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Facile conversion of 4,4,4-trifluorobut-2-yn-1-ols to 4,4,4-trifluorobut-2-en-1-ones

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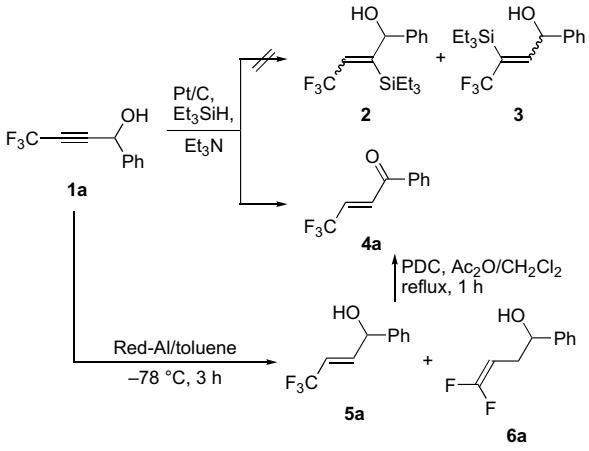
ABSTRACT

Smooth isomerization of 4,4,4-trifluorinated propargylic alcohols **1** opened a new and convenient route to readily get access to the corresponding α,β-unsaturated ketones **4** just by heating a THF solution in the presence of Et_3N.

1. Introduction

Fluorinated materials have been drawing considerable attention of organic chemists due to their unique characteristics and wide application to a variety of fields.[1] Development of building units with fluorine-containing groups as well as appropriate functionalities is considered to be one of the most efficient ways for ready construction of such useful materials. In this article, we would like to report our recent results on the interesting conversion of trifluorinated propargylic alcohols **1** into the corresponding α,β-unsaturated carbonyl compounds **4** just by treatment with mild tertiary amines like triethylamine.

The present isomerization of **1a** to **4a** was encountered by chance when the following platinum-catalyzed hydrosilylation of alkynes was applied[2] to our terminally trifluoromethylated propargylic alcohols[3] (Scheme 1). Exploration of suitable reaction conditions eventually clarified that neither Pt/C nor Et_3SiH was required for the formation of the α,β-unsaturated ketone **4a** and it was Et_3N, which actually affected this transformation.[4] We have previously disclosed the synthetic pathway to get access to such ketones **4** by successive Red-Al reduction and PDC oxidation.[5] However, the first step, conversion of the propargylic alcohol **1a** to the corresponding allylic counterpart **5a**, was sometimes suffered from overreduction to the difluorinated homoallylic alcohol **6a** (possibly as the result of S_N2' type attack of hydride to the resultant **5a**)[6] whose separation from the desired **5a** was quite troublesome task. Considering such difficulty, the present process would offer the significantly convenient direct alternative route to **4** from **1** if we could find out appropriate conditions for this conversion, which prompted us to start this study.



Scheme 1.

2. Results and discussions

First of all, 4,4,4-trifluoro-1-phenylbut-2-yn-1-ol **1a** was selected as the representative substrate for finding out the appropriate conditions (Table 1). As shown in entry 1, 40 equiv of Et_3N both as a solvent and as a base allowed the complete isomerization of **1a** to furnish **4a** in 92% yield after 4 h reflux. Reduction of the amount of Et_3N to 4 equiv affected the reaction only slightly, and DBU seemed inappropriate due to spontaneous dark colorization of the solution at the addition as well as detection of a number of byproduct peaks from the crude mixture by ^{19}F NMR (entries 2 and 3). On the other hand, less basic pyridine did not promote the reaction at all (entry 4). Different types of solvents were also used in the presence of 4 equiv of Et_3N, and THF was found to be the best among the solvents tested (entries 5–8), and 4 equiv of Et_3N was appropriate (entries 8 and 10). Slow interconversion from **(*Z*)-4a** to **(*E*)-4a** was observed whose energetic preference supposed to lead

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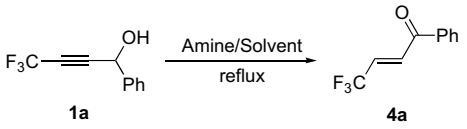
to the exclusive production of the latter (entries 8 and 9). On the basis of these data, treatment of a THF solution of **1** in the presence of 4 equiv of Et_3N at reflux for 8 h has been eventually decided as the best reaction condition which allowed us to isolate **(*E*)-4a** in 94% yield as the sole product.

