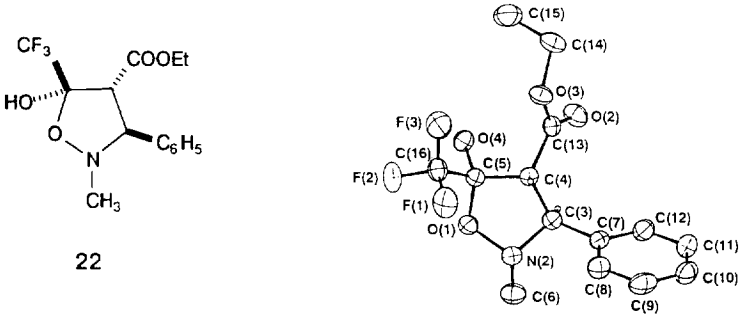


Figure 1 : ORTEP diagram of isoxazolidine **22**[32]

Reactions with the non-fluorinated analogues

We have investigated the previously non reported cycloadditions with non-fluorinated alkenes (*ie* methyl parent compounds).

Diels-Alder reaction. Reactions performed under thermal or high pressure conditions with Danishefsky's diene and the α-methylstyrene or the 1-methyl-1,2-dihydronaphthalene failed, providing polymeric or starting material. Starting materials were recovered when reactions were performed with chromium tricarbonyl complexes of these compounds[22] under high pressure.

1,3-Dipolar reactions. With the non-stabilized azomethine ylide derived from **11**, all attempts of reaction with α-methylstyrene, ethyl ethoxycrotonate, ethyl β-methylcinnamate, and the Hagemann's ester failed. Starting alkenes were recovered even after a long reaction time or at higher temperature. With the nitrone **17**, the replacement of a trifluoromethyl group by a methyl group either has no major effect on reactivity (case of α-methylstyrene)[23] or entailed a dramatic loss of reactivity (ethyl acetoacetate, ethyl ethoxycrotonate and ethyl β-methylcinnamate).

Discussion

The success of reactions performed with CF_3-containing alkenes, compared to the unreactivity of methyl parent compounds, clearly shows the activating effect of the CF_3 group. In disubstituted alkenes, bearing only the CF_3 group as electronwithdrawing group, the electronic effect of the CF_3 group sufficiently lowers the LUMO energy level to promote cycloadditions controlled by ($HOMO_{diene/dipole}$-$LUMO_{alkene}$) interactions,[24] despite of its steric hindrance. The reactivity of the trifluoromethylstyrene **2** can be compared to that of the 1-phenylacrylic acid which reacts only slowly with cyclopentadiene (8 days at room temperature).[25] In cycloadditions with nitrones **17**, the similar reactivity of trifluoromethylstyrene **2** and methylstyrene strongly suggests that the reactions occur through different processes ($HOMO_{nitrone}$-$LUMO_{alkene}$) from **2** and ($HOMO_{alkene}$-$LUMO_{nitrone}$) from methyl styrene.[26] However a process involving the two possible frontier orbital interactions cannot be excluded in both cases.

In the absence of any other withdrawing substituent, the s-attracting effect of CF_3 is not strong enough to allow cycloadditions (Diels-Alder and 1,3 dipolar) with trisubstituted olefin to occur. A CF_3-substituted olefin is not able to be complexed by Lewis acids, and other types of activation had to be considered. In Diels-Alder reaction with **5**, high pressure and temporarly use of chromium tricarbonyl complex when a phenyl group is present, have been proved to be efficient.

Trisubstituted olefins bearing both a CF_3 group and another electronwithdrawing group were described to react only with highly reactive dipoles such as nitrile oxide[11a] and diazomethane.[14] We could find conditions to obtain cycloadducts with nitrones or azomethine ylides, even with hindered olefins such as **10, 15**, and **20**; the CF_3 group acts as the second electronwithdrawing group required with trisubstituted alkenes. To the best of our knowledge the successful cycloaddition with **20** is the first example of the enol form of a β-ketoester acting as a dipolarophile.

