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Ruthenium-Catalyzed One-Pot Tandem Isomerization–Transfer Hydrogenation Reactions of γ-Trifluoromethylated Allylic Alcohols and β-Trifluoromethylated Enones

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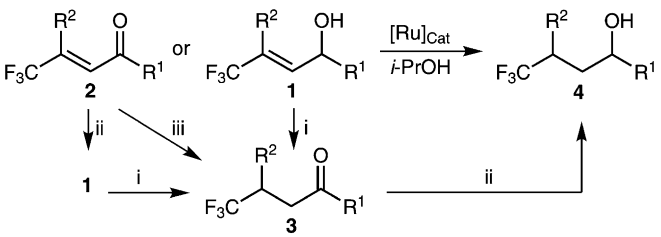
Abstract: The ruthenium–2-propanol combination was found to transform γ-trifluoromethylated allylic alcohols and β-trifluoromethylated enones into the corresponding saturated alcohols in excellent yields *via* a one-pot tandem process involving isomerization and transfer hydrogenation(s). High stereospecificity was demonstrated and evidence for two mechanistic pathways is provided. The method was applied to a rapid synthesis of trifluoromethylated citronellol.

Keywords: allylic compounds; enones; fluorine; isomerization; ruthenium

Introduction

The importance of fluorinated compounds in all fields of society is firmly established.[1] A better understanding of the fluorine effects combined with a boom of interest for organofluorine chemistry has produced an enormous amount of data on new fluorinated molecules as well as novel, highly sophisticated synthetic methods.[2] In addition, simple transformations of fluorinated substrates into attractive new motifs through catalytic process with minimal atom waste are eagerly sought after. In this context, we recently explored the ruthenium-catalyzed isomerization of fluorinated allylic alcohols.[3] Interestingly, a specific fluorine effect was observed that permutes the rate-determining step from insertion for non-fluorinated allylic alcohols to β-elimination for fluorinated allylic alcohols. As a consequence, enantiospecific isomerizations were successful whereas the enantioselective version is not yet established.[3] This isomerization is an efficient, selective, redox-economical,[4f] atom-economical, one-step internal process for the isomerization of C=C bond of allylic alcohols into saturated carbonyl compounds.[4] An additional value of the isomerization is the potential to further bring chemical diversity by trapping intermediates; indeed, one-pot catalytic tandem reactions that include aldolization and Mannich-type reactions,[5] transfer hydrogenation,[6] C–H activation,[7] fluorination,[8] or sequential reactions through organocatalyzed enamine formation have been reported.[9] Tandem reactions minimize the overall cost of a synthetic sequence, a point that makes this approach increasingly popular and led us to investigate the tandem ruthenium-catalyzed isomerization-transfer hydrogenation of not only γ-CF_3 allylic alcohols but also β-CF_3 enones (Scheme 1). This method offers a synthetic opportunity to build the motif γ-CF_3 alcohol. For this purpose, 2-propanol was used as both the solvent and the hydrogen source thus avoiding the use of hydrogen gas that would be necessary in a classical hydrogenation.



Scheme 1. Tandem isomerization–transfer hydrogenation from γ-CF_3 allylic alcohols or β-CF_3 enones.

From γ-CF_3 allylic alcohols **1**, an isomerization reaction (i) would lead to the intermediate ketones **3** that further react in a transfer hydrogenation of C=O bond (ii) to give saturated alcohols **4**. The net transformation being the conversion of allylic alcohols into saturated alcohols, which is equivalent to a selective hydrogenation of the C=C allylic bond (Scheme 1, **1**→**3**→**4**).

Because allylic alcohols **1** are synthesized from enones **2** by reduction, we surmised that a one-pot process starting from **2** would lead to saturated alcohols **4**. Indeed, a transfer hydrogenation of C=O bond of enones **2** would give **1** that further react as they would have when used as starting material (Scheme 1, **2**→**1**→**3**→**4**). However, a second mechanistic pathway could also operate via hydride addition on the C=C bond of enones **2** (iii) to generate intermediate enolate anions, which upon quenching with a protic source (*i*-PrOH) produce saturated ketones **3**. A consecutive transfer hydrogenation of C=O bond of **3** would provide **4** (Scheme 1, **2**→**3**→**4**). The net transformation being the conversion of β-CF_3 enones into saturated γ-CF_3 alcohols, which is equivalent to a double reduction of C=O and C=C bonds of an α,β-unsaturated system. Tandem processes starting from non-fluorinated enones are efficiently catalyzed by iridium complexes,[10] but lead to incomplete conversions or non-specific reactions when catalyzed by ruthenium complexes.[11] However, the tandem isomerization-hydrogen transfer has never been studied with fluorinated substrates. New insights into the effect of the CF_3 group in terms of reaction mechanism and stereocontrol are presented.

