(Trifluoroisopropenyl)tributyltin as a Novel α-(Trifluoromethyl)ethenyl Carbanion Synthetic Equivalent. Preparation and Its Palladium-Promoted Coupling with Acyl Chlorides

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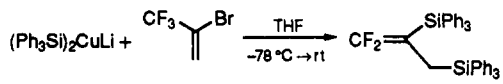
Organofluorine compounds have attracted much attention in various fields, such as those of medicine,[1] agrochemicals,[2] and polymers,[3] for their unique physiological and physical properties. Compounds bearing a CF_3 group have been of special interest and efforts have been made to develop effective routes to these fluorinated compounds.[4] Trifluoromethylation,[5] fluorination,[6] and halogen-exchange reactions[7] are possible methods for introducing the trifluoromethyl group into a molecule. However, such methods suffer from low reactivity and low selectivity. An attractive alternative approach is to prepare intermediates carrying a CF_3 group which would serve as precursors for further elaboration.[8] The latter method is now becoming an important strategy for the construction of trifluoromethylated molecules. In particular it allows the synthesis of fluorinated aliphatic compounds under conditions mild enough to prevent reactions of even reactive functional groups. The development of a simple method for the preparation of trifluoromethylated building blocks and their utilization for the synthesis of desired CF_3-containing compounds represent a worthwhile undertaking.

Many efforts have been made to exploit the utilization of 2-bromotrifluoroisopropene (2-BrTFP) in the construction of fluorinated compounds.[9] One such effort has been to prepare (trifluoroisopropenyl)metal reagents such as (trifluoroisopropenyl)magnesium and -lithium reagents,[6a,10] but their use has been severely limited by their extremely facile defluorination. A recent success in the preparation of stable (trifluoroisopropenyl)metal reagents is that of the (trifluoroisopropenyl)zinc reagent.[11] Although this stable zinc reagent showed excellent reactivity toward aryl and vinyl halides in the presence of a palladium catalyst, it failed to react with such electrophiles as acyl chlorides. Thus, the synthesis of other new (trifluoroisopropenyl)-metal reagents and exploitation of their utility are still much desirable. In the course of our studies on the reaction of 2-BrTFP with nucleophiles, we found a novel (trifluoroisopropenyl)metal reagent, (trifluoroisopropenyl)tributyltin, could be conveniently prepared by stannylcupration of 2-BrTFP and this tin reagent could be used as an effective precursor of α-(trifluoromethyl)vinyl ketones. Herein, we report the results of our work in detail.

The reaction of 2-bromotrifluoropropene with nucleophiles has been little exploited. Ignatova has reported that, owing to its electron deficiency, nucleophilic additions of amines to 2-BrTFP occur readily with the formation of adducts from attack of amines at C-1 of 2-BrTFP.[12] We envisaged that a wide variety of species might serve as nucleophiles in this reaction. In view of the versatility of tin compounds in synthetic organic chemistry,[13] we became especially interested in the stannylcupration of 2-BrTFP. Indeed, we found stannylcupration of 2-BrTFP occurred when it was added to a solution of (tributylstannyl)cuprate in THF. In contrast to the nucleophilic additions of amines to 2-BrTFP, stannylcupration of 2-BrTFP afforded (trifluoroisopropenyl)tributyltin (1) along with [3,3-difluoro-2-(tributylstannyl)prop-2-enyl]tributyltin (2).[14] The ratio of 1 to 2 was dependent on the kind of the copper(I) salt used; use of copper(I) iodide resulted in the predominent formation of 1 while use of copper(I) cyanide led to a 3:2 mixture of 1 and 2 (Scheme 1).