The stereo- and regioselectivity of these reactions depend on the structure of the two partners. In Diels-Alder reaction the regioselectivity is the result of the directing effects of both electrondonating substituents on the diene, and the electronic influence of the phenyl and the trifluoromethyl groups on the alkene.[27] However the lack of stereoselectivity in these reactions was unexpected. A phenyl substituent is known to stabilise the

endo-phenyl transition state (p-stacking).[28] Furthermore, the steric hindrance of a CF_3 group should favor its *exo* approach.[3b,29] The 1:1 *endo*/*exo* ratio of products suggests that secondary electronic interactions between the unsaturated system of the diene and the CF_3 group exist and are stabilizing enough to oppose other effects.

In 1,3 dipolar cycloadditions with the nitrone **17**, the GC monitoring of the reaction indicates that products are the kinetic ones. The regioselectivity is governed by steric demands: the oxygen of the nitrone adding preferentially the more substituted carbon.[30] The lack of stereoselectivity observed with the trifluoromethylstyrene can be explained as for Diels-Alder reactions. From the ethyl trifluoromethylcinnamate **10** or with ethyl trifluoroacetoacetate **20**, the high stereoselectivity indicates that, unlike a phenyl group, an ester group governs the stereochemistry of the reaction, through secondary interactions with the dipole, which greatly predominate those of the CF_3 group. The approach of the CF_3-analogue of Hagemann's ester **15** towards the azomethine ylide is also directed by the ketonic group (*endo* approach) despite of the hindrance of the cyclic framework. The conservation of the stereochemistry of starting olefins in all these cycloadditions strongly suggests concerted process.[31]

In conclusion, the σ-electron withdrawing character of a CF_3 group has been proved to be very effective in cycloaddition reactions and allowed the synthesis of highly functionalized CF_3-containing polycyclic and heterocyclic compounds to be performed. New compounds could be prepared in good yields, such as isoxazolidines and pyrrolidines and a phenanthrenone. Chiral versions of these reactions are under investigation.

Acknowledgments

We thank Dr Bois (Laboratoire de Chimie des Métaux de Transition, Université Pierre et Marie Curie, Paris VI) for X-ray determinations.[32] We thank also the European Union (HCM Network "Synthesis and molecular Recognition of Fluorinated Bioactive Molecules" (ERBCHRXCT 93 0279) for financial support.

Experimental section

NMR spectra have been performed with $CDCl_3$ solution on a Varian EM390, FH dual probehead, and/or Bruker AC 200 and ARX 400 (^1H: 90, or 200 or 400 MHz, ^{19}F: 84, 188 or 376 MHz and ^{13}C :50, 75 or 100 MHz). Chemical shifts are reported in ppm relative to Me_3Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C-F coupling. For the determination of fine coupling constants an acquisition of 16K data points, a Lorenz-Gauss transformation of the FID, and a zero filling to 64K were performed in order to obtain a minimum of resolution of 0.2 Hz/pt (^1H and ^{19}F) or 0.5 Hz/pt (^{13}C). Cosy, hmqc, hmbc experiments were performed on a multinuclear probehead equipped with a Z-gradient coil. The $\{^1H\},^{19}F$, $\{^{19}F\},^1H$ and heteroNOE experiments were performed on an inverse dual probehead. GC/MS analyses were obtained at 70 eV EI (capillary column CPSIL-5, 25 m). GC analysis was performed on a capillary column SE30, 10 or 25 m).

3-Methoxy-4-phenyl-4-trifluoromethyl-1-trimethylsiloxycyclohex-1-ene (3). 1-Trifluoromethyl styrene **2**[15] (2 g, 11.6 mmol), Danishefsky's diene **1** (3 g, 17.5 mmol), hydroquinone (10 mg) and anhydrous THF (15 mL) were placed in a Pyrex tube. The reaction vessel was purged with Argon, sealed, and heated in