Results and Discussion

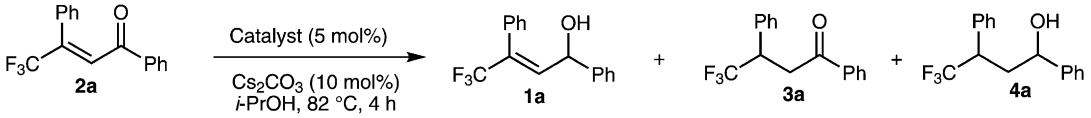
Optimization studies were performed with enone **2a** in order to screen the reaction parameters and to determine the best conditions. Various ruthenium complexes (see Table 1) were evaluated in the reaction of enone **2a** in 2-propanol at reflux in the presence of cesium carbonate as base. With the notable exception of $RuCl_2(PPh_3)_3$ that affords **4a** in 98% isolated yield after 4 h of reaction, none of other catalysts provided more that 16% yield of the desired saturated alcohol **4a** within the same reaction time.

The catalyst loading could be reduced to 1 mol% but the reaction time increased up to 36 h. The nature of the base was next investigated as well as the ratio catalyst/base (Table 2). Clearly, a base is essential for the reaction with a strong preference for Cs_2CO_3 that allows a complete conversion within 4 h. The optimal amount was established at 10 mol% of Cs_2CO_3, i.e., a 1:2 ratio of $RuCl_2(PPh_3)_3/Cs_2CO_3$. The use of lower or higher quantities is detrimental to the conversion.[12] For similar reasons, the starting concentration of enone **2a** (or allylic alcohol **1a**) in *i*-PrOH was fixed at 0.2 M.

Methanol and ethanol were also examined as hydrogen sources. Although the reaction proceeded in these alcoholic media, the conversion was only partial within a reasonable time while the reaction was complete in less than 4 h in 2-propanol. The optimized conditions for transformations of **1a** and **2a** into **4a** are: 5 mol% $RuCl_2(PPh_3)_3$ in *i*-PrOH (0.2 M) at 82 °C with 10 mol% Cs_2CO_3 (see the Supporting Information for full details). The optimized results applied to various allylic alcohols are compiled in Table 3 and those for enones in Table 4.

For the transformation of allylic alcohol **1a** into **4a**, we monitored the reaction by ^{19}F NMR (Scheme 2).

Table 1. Screening of catalysts.



Catalyst	Yields determined by ^{19}F NMR [%]			
	2a	**1a**	**3a**	**4a**
$RuCl_2(PPh_3)_3$	0	0	0	100
$[Ru(Cp^*)(MeCN)_3]PF_6$	57	36	7	0
$[Ru(Cp^*)P(OMe)_3(MeCN)_2]PF_6$	100	0	0	0
$[RuCl_2(COD)]_n$	93	1	6	0
$RuCl_3 \cdot x\,H_2O$	100	0	0	0
$[RuCl_2(p\text{-Cym})]_2$	0	85	2	6
$RuCl(Cp)(PPh_3)_2$	1	86	3	6
$[RuCl_2(C_6H_6)]_2$	5	82	2	2
$RuCl_2(p\text{-Cym})(PMe_3)$	54	19	17	2
$RuCl(Ind)(PPh_3)_2$	6	39	35	16

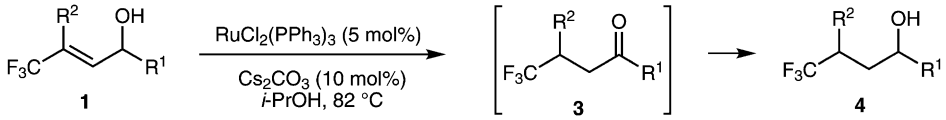
Table 2. Screening of bases [transformation of **2a** into **4a** with the aid of 5 mol% $RuCl_2(PPh_3)_3$].

Base (mol%)	Time [h]	Yields determined by ^{19}F NMR [%]			
		2a	**1a**	**3a**	**4a**
none	2	99	0	1	0
	4	98	0	2	0
K_2CO_3 (10)	2	81	6	8	5
	4	46	27	15	12
Cs_2CO_3 (5)	2	0	0	9	91
	4	0	0	2	98
Cs_2CO_3 (10)	4	0	0	0	100
Cs_2CO_3 (20)	4	0	0	6	92
Cs_2CO_3 (50)	4	8	24	54	9
Cs_2CO_3 (100)	4	4	13	38	8
t-BuOK (10)	2	0	8	74	18
	4	0	7	71	22
i-PrONa (10)	2	0	12	57	31
	4	0	10	48	42
KOH (10)	2	0	0	73	27
	4	0	0	64	36
NaOH (10)	2	0	0	50	50
	4	0	0	44	55

The starting allylic alcohol **1a** was completely converted within the first 20 minutes of the process into ketone **3a**, which reached a maximum concentration before being consumed to end up with the two diastereomeric saturated alcohols **4a**. This study clearly indicates that ketone **3a** is the intermediate resulting from the isomerization step in the tandem process. Secondary allylic alcohols **1a–l** (Table 3, entries 1–12) lead to saturated alcohols **4a–l** in excellent yields albeit with poor diastereoisomeric ratios (71:29 at the best) indicating an almost complete lack of open chain 1,3-stereocontrol. Fortunately, the diastereoisomers are separable by silica gel column chromatography, in most cases.