1 probably derives from a nucleophilic attack of (tributylstannyl)cuprate on C-2 of 2-BrTFP (Scheme 2, path a). The fact that 1 could not react further with (tributylstannyl)cuprate implied that 2 was a product of a nucleophilic attack of (tributylstannyl)cuprate on C-1 of

(1) Filler, R.; Kobayashi, Y. In *Biomedicinal Aspects of Fluorine* Chemistry; Elsevier Biomedical Press: Amsterdam, 1982.
(2) Yoshioka, H.; Takayama, C.; Matsuo, N. J. *Synth. Org. Chem. Jpn.* **1984**, *42*, 809.
(3) (a) Fielding, H. C. In *Organofluorine Chemicals and Their Industrial Applications*; Banks, R. E., Ed., Ellis Horwood: Chichester, 1979; p 214. (b) Smith, S. In *Preparation, Properties, and Industrial Applications of Organofluorine Compounds*; Banks, R. E., Ed.; Ellis Horwood: Chichester, 1982; p 235.
(4) (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Fuchigami, T. J. *Synth. Org. Chem. Jpn.* **1984**, *42*, 775.
(5) (a) Wiemers, D. W.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832 and references cited therein. (b) Umemoto, J.; Ando, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 447. (c) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186 and references cited therein.
(6) (a) Boswell, G. A., Jr.; Ripka, T. C.; Schribner, R. M.; Tillock, C. W. *Org. React.* **1974**, *21*, 1. (b) Umemoto, T.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 3272. (c) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.
(7) Purrington, S. T.; Evertt, T. S.; Bungardner, C. L. *Tetrahedron Lett.* **1984**, *25*, 1329.
(8) (a) Drakesmith, F. G.; Steward, O. J.; Tarrant, P. *J. Org. Chem.* **1967**, *33*, 280. (b) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *25*, 3987 and 3991. (c) Yamazaki, T.; Ishikawa, N. *Chem. Lett.* **1984**, 521. (d) Yokozawa, T.; Ishikawa, N.; Nakai, T. *Chem. Lett.* **1987**, 1971. (e) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276. (f) Morikawa, T.; Nishiwaki, T.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 2407. (g) Ojima, I.; Kato, K.; Nakahashi, K. *J. Org. Chem.* **1989**, *54*, 4511. (h) Prakash, G. K. S.; Krishnamarti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393. (i) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1340. (j) Hanzawa, Y.; Kawagoe, K.; Yamada, A.; Kobayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 219. (k) Uneyama, K.; Momota, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3378. (l) Shi, G.; Xu, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 607.
(9) (a) Ojima, I. *Chem. Rev.* **1988**, *88*, 1011. (b) Mcbee, E. T.; Hsu, C. G.; Pierce, O. R.; Roberts, C. W. *J. Am. Chem. Soc.* **1955**, *77*, 915. (c) Gacde, B.; Balthazor, T. B. *J. Org. Chem.* **1983**, *48*, 276. (d) Ojima, i.; Yatabe, M.; Fuchigami, T. *J. Org. Chem.* **1982**, *47*, 2051. (e) Kumadaki, I. J. *Synth. Org. Chem. Jpn.* **1984**, *42*, 786.
(10) Fuchigami, T.; Yamanouchi, A.; Ojima, I. *Synthesis* **1984**, 766.
(11) (a) Jiang, B.; Xu, Y. *J. Org. Chem.* **1991**, *56*, 7336. (b) Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 511.
(12) Ignatova, Yu. L.; Karimova, O. V.; Kil'disheva, O. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 480.
(13) Pereyre, M.; Quintard, Jean-Paul; Rahm, A. In *Tin in Organic Chemistry*; Butterworth: London, 1987.
(14) The structure of compound 2 was determined by correlation of its ^1H NMR and ^{19}F NMR with those of compound 5, which was obtained by reaction of $(Ph_3Si)_2CuLi$ with 2-BrTFP in 76% yield (eq 2).



(equ 2)

5

[3,3-Difluoro-2-(triphenylsilyl)prop-2-enyl]triphenylsilane (5): white solid; mp 155–157 °C; ^1H NMR ($CDCl_3$) δ 2.4 (s, 2H), 7.24–7.50 (m, 30H); ^{19}F NMR(CCl_4) δ −7.0 (d, J = 50 Hz, 1F), +14.0 (d, J = 50 Hz, 1F); IR (KCl) 3030, 1730, 1610, 1590, 1010, 700, 690 cm^{-1}; MS m/z (relative intensity) 516 (0.38), 335 (0.15), 260 (100). Anal. Calcd for $C_{39}H_{32}F_2Si_2$: C, 78.74; H, 5.42; F, 6.39. Found: C, 78.94; H, 5.21; F, 6.51.