an oil bath at 140 °C for 140 h. The mixture of stereoadducts **3a** and **3b** (3.19 g, 80%) was isolated after filtration (SiO_2, eluent: pentane) of the solution. **3a** and **3b**: ^{19}F NMR δ -69.6 and -69.9 (1:1); ^1H NMR δ 0.05 and 0.15 (1:1) (s, 9 H, Me_3Si), 2.3 (m, 4H, H-5, H-6), 3.45 and 3.50 (1:1) (s, 3 H, OCH_3), 4.6 (m, 1 H, C*H*OMe), 5.15 (m, 1 H, H-2), 7.4 (m, 5 H, Ph), ^{13}C NMR δ 20.1 (Me_3Si), 26.4 and 26.8 (C-5), 26.9 (C-6), 49.9 and 50.9 (q, ^2J = 23 Hz, C-4), 56.2 and 57.5 (OCH_3), 75.2 and 78.7 (C-3), 102.4 and 104.2 (C-2), 127.0 (q, ^1J = 275 Hz, CF_3), 127.6, 127.7, 127.9, 134.6; M.S (GC coupled) (EI) **3a** 329 (M-CH_3, 4), 313 (18), 159 (17), 158 (44), 157 (100), 142 (15), 141 (35), 103 (5), 45 (7); **3b** 329 (M-CH_3, 3), 313 (8), 158 (25), 157 (100), 142 (12), 141 (30), 73 (27), 45 (16).

4-Trifluoromethyl-4-phenyl-2-cyclohexen-1-one (4). To the crude mixture **3a** and **3b** (3.19 g) in solution in acetonitrile (30 mL) freshly distilled Me_3SiBr (1.55 mL, 11.8 mmol) was added dropwise under Argon at room temperature. After stirring (1 h), the black solution was diluted in ether (50 mL) and hydrolysed with aqueous NH_4Cl (10 mL). The organic layer was washed with brine, dried ($MgSO_4$), and solvents were evaporated. After chromatography on SiO_2 column (pentane/Et_2O, 98:2), compound **4** was isolated in pure form (2.2 g, 80% yield): mp 62-64 °C (cyclohexane); ^{19}F NMR δ- 74.2; ^1H NMR δ 2.2 (m, 2 H); 2.6 (m, 2 H); 6.3 (d, ^3J = 11 Hz, 1 H, H-2); 7.3 (dd, $^3J_{HH}$ = 11 Hz, $^4J_{HF}$ = 1.8 Hz, 1 H, H-3); 7.4 (m, 5 H, Phenyl); ^{13}C NMR δ 28.9 (C-5), 33.2 (C-6), 50.0 (q, ^2J = 26 Hz, C-4); 126.6 (q, ^1J = 283 Hz, CF_3), 128.2, 128.6, 128.8, 134.8 (Ph), 131.9 (C-2), 146.0 (C-3), 196.9 (CO); M.S. (EI) 240 (M^+, 19), 212 (34), 184 (29), 171 (M - CF_3, 40), 164 (7), 143 (13), 128 (24), 115 (100), 77 (7), 68 (92). Anal. Calcd for $C_{13}H_{11}F_3O$: C, 65.00; H, 4.61. Found: C, 64.92; H, 4.70.

4a-Trifluoromethyl-4a,9,10,10a-tetrahydrophenanthren-2(1-H)-one (7). An anhydrous THF solution of trifluoromethyldihydronaphthalene **5**[17] (435 mg, 2.2 mmol), Danishefsky's diene (570 mg, 3.3 mmol) and hydroquinone (10 mg) in pentane solution 5 mL) were heated at 50 °C under 15 Kbar for 66 h. After decompression, THF was evaporated and the crude mixture was diluted in acetonitrile (10 mL), and freshly distilled Me_3SiBr (0.3 mL, 2.3 mmol) was added dropwise. After stirring 1h at r.t., the black solution was diluted in ether (50 mL) and hydrolysed with aqueous NH_4Cl (5 mL). The organic layer was washed with brine, dried (MgSO4), and solvents were evaporated. After chromatography on SiO_2 column (pentane/Et_2O: 8:2), pure compound 7 was isolated (135 mg, 20%): ^{19}F NMR δ - 70.5; 1H NMR δ 1.7 (m, 1 H), 2.2 (m, 1 H), 2.3 (m, 2 H), 2.9 (m, 3 H), 6.2 (d, ^3J = 11 Hz, 1 H, H-3), 7.2 (m, 5 H, H-4 and C_6H_4); ^{13}C NMR δ 23.9, 24.8 (C-9, C-10), 33.7 (C-10a), 40.0 (C-1), 48.2 (q, ^2J = 24 Hz, C-4a), 126.4 (C-3), 126.9 (q, ^1J = 285 Hz, CF_3), 128.4, 129.5, 130.0, 130.2, 130.7, 136.7), 146.4 (C-4), 197.5 (CO); M.S (EI) 266 (M^+, 35), 246 (M - HF, 29), 224 (14), 209 (12), 197 (M - CF3, 100), 179 (42), 169 (42), 153 (24), 141 (70), 129 (77), 128 (67), 115 (57), 102 (13), 91 (17), 77 (18), 69 (45), 68 (59), 63 (30), 51 (40). Anal. Calcd for $C_{15}H_{13}F_3O$: C, 67.66; H, 4.92; Found : C, 67.45; H, 4.78.