We observed for allylic alcohol **1j** (Table 3, entry 10) a debromination which may be the result of an oxidative addition of a ruthenium(0) complex followed by a reductive elimination in the protic media to give alcohols **4j** and **4a** as an inseparable mixture. Intriguingly, the allylic alcohol **1k** that features a *t*-Bu carbinol moiety (Table 3, entry 11) is slowly converted into ketone **3k** and not further processed into alcohol **4k** (see later in the text for a similar observation from enone **2k** and interpretation). The substrate scope was extended to primary allylic alcohols **1m** and **1n** (Table 3, entries 13 and 14) that are efficiently transformed into alcohols **4m** and **4n** in excellent yields. The intermediate aldehydes **3m** and **3n** have never been observed; they react very quickly with the hydride source and thus are not subjected to undesired aldol reactions. This result nicely complements our previous results on the isomerization of allylic alcohols in toluene for which only secondary allylic alcohols were successfully isomerized.[3] We now have a complete toolbox for both primary and secondary CF_3-allylic alcohols. Interestingly, alcohol **4n** is a CF_3 analogue of citronellol, a fragrance with organoleptic

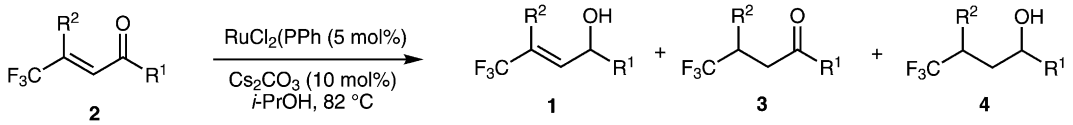
Table 3. Scope of tandem isomerization–transfer hydrogenation of γ-CF_3 allylic alcohols **1**.



Entry	R^1	R^2	Time [h]	Products [%][a]			4	Yield [%][b]
				1	**3**	**4** (*dr*)		
1	Ph	Ph	4	0	0	100 (56:44)	**4a**	98
2	Ph	Me	12	0	0	94 (29:71)	**4b**	90
3	Ph	Bn	24	0	0	100 (42:58)	**4c**	91
4	Ph	*p*-$MeOC_6H_4$	24	0	0	100 (59:41)	**4d**	99
5	Ph	*p*-$CF_3C_6H_4$	2	0	0	100 (45:55)	**4e**	92
6	Me	Ph	24	0	0	100 (51:49)	**4f**	90
7	Me	Bn	12	0	0	95 (33:67)	**4g**	95
8	Me	*o*-$MeOC_6H_4$	24	0	0	100 (55:45)	**4h**	91
9	Me	*p*-$MeOC_6H_4$	24	0	0	100 (46:54)	**4i**	95
10	Ph	*p*-BrC_6H_4	24	0	10	43 (47:53)	**4j**	42[c]
11	*t*-Bu	Ph	24	70	30	0	**4k**	0
12	Bn	H	24	0	0	100	**4l**	82
13	H	Ph	20	5	0	95	**4m**	90
14	H	$(CH_3)_2C{=}CH(CH_2)_2$	24	0	0	100	**4n**	99

[a] Ratios were determined by ^{19}F NMR using trifluorotoluene as internal standard.
[b] Yield of isolated alcohols **4**.
[c] Product **4j** was isolated as a mixture with debrominated compound **4a** in a ratio **4j**/**4a** = 1:1.

Table 4. Scope of tandem isomerization–transfer hydrogenation of β-CF_3 enones **2**.