Table 1
Investigation of the reaction conditions[a]



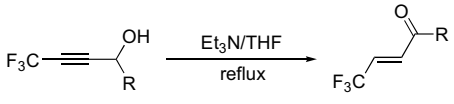
1a **4a**

Entry	Solvent	Amine[b]	Time (h)	Yield of **4a**[c] (%)	*E*[c,d] (%)
1	—	Et_3N (40)	4	92	79
2	—	Et_3N (4)	4	77	68
3	—	DBU (4)	4	44	72
4	—	Pyridine (4)	4	0	—
5	CH_2Cl_2	Et_3N (4)	4	88	79
6	Toluene	Et_3N (4)	2	73	91
7	Hexane	Et_3N (4)	2	38 [24][e]	57
8	THF	Et_3N (4)	4	87 (85)[f]	78
9	THF	Et_3N (4)	8	(94)[f]	>99
10	THF	Et_3N (1)	4	72	75
11	THF	—	2	0 [89][e]	—

[a] All reactions were carried out with 1 mmol of the substrate in 5 mL of a solvent at reflux temperature.
[b] In the parenthesis was shown the equivalent of an amine used.
[c] Determined by ^{19}F NMR unless otherwise noted.
[d] Percentage of **(*E*)-4a**.
[e] Recovery of the starting material.
[f] Isolated yield.

Since we have successfully determined suitable reaction conditions for this facile Et_3N-mediated transformation from propargylic alcohols **1** to α,β-unsaturated ketones **4**, our interest was turned to prove scope and limitation of this intriguing process. The results were summarized in Table 2. All substrates **1** were found to work well except for **1h** with a 2-phenylethyl substituent at the propargylic position, which was intact under these conditions (entry 10).[7] Detailed analysis of this data also furnished the information that an electron-withdrawing moiety on the benzene ring efficiently accelerated the conversion (entries 5 and 6) but retardation was noticed for substrates with an electron-releasing group (entries 3 and 4). These results allowed us to depict the possible mechanism for the present transformation as shown in Scheme 2.

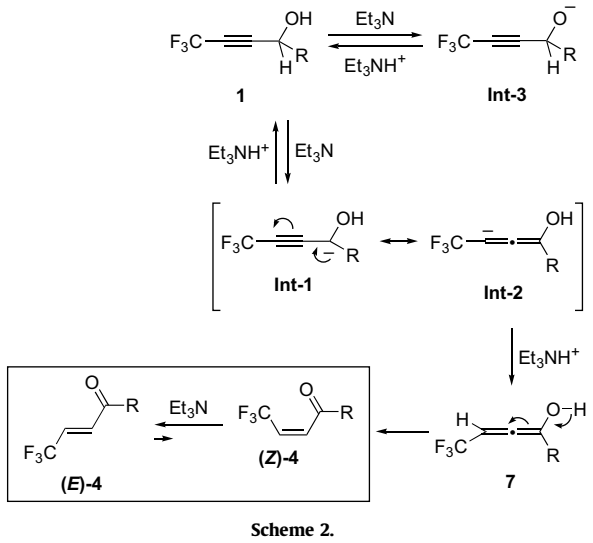
Table 2
Isomerization of various propargylic alcohols **1**[a]



1 **4**

Entry	R	Time (h)	Yield[b] (%)		*E*[c] (%)
1	Ph–	4	85	(**a**)	78
2	Ph–	8	94	(**a**)	>99
3	4-MeO–C_6H_4–	1	34[c]	(**b**)	70
4	4-MeO–C_6H_4–	12	95	(**b**)	>99
5	4-Br–C_6H_4–	0.5	>99	(**c**)	77
6	4-O_2N–C_6H_4–	0[d]	95	(**d**)	74
7	(*E*)-PhCH=CH–	9	80	(**e**)	>99
8	1-Naphthyl–	9	90	(**f**)	>99
9	2-Furyl–	8	93	(**g**)	94
10	$PhCH_2CH_2$–	8	0	(**h**)	—