4a-Trifluoromethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (8). An ethanolic solution of 7 (100 mg, 0.38 mmol) was stirred under hydrogen atmosphere (1 bar) in the presence of a catalytic amount of Pd (5 % on C) for 3h at r.t. After filtration of catalyst and evaporation, the crude product was filtered on SiO_2 (pentane-Et_2O 9:1) and compound **8** was isolated (100 mg, 98%). This compound (100 mg, 0.37 mmol) in solution in EtOH was added dropwise to a suspension of $NaBH_4$ (15 mg, 0.4 mmol) in ethanol (5 mL). After stirring (1h) at r.t., the reaction medium was treated by aqueous NH_4Cl. The organic layer was extracted (Et_2O), washed (brine), dried ($MgSO_4$). Evaporation of the solvent give the compound **8** (90 mg 90%): mp

70-72 °C (cyclohexane); ^{19}F NMR δ - 71.4; 1H NMR δ (C_6D_6) 0.84 (m, 1 H, H-3a), 0.99 (ddd, ^3J = 11.1 Hz, ^2J = 12.6 Hz, ^3J = 12.9 Hz, 1 H, H-1a), 1.20 (tdd, ^3J = 2.8 Hz, ^3J = 6.4 Hz, ^2J = 14.1 1 H, H-10a), 1.30 (m, 1 H, H-1b), 1.46 (m, 2 H, H-4a, H-3b), 1 95 (dddd, ^3J = 2.6, ^3J = 3.9, ^3J = 3.9 Hz, ^3J = 12.9 Hz, 1 H, H-10a, heteroNOe 10 %), 2.2 (m, 1 H, H-10b), 2.36 (td, ^3J = 3.6 Hz, ^2J = 14.0, 1 H, H-4b), 2.56 (m, 2 H, H-9); 3.20 (tt, ^3J = 4.3 Hz, ^3J 11.1 Hz, 1 H, H-2), 6.85-7.2 (m, 4 H); ^{13}C NMR δ (C_6D_6) 23.8 (q, $^5J_{CF}$ = 2.1 Hz, C-10a), 24.6 (C-9), 27.9 (q, $^4J_{CF}$ = 2.7 Hz, C-4), 30.4 (C-3), 37.1 (C-1), 46.3 (q, $^2J_{CF}$ = 22.5 Hz, C-4a), 69.5 (C-2), 126.3, 127.5, 127.7, 128.4 (q, $^1J_{CF}$ = 284.5 Hz, CF_3), 130.1, 130.6, 138.1; MS (EI) 252 (M-H_2O, 55), 183 (M-H_2O, -CF_3, 100), 141 (56), 129 (39), 128 (20), 111 (17), 57 (13), 55 (10). Anal. Calcd for $C_{15}H_{17}F_3O$: C, 66.7; H, 6.34. Found: C, 66.8, H, 6.52

1-Trifluoromethyl-3,4-dihydronaphthalene tricarbonylchromium complex (9). To a solution of 1-trifluoromethyl-3,4-dihydronaphthalene **5** (1g, 5 mmol) in dioxane (50 mL) was added $Cr(CO)_3(NH_3)_3$ (1.05 g, 5.6 mmol) in one portion. The mixture was refluxed overnight under a flow of N_2. Dioxane was evaporated and the residue was filtered on SiO_2 (pentane/ether 8:2). Orange crystals of complexe **9** (1.28 g, 77%) were obtained after recrystallization. **9**: mp: 92-94 °C (pentane/ether); ^{19}F NMR δ -64.7 ppm; ^1H NMR (acetone-d-6) δ 2.7 (m, 2 H, CH_2), 2.9 (m, 2 H, CH_2), 5.7 (m, 4 H, Ph), 6.9 (m, 1 H, C=C*H*). Anal. Calc. for $C_{14}H_9O_3F_3Cr$: C, 50.3; H, 2.71. Found: C, 50.1; H, 2.55