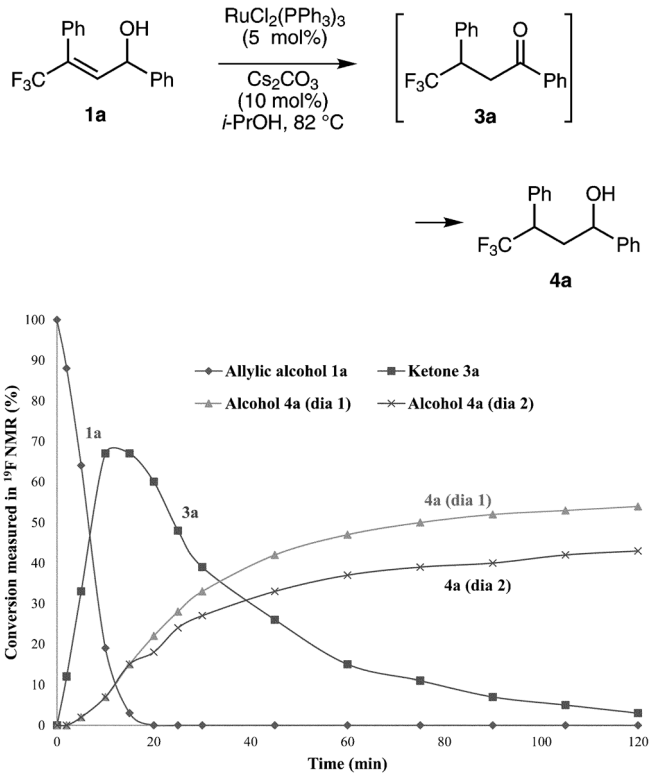


Entry	R^1	R^2	Time [h]	Products [%][a]				**4**	Yield [%][b]
				2	**3**	**1**	**4** (*dr*)		
1	Ph	Ph	4	0	0	0	100 (56:44)	**4a**	93
2	Ph	Me	12	0	0	0	96 (25:75)	**4b**	92
3	Ph	Bn	24	0	23	63	2 (50:50)	**4c**	n.d.
4	Ph	*p*-$MeOC_6H_4$	24	0	0	0	100 (59:41)	**4d**	93
5	Ph	*p*-$CF_3C_6H_4$	2	0	0	0	100 (46:54)	**4e**	93
6	Me	Ph	24	0	7	0	93 (55:45)	**4f**	92
7	Me	Bn	12	0	0	0	100 (32:68)	**4g**	90
8	Me	*o*-$MeOC_6H_4$	24	0	0	0	100 (53:47)	**4h**	94
9	Me	*p*-$MeOC_6H_4$	24	0	0	3	97 (51:49)	**4i**	94
10	Ph	*p*-BrC_6H_4	24	0	14	0	64 (58:42)	**4j**	64[c]
11	*t*-Bu	Ph	24	0	100	0	0	**4k**	n.d.

[a] Ratios were determined by ^{19}F NMR using trifluorotoluene as internal standard.
[b] Yield of isolated alcohols **4**.
[c] Product **4j** was isolated as a mixture with debrominated compound **4a** in a ratio **4j**/**4a** = 4:1.

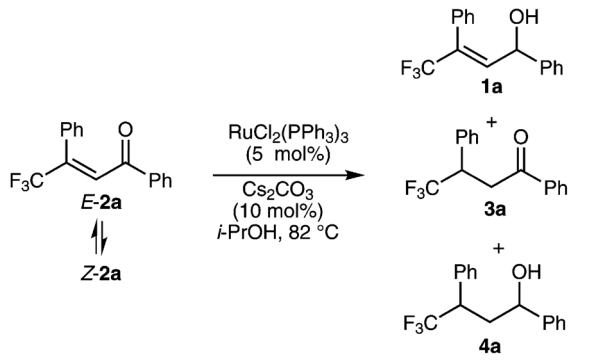
properties dissimilar to those of the natural product.[13]

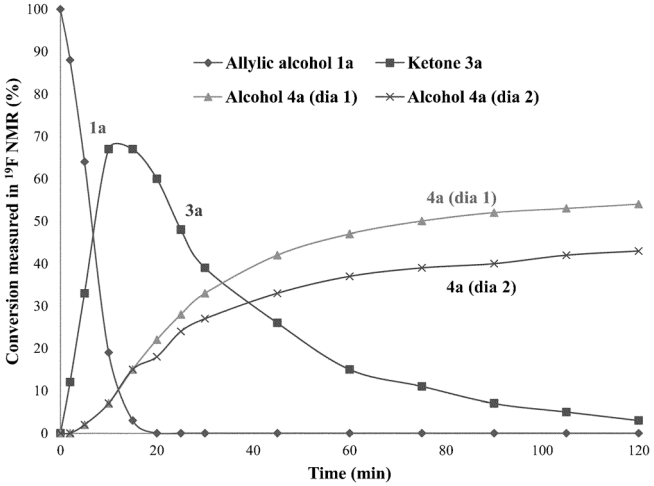
The preparation of γ-CF_3 secondary allylic alcohols **1a–k** required the chemoselective reduction of the C=O bond of the corresponding β-CF_3 enones **2a–k**. In order to gain an additional reaction step, we decided to investigate the tandem reaction conditions directly on these β-CF_3 enones. Interestingly, the saturated alcohols **4a–k** (Table 4) were obtained in high yields, while non-fluorinated enones under ruthenium-catalyzed conditions usually afford moderate yields of saturated alcohols.[11] It is notable that the reactivity of our trisubstituted substrates that nevertheless feature a highly electron-withdrawing and bulky CF_3 group is excellent. This fluorine-accelerated tandem reaction originates from a facilitated insertion step in the isomerization thanks to the presence of the CF_3 group. Enone **2c** (Table 4, entry 3) was fully converted but the reaction stopped at allylic alcohol **1c** although **1c** was independently fully converted within 4 h (Table 3, entry 3). In the transformation of **2c**, a side-product resulting from the isomerization of the C=C bond to the benzylic position was observed. Debromination of bromo-substituted aryl derivatives took place here again, but to a lesser extent, (Table 4, entry 10).