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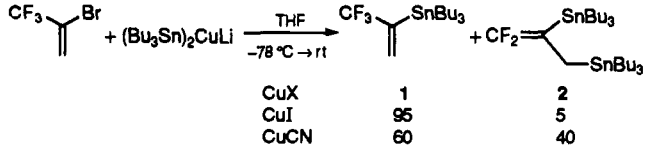
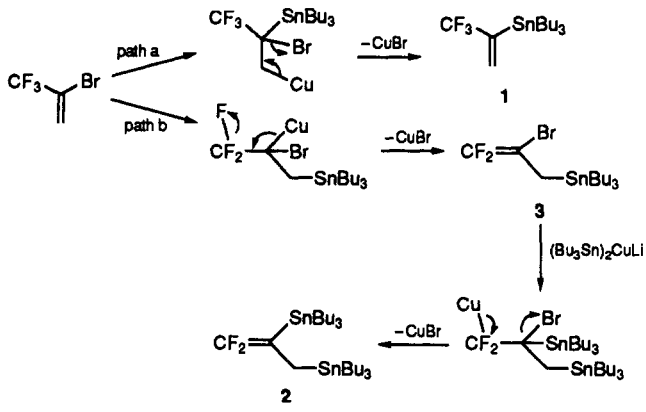
Scheme 1. Molar ratio of 1 to 2 determined by ^{19}F NMR



CuX	1	2
CuI	95	5
CuCN	60	40

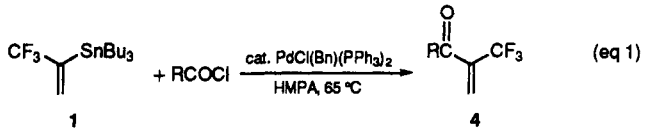
Scheme 2



2-BrTFP followed by a further reaction of the intermediate **3** thus formed with (tributylstannyl)cuprate (Scheme 2, path b).

Thus, **1** was prepared in 90% yield from 2-BrTFP and lithium tributylstannate in the presence of CuI. With this tin reagent in hand, we undertook a study of of its reactivity with acid chlorides.

In modern organic synthesis, the cross-coupling of organotin reagents with various electrophiles in the presence of a catalytic amount of palladium has been shown to be an efficient method for the formation of a carbon–carbon bond.[15] The cross-coupling of (perfluorovinyl)tin reagent with aryl iodides has been reported.[16] This stimulated an interest in the feasibility of using this vinyltin reagent for cross-coupling with electrophiles in the presence of transition metals. Gratifyingly, it was found that **1** undergoes the coupling reaction with various acyl halides promoted by palladium with normal reactivity to afford α-(trifluoromethyl)vinyl ketones in good yields (eq 1). The results are summarized in Table 1.



As the results show, reactions with aroyl and alkenoyl chlorides proceeded smoothly in the presence of 1 mol % of $PdCl(Bn)(PPh_3)_2$ at 65 °C in HMPA, and the corresponding coupling products were obtained in high yields. In the case of 4-bromobenzoyl chloride, the bromine substituent in the benzene ring remained intact and *p*-bromophenyl (α-trifluoromethyl)ethenyl ketone (**4a**) was obtained as the sole product in 89% yield (Table 1, entry 1). The coupling reaction with **1** could be extended to alkanoyl chlorides, but in these cases a prolonged reaction time was required to obtain satisfactory yields (Table 1, entries 7–9). It should be noted that in all the cases studied no decarbonylation–coupling product was detected.[15]

It is noteworthy that the present reaction can be exploited for the introduction of a CF_3-containing side chain to a steroidal compound (Table 1, entry 9) whose further elaboration should provide some interesting CF_3 analogues of biological interest.

From a synthetic viewpoint, α-(trifluoromethyl)vinyl ketones should be useful intermediates because of their potential for further functionalization. However, no efficient method for the synthesis of this kind of compounds has previously been available. Thus, the reaction outlined provides a convenient synthesis for these compounds.

In conclusion, we have synthesized (trifluoroisopropenyl)tributyltin via a novel synthetic route. This tin reagent readily undergoes cross-coupling with various acyl chlorides to afford α-(trifluoromethyl)vinyl ketones, which might be utilized further in a variety of ways in constructing fluorinated compounds.