Diels-Alder reaction of 1-trifluoromethyl-3,4-dihydronaphthalene chromium tricarbonyl (9). A solution of complex **9** (500 mg, 1.5 mmol) in anhydrous THF and Danishefsky's diene (510 mg, 3 mmol) were heated at 50 °C under 15 Kbar for 66 h. After decompression, the mixture was poured in $CHCl_3$ (50 mL), maintained 5 h under sunlight and filtered on silica (CH_2Cl_2). Solvents were evapored and the residue was diluted in CH_3CN (10 mL). Me_3SiBr (1.5 mmol, 0.2 mL) was added dropwise. After of stirring (1h) at rt, the reaction mixture was diluted in ether and washed with aqueous NH_4Cl, brine and dried ($MgSO_4$). After chromatography (pentane/ether 8:2), 4a-trifluoromethyl-4a,9,10,10a-tetrahydrophenanthren-2-one **7** (260 mg, 65%) was isolated.

Cycloaddition with azomethine ylide from 11. *General procedure*: To a cooled (0 °C) solution of alkene (2-6 mmol), N-(trimethylsilylmethyl)-N-(pentoxymethyl)-benzylamine **11** (1.2 equiv.) in CH_2Cl_2 (10 mL), stirred under Ar, was added dropwise a solution of CF_3COOH in CH_2Cl_2 (1 mL, 10% molar) over 20-30 min. (1 drop a minute). The reaction mixture was warmed to r. t. and stirred for additional 3 h. The solution was diluted in ether (10 mL), extracted, and the organic layer was washed with an aqueous solution of $NaHCO_3$, brine, and dried ($MgSO_4$). After evaporation, the resulting oil was purified by chromatography (pentane/ethyl acetate).

Reaction with 1-trifluoromethylstyrene 2. 1-Trifluoromethylstyrene **2** (1g, 5.8 mmol) and N-(trimethylsilylmethyl)-N-(pentoxymethyl)-benzylamine **11** (2g, 7 mmol) were reacted with a solution of CF_3COOH (0.6 mL, 0.58 mmol) in CH_2Cl_2 to give a crude product (2g). A chromatography (pentane/ethyl acetate 6:4) afforded the 3-trifluoromethyl-3-phenyl-N-benzylpyrrolidine **12** (1.4 g, 80%): ^{19}F NMR δ - 73.3 ppm; ^1H NMR δ 2.3-2.8 (m, 4 H, H-4 and H-5), 3.1 (d, *J* 10 Hz, 1 H, H-2), 3.25 (d, *J* 10 Hz, 1 H, H-2'), 3.7 (s, 2 H, CH_2Ph), 7.2 (m, 10 H, Ph), ^{13}C NMR δ 33.6 (C-4), 53.5 (C-5), 56.5 (q, ^2J = 32 Hz, C-3), 59.9 (CH_2N), 60.6 (CH_2N), 127.1, 127.7, 128.1, 128.4, 128.6, 128.7, 136.9, 138.9, 127.2 (q, ^1J = 275 Hz, CF_3); MS (EI) 305 (M+, 75), 228 (7), 214 (12), 134 (11), 133 (52), 132 (66), 103 (14), 92 (30), 91 (100), 77 (9), 65 (34), 51 (18). Anal. Calcd for $C_{18}H_{18}F_3N$: C, 70.8, H, 5.94, N, 4.59. Found: C, 70.9; H, 5.80; N, 4.50.