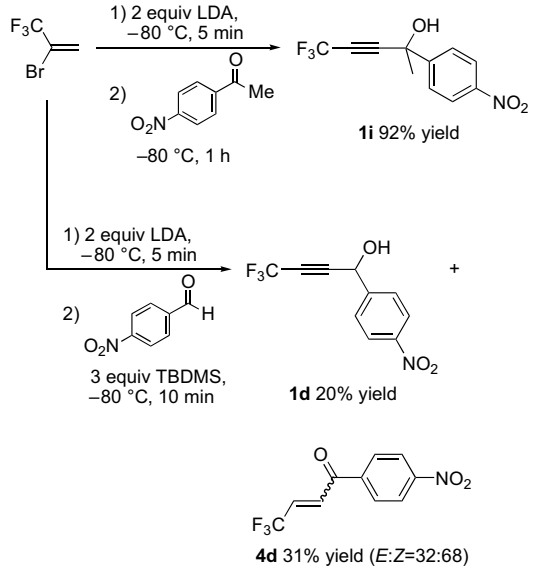
[a] All reactions were carried out with 1 mmol of the substrate and 4 mmol of Et_3N in 5 mL of THF at reflux temperature.
[b] Isolated yield unless otherwise noted.
[c] Percentage of ***E*-4** and yield determined by ^{19}F NMR.
[d] Spontaneous reaction at rt was occurred.



Scheme 2.

Thus, deprotonation from **1** would furnish two equilibrating anionic species **Int-1** and **Int-3**, and the former intermediate possesses the allenyl anion resonance structure, **Int-2**. Reprotonation of **Int-2** would lead to the allenol **7**,[8] which was then converted to a mixture of β-trifluoromethylated α,β-unsaturated ketones **(*E*)-** and **(*Z*)-4**, usually the latter preferred as the kinetically controlled products due to favorable π^*_{CF3}–$\pi_{C=O}$ orbital interaction.[9] Eventually, slow isomerization (see entries 1 vs 2 and 3 vs 4 in Table 2) was occurred so as to afford the sterically less crowded and thus, thermodynamically preferable **(*E*)-4** by way of reversible 1,4-addition of Et_3N, resulting in isolation of this stereoisomer as the exclusive or the sole products. The key of this process would be 1) sufficient contribution to acidity of **1** by an aromatic substituent, and 2) irreversibility of **7** to **1** due to much lower acidity of the former proton attached to the sp^2 carbon atom of the allenyl framework than the one in the latter at the propargylic position. Under these conditions, no defluorination was noticed possibly because of the presence of protons like Et_3NH^+ as well as O*H* in **1** possessing enough acidity to quickly quench the resultant vinylic anion, **Int-2**.

Preparation of propargylic alcohols **1** as the substrates for the present reaction was usually initiated by the action of 2 equiv of LDA to 2-bromo-3,3,3-trifluoropropene, followed by trapping of the resultant CF_3-containing lithium acetylide by appropriate carbonyl compounds.[10] Although this method usually attained excellent chemical yields for a variety of electrophiles,[3b] it is empirically understood that aromatic aldehydes with an electron-withdrawing moiety were not the substrate of choice: thus, although *p*-Br–C_6H_4–CHO afforded the corresponding propargylic alcohol **1c** in 85% yield,[11] a much stronger NO_2 moiety at the same position only led to a complex mixture. Considering that effective activation of the carbonyl compounds was expected by this substituent, this problem would stem from the instability of the product **1d** and we have assumed that the strong activation by the *p*-NO_2 group would render the propargylic proton labile enough to be quickly abstracted by the intermediary alkoxide (for example, **Int-3** in Scheme 2). The isomerized α,β-unsaturated ketones **(*E*)-** and **(*Z*)-4d** thus obtained would be sufficiently reactive toward co-existing nucleophiles by a strongly electron-withdrawing CF_3 group to result in formation of a complex mixture. The experimental result that *p*-O_2N–C_6H_4–C(O)CH_3 cleanly afforded the desired product **1i** without the propargylic proton in 92% yield (Scheme 3) apparently supported this idea and anticipated us that in situ capture of the resultant lithium alkoxide would remove or, at least, reduce a chance for isomerization to **4d**, rendering **1d** more easily accessible. Then, brief investigation of appropriate reaction conditions



Scheme 3.

clarified that introduction of a mixture of *p*-O_2N–C_6H_4–CHO and TBDMSCl was effective for suppression of formation of a variety of byproducts. Actually, although improvement are still required, this modification enabled the cleaner reaction to form basically **1d** and **4d** with the former obtained in 20% yield along with 31% of the latter in an *E*:*Z* ratio of 32:68.[12]

In summary, we have successfully demonstrated the present isomerization from propargylic alcohols **1** to the corresponding α,β-unsaturated ketones **4**, which proceeded simply by refluxing the THF solution in the presence of Et_3N. Success of this process is highly dependent on the acidity of the propargylic proton in **1** and because an electron-withdrawing aromatic substituent effectively activate this proton, isomerization was occurred more smoothly. Although this method was applicable only to materials with an aromatic substituent at the propargylic position, advantage of this process is quite apparent when the tedious previous two-step route as shown in Scheme 1 was considered.