Experimental Section

^1H NMR spectra were recorded on a Varian JEOL FX-90, Varian XL-200, or Bruker AM-300 spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (0.00) as an external standard; downfield shifts were designated as negative. Infrared spectra were taken on a Shimadzu 440-IR spectrometer, and mass spectra were done on a Finnigan 4021 GC/MS/DC instrument. All reactions as well as column chromatography were monitored routinely with the aid of TLC or ^{19}F NMR spectroscopy.

HMPA and THF were distilled from sodium and $LiAlH_4$, respectively. Lithium tributylstannate[17] and $Pd(Bn)Cl(PPh_3)_2$[18] were prepared as previously described. All the chlorides were prepared generally by reaction of the corresponding acids with $SOCl_2$, ClCOCOCl, or PCl_5.

Preparation of (Trifluoroisopropenyl)tributyltin (1). To a suspension of CuI (1.43 g, 7.5 mmol) in THF (5 mL) cooled at −10 °C was added dropwise a THF solution of Bu_3SnLi(10ml, 15mmol), and the dark mixture was stirred at −10 °C for additional 30 min and then was cooled down to −78 °C. 2-Bromotrifluoropropene (1.32 g, 7.5 mmol) was introduced via syringe at −78 °C, and the resulting solution was stirred at −78 °C for 0.5 h and then at room temperature for 1 h. The solvent was removed and the residue was dissolved in diethyl ether (100 mL). After removal of the solids by filtration, the filtrate was concentrated and distilled at reduced pressure to afford **1** in 90% yield (bp 70 °C/1 mm). The residue was subjected to silica gel chromatography using petroleum ether as the eluent to afford **2** (ca. 3% yield).

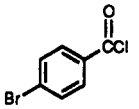
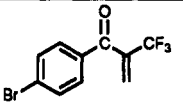
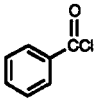
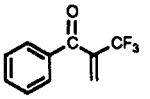
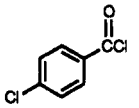
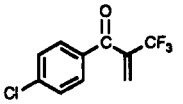
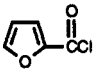
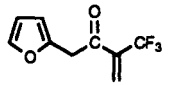
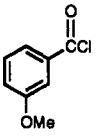
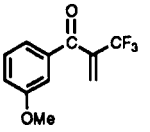
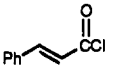
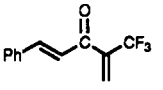
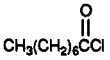
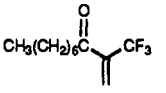
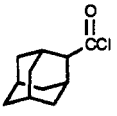
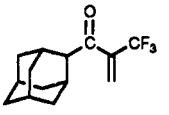
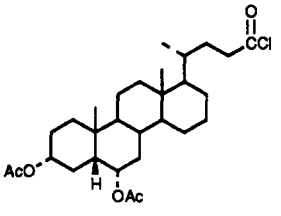
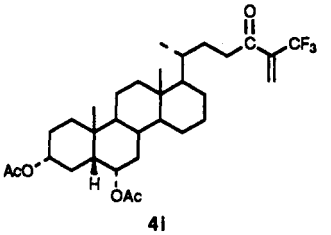
(Trifluoroisopropenyl)tributyltin (1): colorless oil; ^1H NMR($CDCl_3$) δ 0.70–1.70 (m, 27H), 5.84 (s, 1H), 6.36 (s, 1H); ^{19}F NMR (CCl_4) δ −16.0 (s).

[3,3-Difluoro-2-(tributylstannyl)prop-2-enyl]tributyltin (2): colorless oil; ^1H NMR ($CDCl_3$) δ 0.9–1.80 (m, 54H), 2.3 (s, 2H); ^{19}F NMR (CCl_4) δ −1.0 (d, J = 60 Hz, 1F), +5.0 (d, J = 60 Hz, 1F).