Reaction with ethyl (*E*)-1,1,1-trifluoro-1-phenylbuten-2-oate (10). Ethyl (*E*)-1,1,1-trifluoro-1-phenylbuten-1-oate **10** (500 mg, 2 mmol) and N-(trimethylsilylmethyl)-N-(pentoxymethyl)-benzylamine **11** (700 mg, 2.4 mmol) in CH_2Cl_2, were reacted with a solution of CF_3COOH in CH_2Cl_2 (0.2 mL, 0.2 mmol). The crude oil (1.1g) led, after chromatography (pentane/ethyl acetate, 6:4) to the 3-trifluoromethyl-3-phenyl-4-(ethyl carbethoxy)-N-benzylpyrrolidine **13** (530 mg 70%): ^{19}F NMR δ - 71.3; ^1H NMR δ 0.8 (t, J = 7 Hz, 3 H, CH_3), 3.1-3.3 (m, 4 H), 3.6 (m, 3 H, CH_2O), 3.75 (s, 2 H, CH_2N), 7.2 (m, 10 H, Ph); ^{13}C NMR δ 13.3 (Me), 49.8 (C-4), 56.1 (OCH_2), 57.9 (q, ^2J = 24 Hz, C-3), 59.3, 60.5, 61.0, 127.5 (q, ^1J = 283 Hz, CF_3), 126.9, 127.5, 127.7, 127.9, 128.1, 128.2, 136.9, 138.7, 171.3 (CO). Anal. Calcd for $C_{21}H_{23}O_2NF_3$: C, 66.8; H 5.87; N, 3.71. Found: C, 67.0; H 5.75; N, 3.60.

Reaction with 4-carbethoxy-3-trifluoromethyl-cyclohex-2-ene-1-one (15). 4-Carbethoxy-3-trifluoro methyl-cyclohex-2-ene-1-one **15** (500 mg, 2.1 mmol) and N-(trimethylsilylmethyl)-N-(pentoxymethyl)-benzylamine **11** (780 mg, 2.6 mmol) were reacted with a solution of CF_3COOH (0.21 mL, 0.21 mmol) in CH_2Cl_2. The crude oil (800 mg) led after chromatography (pentane/ethyl acetate, 9:1) to the perhydroisoindolone **16** (370 mg, 48%) and 180 mg of non-indentified products. **16**: ^{19}F NMR δ -71.2; ^1H NMR δ 1.2 (t, J = 7 Hz, 3 H, CH_3), 2.3 (m, 2 H, H-6), 2.5 (m, 2 H, H-5), 2.9 (ddq, $^3J_{HH}$ = 4 Hz, $^3J_{HH}$ = 9 Hz, $^4J_{HF}$ 1 Hz, 1 H, H-7), 3.0 (m, 1 H, H-3, NOE Hetero H/CF_3 = 10%), 3.1 (m, 2 H, H-2), 3.2 (m, 2 H, H-9), 3.6 (m, 2 H, NCH_2Ph), 4.2 (q, J = 7 Hz, 2H, OCH_2), 7.3 (m, 5 H, Ph). ^{13}C NMR d 13.8 (CH_3), 21.8 (C-6), 35.4 (C-5), 43.0 (C-7), 50.7 (C-3), 54.6 (q, ^2J = 24 Hz, C-8), 57.2, 58.8, 59.9 (NCH2), 61.2 (OCH_2), 127.1 (q, ^1J 282 Hz, CF_3), 127.3, 128.4, 128.5, 137.9, 171 8 (COOEt), 208.7 (CO). MS (EI) 369 (M^+, 10), 324 (5), 300 (M-CF_3,5), 278 (8), 254 (5), 133 (80), 91 (100), 65 (15). Anal. Calcd for $C_{19}H_{22}O_3NF_3$: H, 6.00; C, 61.8. Found: H, 6.25, C, 61.9.

Compound 14. An ethanolic solution (15 mL, 95%) of 3-trifluoromethyl-3-phenyl-4-(ethyl carbetoxy)-N-benzylpyrrolidine **13** (460 mg, 1.2 mmol), concentrated HCl (2 mL) and 50 mg of Pd/C was stirred under H_2 (normal pressure). After filtration and evaporation, the residu was crystallised (hexane/CH_2Cl_2/ethanol 7:2:1) to give the chlorhydrate **14** (320mg, 82%) as colorless crystals used for X-ray diffraction: mp 214-216 °C; ^1H NMR δ 0.8 (t, J 7Hz, 3 H), 3.8 (m, 5 H), 4.3 (s, 2 H, CH_2N), 7.3 (m, 5 H, Ph), 9.6 (m large, 2 H, NH_2^+). Anal. Calcd for $C_{14}H_{17}O_2NClF_3$: C, 51.9, H, 5.29; N, 4.33. Found: C, 52.0; H, 5.43; N, 4.41.