3. Experimental section

3.1. General methods

Most of reactions where an organic solvent was employed were performed under argon with magnetic stirring using flame-dried glassware. Anhydrous THF, Et_2O, and CH_2Cl_2 were purchased and used without further purification. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography (TLC) was routinely used for monitoring reactions by generally using a mixture of *n*-hexane and ethyl acetate (v/v). Spherical neutral silica gel (63–210 μm or 40–50 μm) was employed for column chromatography and flush chromatography, respectively. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded (^1H: 300 MHz; ^{13}C: 75 MHz; ^{19}F: 283 MHz) at room temperature whose data were reported as follows: chemical shift (δ scale) in parts per million (ppm) downfield from Me_4Si (δ 0.00 for ^1H and ^{13}C NMR) or C_6F_6 (δ −162.2) used as internal standards, number of protons or fluorines, multiplicity (singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; broad peak, br; etc.), and coupling constant (*J* in Hz). Infrared (IR) spectra were reported in wave number (cm^{-1}).

Substrates **1a**,[3b] **1b**–**1c**,[11] **1e**,[3b] **1f**,[11] and **1h**[3b] were prepared as described in the literature.

3.1.1. 4,4,4-Trifluoro-1-(4-nitrophenyl)but-2-yn-1-ol (*1d*)

To a solution of LDA (2.6 mmol) in THF (5 mL) was added dropwise 2-bromo-3,3,3-trifluoropropene (0.13 mL, 1.3 mmol) at −80 °C and after stirring for 5 min at that temperature, a THF solution (2 mL) of *tert*-butyldimethylsilyl chloride (0.588 g, 3.90 mmol) and 4-nitrobenzaldehyde (0.151 g, 1.00 mmol) was introduced to a reaction mixture. The whole solution was stirred for 10 min at −80 °C, and the solution was extracted with AcOEt three times after quenched with satd NH_4Cl aq. The organic layer was dried over $MgSO_4$ and concentrated. ^{19}F NMR for this crude mixture indicated production of **1d** (24%) and **4d** as the *E*,*Z* mixture (10 and 21%, respectively). The residue was chromatographed on silica gel to afford 0.049 g (0.200 mmol) of propargylic alcohol, **1d**. Yield 20%, R_f=0.37 (CH_2Cl_2) or 0.16 (Hexane:CH_2Cl_2=1:1). Mp 92 °C. ^1H NMR δ 2.67 (1H, d, *J*=5.7 Hz), 5.71 (1H, br s), 7.69–7.74 (2H, m), 8.26–8.33 (2H, m). ^{13}C NMR δ 62.8, 74.0 (q, *J*=53.3 Hz), 85.1 (q, *J*=6.9 Hz), 113.8 (q, *J*=258.0 Hz), 124.1, 127.3, 144.6, 148.1. ^{19}F NMR δ −52.07 (s). IR (KBr) ν 862, 993, 1062, 1132, 1289, 1348, 1516, 1601, 2279, 2879, 3080, 3118, 3452 cm^{-1}. Anal. Calcd for $C_{10}H_6F_3NO_3$: C, 48.99; H, 2.47; N, 5.71. Found C, 48.99; H, 2.75; N, 5.61.

3.1.2. 4,4,4-Trifluoro-1-(2-furanyl)but-2-yn-1-ol (*1g*)

To a solution of LDA (2.6 mmol) in THF (5 mL) was added dropwise 2-bromo-3,3,3-trifluoropropene (0.13 mL, 1.30 mmol) at −80 °C. After stirring for 5 min at that temperature, a THF solution (1 mL) of furfural (0.096 g, 1.00 mmol) was added and stirring was continued for 2 h at −80 °C. Usual work-up and isolation by chromatography afforded 0.141 g (0.742 mmol) of propargylic alcohol, **1g**. Yield 74%, bp 70 °C (0.4 kPa). ^1H NMR δ 2.49 (1H, d, *J*=7.2 Hz), 5.58 (1H, br s), 6.40 (1H, dd, *J*=1.8, 3.3 Hz), 6.49 (1H, d, *J*=3.6 Hz), 7.46 (1H, d, *J*=1.8 Hz). ^{13}C NMR δ 57.3, 72.2 (q, *J*=53.3 Hz), 84.3 (q, *J*=6.2 Hz), 108.8, 110.6, 113.9 (q, *J*=257.4 Hz), 143.6, 150.2. ^{19}F NMR δ −51.61 (s). IR (neat) ν 730, 910, 970, 1000, 1120, 1250, 1490, 2200, 3250 cm^{-1}. Anal. Calcd for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found C, 50.64; H, 2.89.