General Procedure for the Coupling of 1 with Acyl Chlorides. **1** (385 mg, 1 mmol) and acyl chloride (1.5 mmol) were dissolved in HMPA (3 mL) followed by the introduction of $Pd(Bn)Cl(PPh_3)_2$ (1 mol % based on **1**). The resulting mixture was stirred at 65 °C for 3–24 h. Diethyl ether (30 mL) was added, and the ethereal solution was washed successively with aqueous KF solution, dilute aqueous $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. After concentration, the residue

(15) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
(16) Sorokino, R. S.; Beletskaya, I. P.; Kalinovskoii, I. O.; Ribakova, L. F. The Second Soviet Organometallic Chemistry Conference, Gorky, USSR, 1982, abstracts p 100.
(17) Tamborksi, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237.
(18) Fitton, P.; McKoen, J. E.; Ream, B. C. *J. Chem. Soc., Chem. Commun.* **1969**, 370.

Table 1. Palladium-Promoted Coupling of (Trifluoroisopropenyl)tributyltin (1) with Acyl Chlorides[a]

entry	RCOCl	react time (h)	product (4)[b]	yield (%)[c]
1		5	 **4a**	89
2		3	 **4b**	90
3		4	 **4c**	93
4		10	 **4d**	85
5		13	 **4e**	81
6		4	 **4f**	97
7		24	 **4g**	78
8		22	 **4h**	83
9		24	 **4i**	71

[a] All the reactions were performed in HMPA at 65 °C by using 1 equiv of 1 an 1.5 equiv of the acyl chloride and 1 mol % of $Pd(Bn)Cl(PPh_3)_2$. [b] All the new compounds were fully charaterized by ^{19}F NMR, ^1H NMR, IR, MS, and C, H, F elemental analyses or HRMS. [c] Isolated yields based on 1.

was subjected to silica gel chromatography using a mixture of petroleum ether (60–90 °C) and ethyl acetate or acetone as the eluent.

***p*-Bromophenyl α-(trifluoromethyl)ethenyl ketone (4a):** white solid; mp 85–87 °C; ^1H NMR ($CDCl_3$) δ 6.04 (s, 1H), 6.56 (s, 1H), 7.56 (d, J = 6 Hz, 2H); 7.64 (d, J = 6 Hz, 2H); ^{19}F NMR (CCl_4) δ −12.0 (s); IR (KCl) 1660, 1580, 1350, 1120, 980, 780 cm^{-1}; MS m/z (relative intensity) 278 (M, 8.60), 183 (100), 155 (28.38). Anal. Calcd for $C_{10}H_6BrF_3O$: C, 43.04; H, 2.18; F, 20.42. Found: C, 43.23; H, 2.39; F, 20.56.

Phenyl α-(trifluoromethyl)ethenyl ketone (4b): colorless oil; ^1H NMR($CDCl_3$) δ 6.08 (s, 1H), 6.60 (s, 1H), 7.30–7.85 (m, 5H); ^{19}F NMR (CCl_4) δ −12.2 (s); IR (neat) 1660, 1580, 1340, 1120, 980, 710 cm^{-1}; MS m/z (relative intensity) 200 (M, 32.24), 105 (58.58), 77 (63.34), 51 (100). Anal. Calcd for $C_{10}H_7F_3O$: C, 60.00; H, 3.52; F, 28.48. Found: C, 60.02; H, 3.81; 28.29.

***p*-Chlorophenyl α-(trifluoromethyl)ethenyl ketone (4c):** colorless oil; ^1H NMR ($CDCl_3$) δ 6.08 (s, 1H), 6.58 (s, 1H), 7.46 (d, J = 7 Hz, 2H), 7.75 (d, J = 7 Hz, 2H); ^{19}F NMR (CCl_4) δ −12.0 (s); IR (neat) 1660, 1570, 1340, 1120, 960, 830 cm^{-1}; MS m/z (relative intensity) 234 (M, 29.1), 139 (99), 111 (100), 75 (88.6). Anal. Calcd for $C_{10}H_6ClF_3O$: C, 51.19; H, 2.58; F, 24.30. Found: C, 50.97; H, 2.42; F, 24.16.