Scheme 2. Monitoring of the tandem reaction of allylic alcohol **1a**.

Surprisingly, enone **2k** led only to ketone **3k** after 4 h whereas neither alcohol **1k** nor **4k** was observed. A similar reactivity was already mentioned for a *t*-Bu substituted non-fluorinated enone but not with such a good chemoselectivity.[11b] The *t*-Bu group decreases the electrophilic character of the carbonyl function by an inductive effect rendering it less easily reducible and favouring the transfer hydrogenation to the C=C bond. This is a rare case of a chemoselective reduction of a β-CF_3 unsaturated system.[14] To gain mechanistic insights, we conducted deuterium-labelling ex-





Scheme 3. Monitoring of the tandem reaction of enone *E*-**2a**.

periments with *i*-PrOH-2-d_1 in which we observed a significant loss of deuterium due to H–D scrambling on the ruthenium to form $RuHD(PPh_3)_3$ complex[15–16] and a reduced reactivity caused by a kinetic isotopic effect. ^{19}F NMR monitoring of the reaction showed 37% of deuterium incorporation at C-1 for allylic alcohol **1a**, a result in agreement with results observed in the transfer hydrogenation of simple ketones,[16b] 4.4% of deuterium incorporation at C-3 for ketone **3a** and no incorporation of deuterium at C-2 or on the oxygen atom because these two positions are readily exchangeable in the basic media. Deuteration at C-3 originates either from isomerization of deuterated **1a** or from an addition–elimination mechanism on **2a** through coordination of the C=C bond to the metal hydride, a mechanism compatible with pathway **2**→**3**→**4** (Scheme 1).[4e] Next, we monitored by ^{19}F NMR the reaction with β-CF_3 enone **2a** (Scheme 3). In the basic media, a slight *E*/*Z* isomerization of enone *E*-**2a** was observed; however, allylic alcohol *Z*-**1a** was not detected. Enone *E*-**2a** reacted quickly to form allylic alcohol *E*-**1a** and ketone **3a** that both reached a maximum concentration within the first 15 minutes of the process. After that time, enone *E*-**2a** and allylic alcohol **1a** have almost disappeared and ketone **3a** became the main product (*ca.* 75%). Ketone **3a** was then gradually reduced into diastereomeric alcohols **4a**. The fact that allylic alcohol **1a** and ketone **3a** are formed simultaneously in the early stage of the reaction is indicative of a concomitant transfer hydrogenation on the C=O and C=C bond with similar kinetics. The chemoselective C=C bond reduction of enone **2k** into ketone **3k** also supports two mechanistic pathways for which the relative contribution depends on the R^1 and R^2 substituents. These observations led us to propose a dual mechanism involving a 1,2-transfer hydrogenation of the C=O bond and a 1,4-transfer hy-