3.1.3. 4,4,4-Trifluoro-1-methyl-1-(4-nitrophenyl)but-2-yn-1-ol (*1i*)

Yield 92%, R_f=0.38 (*n*-hexane:AcOEt=4:1). ^1H NMR δ 1.87 (3H, s), 3.37 (1H, br s), 7.74–7.83 (2H, m), 8.24–8.28 (2H, m). ^{13}C NMR δ 32.4, 69.2, 72.6 (q, *J*=53.3 Hz), 85.5 (q, *J*=6.2 Hz), 113.9 (q, *J*=258.0 Hz), 123.8, 125.8, 147.6, 150.0. ^{19}F NMR δ −51.95 (s). IR (neat) ν 856, 1100, 1147, 1277, 1350, 1525, 1604, 2274, 2993, 3423 cm^{-1}. Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found C, 50.40; H, 3.20; N, 5.35.

3.1.4. (E)-4,4,4-Trifluoro-1-phenylbut-2-en-1-one[3b] (*4a*)

To a THF (5 mL) solution of 4,4,4-trifluoro-1-phenylbut-2-yn-1-ol **(1a)** (0.200 g, 1.00 mmol) was added triethylamine (0.56 mL, 4 mmol) and the mixture was heated at the reflux temperature under argon atmosphere for 8 h. Addition of 5 mL of 1 *M* HCl aq and extraction with ethyl acetate three times furnished an organic layer, which was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resultant crude material was purified by column chromatography on silica gel. Yield 94%, R_f=0.73 (Hexane:AcOEt=4:1). ^1H NMR δ 6.83 (1H, qd, *J*=8.7, 15.6 Hz), 7.26–7.57 (3H, m), 7.22 (1H, qd, *J*=2.0, 15.5 Hz), 7.96–7.99 (2H, m). ^{19}F NMR δ −66.36 (d, *J*=6.8 Hz).

3.1.5. (E)-4,4,4-Trifluoro-1-(4-methoxyphenyl)but-2-en-1-one (*4b*)

Recrystallized from petroleum ether. Yield 95%, R_f=0.49 (Hexane:AcOEt=4:1). Mp 36 °C. ^1H NMR δ 3.90 (s, 3H), 6.80 (1H, qd, *J*=6.8, 15.6 Hz), 6.99 (2H, d, *J*=8.4 Hz), 7.54 (1H, qd, *J*=1.8, 16.5 Hz), 7.98 (2H, d, *J*=8.7 Hz). ^{13}C NMR δ 55.4, 114.1, 122.7 (q, *J*=269.8 Hz), 129.0, 129.3 (q, *J*=34.7 Hz), 131.0 (q, *J*=5.6 Hz), 131.2, 164.4, 185.9. ^{19}F NMR δ −66.26 (d, *J*=4.5 Hz). IR (KBr) ν 650, 830, 970, 1030, 1130, 1180, 1260, 1310, 1420, 1450, 1520, 1590, 1640, 1670, 2950 cm^{-1}. Anal. Calcd for $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94. Found C, 57.41; H, 3.94.

*3.1.6. 1-(4-Bromophenyl)-4,4,4-trifluorobut-2-en-1-one (**4c**)*

Yield quant, IR (KBr) ν 651, 729, 907, 1008, 1142, 1274, 1297, 1306, 1390, 1472, 1587, 1687, 2253 cm^{-1}. Anal. Calcd for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found C, 50.64; H, 2.89.

3.1.6.1. (E)-Isomer. R_f=0.78 (Hexane:AcOEt=4:1). Mp 51–52 °C. ^{1}H NMR δ 6.84 (1H, qd, J=6.6, 15.6 Hz), 7.49 (1H, qd, J=2.1, 15.6 Hz), 7.68 (2H, m), 7.85 (2H, m). ^{13}C NMR δ 122.4 (q, J=270.0 Hz), 130.1, 130.4 (q, J=5.6 Hz), 130.6 (q, J=34.7 Hz), 132.3, 134.8, 186.8. ^{19}F NMR ($CDCl_3$) δ −62.09 (d, J=6.8 Hz).