2-Furyl α-(trifluoromethyl)ethenyl ketone (4d): colorless oil; ^1H NMR ($CDCl_3$) δ 6.50 (s, 1H), 6.58 (s, 1H), 6.66 (dd, J = 4 and 2 Hz, 1H), 7.30 (d, J = 4 Hz, 1H), 7.69 (d, J = 2 Hz, 1H); ^{19}F NMR (CCl_4) δ −11.9 (s); IR (neat) 1650, 1550, 1450, 1120, 970, 750 cm^{-1}; MS m/z (relative intensity) 190 (M, 26.32), 95 (100), 69 (16.93). Anal. Calcd for $C_8H_5F_3O_2$: C, 50.54; H, 2.65; F, 29.98. Found: C, 50.76; H, 2.54; F, 30.12.

***m*-Methoxyphenyl α-(trifluoromethyl)ethenyl ketone (4e):** colorless oil; ^1H NMR($CDCl_3$) δ 3.88(s, 3H), 6.17(s, 1H),

6.62(s, 1H), 7.10–7.60 (m, 4H); ^{19}F NMR(CCl_4) δ −12.3(s); IR (neat) 1660, 1590, 1340, 1120, 980, 760 cm^{-1}; MS *m/z* (relative intensity) 230 (M, 100), 136 (76.11), 107 (46.71), 92 (65.65), 77 (80). Anal. Calcd for $C_{11}H_8F_3O_2$: C, 57.39; H, 3.94; F, 24.76. Found: C, 57.27; H, 3.83; F, 24.83.

(*E*)-1-Phenyl-4-(trifluormethyl)penta-1,4-dien-3-one (4f): colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.49 (s, 1H), 6.57 (s, 1H), 6.75 (d, J = 16 Hz, 1H), 7.10–7.70 (m, 6H); ^{19}F NMR (CCl_4) δ −12.0 (s); IR (KCl) 1650, 1580, 1340, 1120, 1020, 680 cm^{-1}; MS *m/z* (relative intensity) 226 (m, 62.99), 132 (96.61), 103 (100), 77 (91.22). Anal. Calcd for $C_{12}H_9F_3O$: C, 63.77; H, 4.01; F, 25.20. Found: C, 63.65; H, 4.24; F, 25.11.

***n*-Heptyl-α-(trifluoromethyl)ethenyl ketone (4g)**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6 Hz, 3H), 1.25–1.72 (m, 10H), 2.70 (t, J = 8 Hz, 2H), 6.43 (s, 1H), 6.50 (s, 1H); ^{19}F NMR (CCl_4) δ −12.5 (s); IR(KCl) 2900, 1680, 1440, 1140, 960 cm^{-1}; MS *m/z* (relative intensity) 222 (M, 4.51), 127 (21.1), 95 (100), 58 (89.29). Anal. Calcd for $C_{11}H_{17}F_3O$: C, 59.44; H, 7.71; F, 25.64. Found: C, 59.28; H, 7.56; F, 25.39.

1-Adamantyl α-(trifluoromethyl)ethenyl ketone (4h): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.45–2.15 (m, 15H), 5.79 (s, 1H), 6.12 (s, 1H); ^{19}F NMR (CCl_4) δ −12.8 (s); IR (KCl) 2900, 1680, 1320, 1120, 980 cm^{-1}; MS *m/z* (relative intensity) 163 (3.56), 135 (100). Anal. Calcd for $C_{14}H_{17}F_3O$: C, 65.10; H, 6.34; F, 22.07. Found: C, 65.24; H, 6.29; F, 22.25.

25-Methylene-24-oxo-25-(trifluoromethyl)-5β-cholane-3α,6α-diyl diacetate (4i): white solid; mp 195–197 °C; ^{1}H NMR ($CDCl_3$) δ 0.65 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 2.01 (s, 3H, 3-CH_3CO), 2.04 (s, 3H, 6-CH_3CO), 2.67 (m, 2H, 23-H), 4.70 (m, 1H, 3β-H), 5.16 (m, 1H, 6β-H), 6.43 (s, 1H, vinyl-H), 6.50 (s, 1H, vinyl-H); ^{19}F NMR (CCl_4) δ −12.5 (s); IR (KCl) 2800, 1720, 1660, 1340, 1220, 1120, 1000 cm^{-1}; MS *m/z* (relative intensity) 495 (3.01), 435 (100). Anal. Calcd for $C_{31}H_{45}F_3O_5$: C, 67.12; H, 8.18; F, 10.28. Found: C, 67.41; H, 7.98; F, 10.39.

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