Cycloaddition with Nitrone. General procedure. A conical flask equiped with a condenser was charged with the alkene, the N-(benzylidene)-methylamine-N-oxide **17** (1.2 equiv.) and 30 mL of dried toluene. The mixture was refluxed under N_2. The reaction was monitored by G.C. The toluene was evapored and the residue purified by chromatography on SiO_2 or by recristallisation.

Reaction with 1-trifluoromethylstyrene 2. 1-Trifluoromethylstyrene **2** (1g, 5.8 mmol) and N-(benzylidene)-methylamine-N-oxide **17** (950 mg, 7 mmol) were refluxed in toluene for 48 h. After column chromatography (pentane/CH_2Cl_2/ether 75:25:5) a non-separable mixture (1:1 ratio) of diastereoisomers **17** was obtained (1.1g, 60%): ^{19}F NMR δ -78.2 and -78.9 (ratio 1:1), ^1H NMR δ 2.65 and 2.80 (s, 3 H, CH_3N), 2.7-3.3 (m, 2 H, H-4), 3.4-3.8 (m, 1 H, H-3), 7.2-7.4 (m, 10 H, Ph); ^{13}C NMR δ 43.1 and 43.5 (C-4); 48.3 and 49.3 (CH_3N), 72.6 and 74.0 (C-3), 82.6 (q, ^2J = 30 Hz, C-5), 126.6 (q, ^1J = 270 Hz, CF_3), 127.0-129.1, 136.9, 138.1, 139.0. MS (EI) 307 (M^+, 100), 136 (12), 135 (40), 134 (90), 106 (7) and 307 (M^+, 100), 136 (10), 135 (35), 134 (95), 118 (10), 106 (6). Anal. Calcd for $C_{17}H_{16}ONF_3$: C, 67.1; H, 4.30; N, 4.60. Found: C, 67.4; H, 4.54; N, 4.65.

Reaction with ethyl (*E*)-1,1,1-trifluoro-2-phenylbutenoate (10). Compound **10** (1g, 4.1 mmol) and N-(benzylidene)-methylamine-N-oxide **17** (660 mg, 4.9 mmol) were refluxed for 24h in toluene. The usual work-up and chromatography (pentane/ethyl acetate, 95:5) gave the isoxazolidine **19** as a single isomer (1.1g, 70%): ^{19}F NMR δ -75.4; ^{1}H NMR δ 0.95 (t, *J* = 7 Hz, 3 H), 2.8 (s, 3 H, NCH_3), 3.65 (q, ^{2}J = 7 Hz, 2 H, OCH_2), 4.0 (d, *J* = 10.5 Hz, 1 H, H-4), 4.2 (d, *J* = 10.5 Hz, 1 H, H-3), 7.4-7.6 (m, 10 H, Ph); ^{13}C NMR δ 13.3 (CH_3), 42.8 (C-4), 61.0 (OCH_2), 75.1 (C-3), 83.9 (q, ^{2}J = 31 Hz, C-5), 124.5 (q, ^{1}J = 275 Hz, CF_3), 126.4, 127.9, 128.2, 128.4 128.6, 128.8, 133.5, 135.1 (Ph), 167.3 (CO_2Et); MS (EI) 245 (56), 244 (100), 243 (23), 216 (10), 215 (24), 200 (21), 199 (59), 172 (10), 152 (26), 151 (62), 103 (15), 102 (30), 75 (11), 69 (7). Anal. Calcd for $C_{20}H_{21}O_3NF_3$: C, 63.3; H, 5.31; N, 3.69. Found: C, 63.2; H, 5.20; N, 3.85.

Reaction with ethyl trifluoroacetoacetate (20). Compound **20** (3.0 g, 16.2 mmol) and N-(benzylidene)-methylamine-N-oxide (**17**) (2.6 g, 19.4 mmol) were refluxed for 24 h in toluene. After evaporation of toluene, the crude product was filtered on SiO_2 column and isoxazolidine **22** was obtained by crystalisation from cyclohexane (3.36 g, 65 %): mp 94-96 °C (cyclohexane), ^{19}F NMR δ -84.1; ^{1}H NMR δ 1.15 (t, *J* = 7 Hz, 3 H, CH_3), 2.7 (s, 3 H, CH_3-N), 3.75 (d, $J_{H\text{-}3,H\text{-}4}$ = 11 Hz, H-4), 4.15 (d, d, *J* 11 Hz, H-3), 4.25 (m, 2 H, CH_2-O), 5.6 (br s, 1 H, OH), 7.4 (m, 5 H, C_6H_5); ^{13}C NMR δ 13.7, 43.9 (CH_3-N), 58.7 (C-4), 62.1 (CH_2-O),75.1 (C-3), 98.1 (q, ^{2}J = 33 Hz, C-5), 120.1 (q, ^{1}J = 274 Hz, CF_3), 127.8, 128.9, 129.1, 134.5, 168.9; MS (EI) 136 (20), 135 (100), 118 (12), 108 (10), 107 (20), 91 (16), 66 (24), 51 (15). Anal. Calcd. for $C_{14}H_{16}O_4NF_3$: C, 52.7; H, 5.05; N, 4.39. Found: C, 52.9; H, 4.85; N, 4.26.