3.1.6.2. (Z)-Isomer. R_f=0.47 (Hexane:AcOEt=4:1). ^{1}H NMR δ 6.11 (1H, qd, J=4.8, 12.9 Hz), 6.82 (1H, d, J=12.6 Hz), 7.65 (2H, m), 7.79 (2H, m). ^{19}F NMR ($CDCl_3$) δ −62.12 (d, J=9.3 Hz).

*3.1.7. 4,4,4-Trifluoro-1-(4-nitrophenyl)but-2-en-1-one (**4d**)*

Yield 95%, IR (neat) ν 648, 716, 723, 908, 1144, 1275, 1289, 1310, 1388, 1532, 1653, 1687, 2257 cm^{-1}. Anal. Calcd for $C_{10}H_6F_3NO_3$: C, 48.99; H, 2.47; N, 5.71. Found C, 49.27; H, 2.60; N, 5.59.

3.1.7.1. (E)-Isomer. R_f=0.63 (Hexane:AcOEt=4:1). ^{1}H NMR δ 6.90 (1H, qd, J=6.6, 15.3 Hz), 7.53 (1H, qd, J=2.1, 15.6 Hz), 8.15 (2H, m), 8.39 (2H, m). ^{13}C NMR δ 122.2 (q, J=270.0 Hz), 124.1, 129.8, 130.2 (q, J=5.6 Hz), 131.7 (q, J=35.4 Hz), 140.5, 150.7, 186.7. ^{19}F NMR δ −66.55 (d, J=6.8 Hz).

3.1.7.2. (Z)-Isomer. R_f=0.33 (Hexane:AcOEt=4:1). ^{1}H NMR δ 6.21 (1H, qd, J=7.8, 12.6 Hz), 6.88 (1H, d, J=12.6 Hz), 8.10 (2H, m), 8.37 (2H, m). ^{19}F NMR ($CDCl_3$) δ −62.05 (d, J=6.8 Hz).

*3.1.8. (1E,4E)-6,6,6-Trifluoro-1-phenylhexa-1,4-dien-3-one[13] (**4e**)*

Yield 80%, R_f=0.65 (Hexane:AcOEt=4:1). ^{1}H NMR ($CDCl_3$) δ 6.76 (1H, qd, J=6.6, 15.3 Hz), 6.95 (1H, d, J=16.2 Hz), 7.13 (1H, qd, J=1.8, 15.6 Hz), 7.44–7.46 (3H, m), 7.60–7.62 (2H, m), 7.73 (1H, d, J=15.9 Hz). ^{19}F NMR ($CDCl_3$) δ −66.34 (d, J=6.8 Hz).

*3.1.9. (E)-4,4,4-Trifluoro-1-(1-naphthyl)but-2-en-1-one (**4f**)*

Yield 90%, R_f=0.70 (Hexane:AcOEt=4:1). ^{1}H NMR δ 6.76 (1H, qd, J=6.6, 15.6 Hz), 7.42 (1H, qd, J=2.1, 15.6 Hz), 7.53–7.67 (4H, m), 7.86 (1H, dd, J=1.1, 7.4 Hz), 7.93 (1H, dd, J=1.8, 7.5 Hz), 8.54 (1H, d, J=8.4 Hz). ^{13}C NMR δ 122.6 (q, J=266.2 Hz), 124.2, 125.4, 126.8, 128.3, 128.6, 129.2, 130.0 (q, J=35.3 Hz), 130.3, 133.8, 133.8, 133.9, 134.7 (q, J=5.6 Hz), 191.2. ^{19}F NMR δ −66.24 (d, J=6.8 Hz). IR (neat) ν 650, 800, 830, 990, 1150, 1280, 1300, 1320, 1530, 1600, 1660, 3150 cm^{-1}. Anal. Calcd for $C_{14}H_9F_3O$: C, 67.20; H, 3.63. Found C, 67.02; H, 3.78.

*3.1.10. (E)-4,4,4-Trifluoro-1-(2-furanyl)but-2-en-1-one[14] (**4h**)*

Yield 93%, R_f=0.68 (Hexane:AcOEt=4:1). ^{1}H NMR δ 6.62 (1H, dd, J=1.7, 3.5 Hz), 6.85 (1H, qd, J=6.6, 15.6 Hz), 7.36 (1H, dd, J=0.8, 3.6 Hz), 7.39 (1H, qd, J=2.3, 15.6 Hz), 7.71 (1H, dd, J=0.8, 1.6 Hz). ^{19}F NMR δ −66.33 (d, J=6.8 Hz).

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