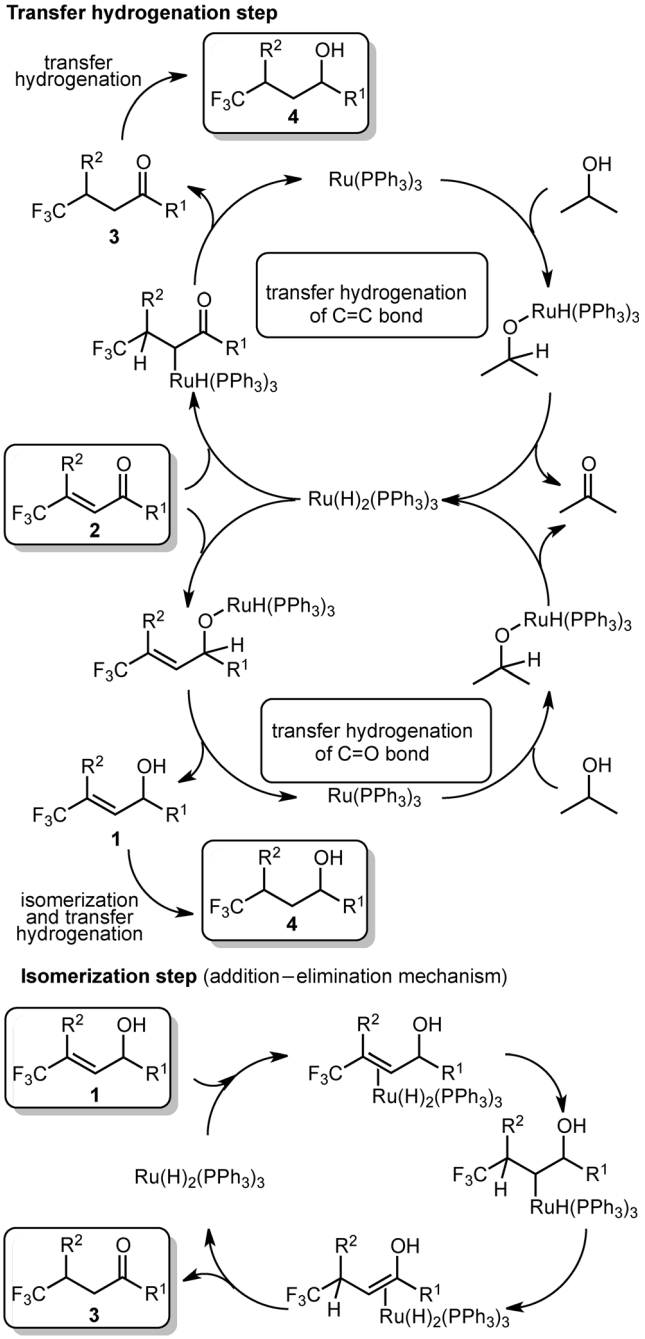
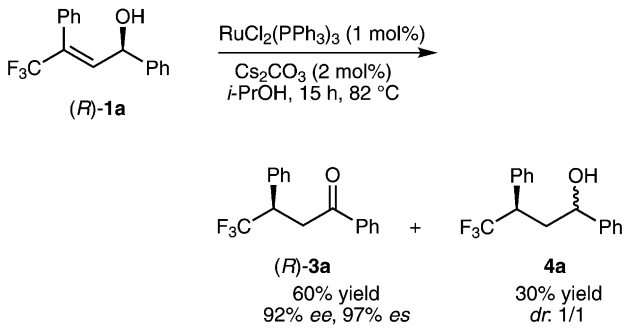


Figure 1. Proposed mechanism for each step of the tandem process.

drogenation of the C=C bond (Figure 1, *top*). In the literature, mechanistic evidence is given for the formation of a ruthenium dihydride species as the active catalyst in the transfer hydrogenation of ketones catalyzed by $RuCl_2(PPh_3)_3$ (the pre-catalyst), *via* two consecutive substitution reactions of chlorine atoms by isopropoxide, followed by a β-elimination.[15] Transfer hydrogenation would take place through the $Ru(H)_2(PPh_3)_3$ species followed by the formation of a ruthenium(0) complex $Ru(PPh_3)_3$ after reductive elimination. This latter complex could be responsible for the debromination of substrates **1j** and **2j**.

As described on the top of Figure 1, $Ru(H)_2(PPh_3)_3$ first reacts with enones through hydroruthenation of either the C=C or the C=O bond and reductive elimination to liberate the saturated ketone **3** in the former case or the allylic alcohol **1** in the latter case both accompanied by the ruthenium(0) species. A further hydride transfer reaction may then furnish the saturated alcohol **4**. Ruthenium(II) catalyst is regenerated by oxidation of 2-propanol. In contrast to the isomerization mechanism invoking oxygen coordination proposed for isomerization run in toluene,[3] the isomerization conducted in *i*-PrOH with the aid of $Ru(H)_2(PPh_3)_3$ species occurs through an addition–elimination mechanism (Figure 1, *bottom*).[4d,e] Coordination of the ruthenium dihydride to the C=C bond of the allylic alcohol followed by hydroruthenation led to a first intermediate that further evolves by β-elimination and prototropy to liberate the ketone with regeneration of the active ruthenium catalyst $Ru(H)_2(PPh_3)_3$. In light of our observations and literature precedents, we propose the mechanism depicted in Figure 1.

Recently, we reported the ruthenium-mediated *syn*-specific 1,3-hydrogen shift of enantioenriched allylic alcohols in toluene as solvent.[3] We now demonstrate that the tandem isomerization-transfer hydrogenation in 2-propanol as solvent and source of hydride is also a highly enantiospecific process with 97% *es* (*es* = enantiospecificity = 100 × *ee* product/*ee* substrate). Two stereogenic centres are formed but only the one at C-3 is controlled because poor diastereoselection was observed in the transfer hydrogenation step (Scheme 4).[17] The reaction was voluntarily stopped when **1a** was fully reacted but before complete conversion into **4a**.



Scheme 4. Tandem isomerization-transfer hydrogenation of enantioenriched allylic alcohol **1a**.