Reaction with ethyl (*Z*)-1,1,1-trifluoro-2-propyloxyoxobutenoate (21). Compound **21** (500 mg, 2.2 mmol) and N-(benzylidene)-methylamine-N-oxide (**17**) (350 mg, 2.6 mmol) were refluxed for 24 h in toluene. The crude product was a mixture (8:2 ratio) of the two diastereoisomers **23a** and **23b**. Chromatography (pentane/ethyl acetate : 95:5) afforded isoxazolidines **23a** (390 mg, 50%) and **23b** (130 mg, 15%).

23a. ^{19}F NMR δ -78.9; ^{1}H NMR δ 1.1 (t, *J* = 7 Hz, 3 H,CH_3), 1.3 (t, 3 H, *J* =7 Hz, CH_3), 1.7 (q, 2 H, *J* = 7 Hz, CH_2), 2.8 (s, 3 H, CH_3N), 3.65 (d, *J* = 10.8 Hz, 1 H, H-4),3.7-4.2 (m, 4 H, two OCH_2), 4.3 (d, *J* 10.8 Hz, 1 H, H-3), 7.5 (m, 5 H, Ph);^{13}C NMR d 10.4, 13.8 (CH_3), 23.1 (CH_2), 44.2 (CH_3N), 61.2, 61.7 (OCH_2), 65.9 (C-4), 73.7 (C-3), 100.7 (q, ^{2}J 33 Hz, C-5), 123.1 (q, ^{1}J = 274 Hz, CF_3), 128.1, 128.7, 128.8, 135.6, 165.9 (CO_2Et); MS (EI) 361 (M^+,40), 292 (28), 204 (10), 160 (20), 135 (20), 134 (60), 118 (100), 104 (10). Anal. Calcd for $C_{16}H_{22}O_3NF_3$: C, 56.5; H, 6.14; N, 3.88. Found: C 56.6, H, 6.30; N, 3.75.

23b. ^{19}F NMR δ -81.1; ^{1}H NMR δ 0.9 (t, *J* = 7 Hz, 3 H, CH_3), 1.0 (t, *J* = 7 Hz, 3 H, CH_3), 1.55 (m, 2 H, CH_2), 2.75 (s, 3 H, NCH_3), 3.7 (t, *J* = 7 Hz, 2 H, OCH_2), 3.8 (q, *J* = 7 Hz, 2 H, OCH_2), 3.85 (d, *J* = 7.5 Hz, 1 H, H-4), 3.95 (d, *J* = 7.5 Hz, H-3), 7.3 (m, 5 H, Ph), ^{13}C NMR d 10.1 (CH_3), 13.4 (CH_3), 22.8 (CH_2), 43.7 (C-4), 60.3, 60.6, 66.1, 74.6 (C-3), 101.5 (q, ^{2}J = 30 Hz, C-5); 123.5 (q, ^{1}J = 272 Hz, CF_3), 127.2, 128.4, 129.5, 133.9, 167.5 (COOEt); MS (EI) 361 (M^+, 100), 302(6), 253 (2), 136(20), 135 (40), 134 (45), 120 (14). Anal. Calcd for $C_{16}H_{22}O_3NF_3$: C, 56.5; H, 6.14; N, 3.88. Found: C, 56.7; H, 6.35; N, 3.65.

References and note

This paper constitues a part of the Ph Dissertation of Dr T. Lequeux (Paris-XI, Orsay, 12-15-1993.

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(*Received* 15 *June* 1995)