Conclusions

In summary, we have described tandem isomerization-transfer hydrogenation(s) of γ-CF_3 allylic alcohols and β-CF_3 enones that allows the synthesis of saturated alcohols in high yields. Apart from the fact that these fluorinated substrates were not previously investigated in such a tandem process, the main discoveries are: (i) the high yield ruthenium-catalyzed transformation of enones thanks to a fluorine-accelerated isomerization and (ii) the dual mechanism. Indeed, mechanistic evidence is given to validate a dual mechanism starting from enones according either to a 1,2-transfer hydrogenation - isomerization – 1,2-transfer hydrogenation (**2**→**1**→**3**→**4**) or *via* a 1,4- followed by a 1,2-transfer hydrogenation (**2**→**3**→**4**). In addition, the reaction conditions allow for an enantiospecific process with stereocontrol at C-3 albeit without diastereoselection at C-1.

Experimental Section

General Information

^1H (300 MHz), ^{13}C (75.5 MHz) and ^{19}F (282 MHz) NMR spectra were recorded on Bruker AVANCE 300. Chemical shifts in NMR spectra are reported in parts per million from TMS or $CFCl_3$ resonance as the internal standard. IR spectra were recorded on a Perkin–Elmer IRFT 1650 spectrometer. The conversion and ratio of the corresponding products were determined by ^{19}F NMR analysis adopting α,α,α-trifluorotoluene as internal standard with a D1 value = 5 s. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. Some catalysts were generously provided by Johnson-Matthey. Characterization data and general procedure for the synthesis of allylic alcohols **1**, enones **2**, and ketone **3** were previously reported.[3]

General Procedure for the Tandem Redox Isomerization–Transfer Hydrogenation of γ-CF_3 Allylic Alcohols (1) or β-CF_3 Enones (2)

In a Schlenk tube under nitrogen, were added γ-CF_3 allylic alcohol **1** or β-CF_3 enone **2** (0.25 mmol) and cesium carbonate (8.1 mg, 0.025 mmol) in 2-propanol (1.25 mL). Complex $RuCl_2(PPh_3)_3$ (12 mg, 0.0125 mmol) was then added and the mixture was heated at 82 °C until ^{19}F NMR shows full conversion. After evaporation of solvent, the crude product was

purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 50/1) to give each diastereoisomers of the corresponding saturated alcohol **4**.

4,4,4-Trifluoro-1,3-diphenylbutan-1-ol (4a): *Diastereoisomer 1:* colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.73 (bs, 1H), 2.09 (ddd, 1H, J = 14.2 Hz, J = 11.7 Hz, J = 2.5 Hz), 2.28 (ddd, 1H, J = 14.2 Hz, J = 10.9 Hz, J = 3.4 Hz), 3.63–3.75 (m, 1H), 4.22 (bd, 1H, J = 10.8 Hz), 7.15–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 38.3 (q, J = 2.0 Hz), 47.0 (q, J = 26.9 Hz), 70.6, 125.7, 127.2 (q, J = 279.6 Hz), 128.1, 128.5, 128.8, 129.0, 129.5, 134.4 (q, J = 2.0 Hz), 144.3; ^{19}F NMR ($CDCl_3$): δ = −70.1 (d, J = 9.6 Hz); HR-MS: m/z = 280.1078, calcd. for $C_{16}H_{15}F_3O$ (M^+): 280.1075; IR (neat): ν = 3393, 3037, 1256, 1152, 1108, 1052, 753, 699 cm^{-1}.

Diastereoisomer 2: colourless oil. ^{1}H NMR ($CDCl_3$) δ = 1.85 (bs, 1H), 2.37–2.46 (m, 2H), 3.06–3.20 (m, 1H), 4.51 (bt, J = 7 Hz, 1H), 7.22–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 38.0, 46.8 (q, J = 27.1 Hz), 72.3, 126.4, 126.9 (q, J = 280.1 Hz), 128.5, 128.6, 128.9, 129.0, 129.3, 134.7, 142.9; ^{19}F NMR ($CDCl_3$): δ = −70.2 (d, J = 9.3 Hz); HR-MS: m/z = 280.1083, calcd. for $C_{16}H_{15}F_3O$ (M^+): 280.1075; IR (neat): ν = 3374, 2931, 1454, 1257, 1149, 1108, 1019, 748, 699 cm^{-1}.

4,4,4-Trifluoro-3-methyl-1-phenylbutan-1-ol (4b): *Diastereoisomer 1:* white solid; ^{1}H NMR ($CDCl_3$): δ = 1.20 (d, J = 6.9 Hz, 3H), 1.58–1.63 (m, 1H), 1.85 (bs, 1H), 2.14 (ddd, 1H, J = 13.9 Hz, J = 10.2 Hz, J = 3.6 Hz), 2.49–2.60 (m, 1H), 4.77 (dt, J = 3.6 Hz, J = 10.2 Hz, 1H), 7.30–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 12.4 (q, J = 3.0 Hz), 34.9 (q, J = 26.6 Hz), 38.7 (q, J = 2.2 Hz), 71.1, 125.8, 128.2, 128.9 (q, J = 278.9 Hz), 128.9, 144.3; ^{19}F NMR ($CDCl_3$): δ = −74.0 (d, J = 9.2 Hz); HR-MS; m/z = 218.0924, calcd. for $C_{11}H_{13}F_3O$ (M^+): 218.0918; IR (neat): ν = 3396, 2910, 1262, 1169, 1131, 1092, 1050, 1016, 907, 731, 700 cm^{-1}.

Diastereoisomer 2: colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.16 (d, J = 7.0 Hz, 3H), 1.74–1.89 (m, 1H), 1.88 (bs, 1H), 2.06 (dt, J = 5.8 Hz, J = 14.0 Hz, 1H), 2.26–2.36 (m, 1H), 4.79–4.84 (m, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, J = 3.3 Hz), 35.3 (q, J = 26.5 Hz), 39.3 (q, J = 2.0 Hz), 72.7, 126.0, 128.3, 128.6 (q, J = 279.3 Hz), 128.9, 143.8; ^{19}F NMR ($CDCl_3$): δ = −73.5 (d, J = 9.0 Hz); HR-MS: m/z = 218.0927, calcd. for $C_{11}H_{13}F_3O$ (M^+): 218.0918; IR (neat): ν = 3368, 2959, 1266, 1167, 1128, 1092, 1018, 756, 700 cm^{-1}.

3-Benzyl-4,4,4-trifluoro-1-phenylbutan-1-ol (4c): Two diastereoisomers (A:B = 1:1.4): light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.68–1.84 (m, 2H, H_{2A+B} + OH_{A+B}), 1.91–2.12 (m, 1H, $H_{2'A+B}$), 2.48–2.76 (m, 2H, H_{4A+B} + H_{3A+B}), 3.01–3.10 (m, 1H, $H_{4'A+B}$), 4.37–4.42 (m, 1H, H_{1B}), 4.61–4.65 (m, 1H, H_{1A}), 7.03–7.32 (m, 10H, H_{ArA+B}); ^{13}C NMR ($CDCl_3$): δ = 34.7 (q, J = 2.9 Hz, C_{4B}), 35.2 (q, J = 3.1 Hz, C_{4A}), 36.9 (q, J = 1.8 Hz, C_{2B}), 37.4 (q, J = 1.5 Hz, C_{2A}), 41.3 (q, J = 24.9 Hz, C_{3A}), 41.5 (q, J = 25.3 Hz, C_{3B}), 71.9 (C_{1B}), 72.0 (C_{1A}), 125.9 (C_{Ar}), 126.0 (C_{Ar}), 126.8 (C_{Ar}), 126.9 (C_{Ar}), 128.1 (C_{Ar}), 128.3 (q, J = 280.1 Hz, CF_{3B}), 128.4 (q, J = 280.4 Hz, CF_{3A}), 128.7 (C_{Ar}), 129.3 (C_{Ar}), 129.4 (C_{Ar}), 138.0 (C_{Ar}), 143.5 (C_{Ar}), 144.0 (C_{Ar}); ^{19}F NMR ($CDCl_3$): δ = −70.8 (d, J = 8.1 Hz, A), −71.3 (d, J = 8.9 Hz, B); HR-MS: m/z = 294.1236, calcd. for $C_{17}H_{17}F_3O$ (M^+): 294.1231; IR (neat): ν = 3389, 3028, 1456, 1255, 1175, 1148, 1109, 1082, 734, 697 cm^{-1}.

5,5,5-Trifluoro-4-(4-methoxyphenyl)pentan-2-ol (4d): *Diastereoisomer 1:* light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.79 (bs, 1H), 2.09–2.18 (m, 1H), 2.28–2.40 (m, 1H), 3.67–3.81 (m, 1H), 3.84 (s, 3H), 4.32–4.35 (m, 1H), 6.93–6.97 (m, 2H), 7.26–7.37 (m, 7H); ^{13}C NMR ($CDCl_3$): δ = 38.1 (q, J = 1.8 Hz), 46.0 (q, J = 26.9 Hz), 55.3, 70.5, 114.2, 125.6, 126.1 (q, J = 2.0 Hz), 127.2 (q, J = 279.6 Hz), 127.9, 128.7, 130.4, 144.2, 159.5; ^{19}F NMR ($CDCl_3$): δ = −70.5 (d, J = 9.6 Hz); HR-MS: m/z = 310.1185, calcd. for $C_{17}H_{17}F_3O_2$ (M^+): 310.1181; IR (neat): ν = 3417, 2943, 1515, 1244, 1179, 1151, 1105, 1053, 1034 cm^{-1}.

Diastereoisomer 2: light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.86 (bs, 1H), 2.34–2.49 (m, 2H), 2.98–3.13 (m, 1H), 3.82 (s, 3H), 4.51 (t, 1H, J = 7.3 Hz), 6.88–6.93 (m, 2H), 7.16–7.19 (m, 2H), 7.23–7.26 (m, 2H), 7.30–7.40 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 37.9 (q, J = 1.8 Hz), 46.0 (q, J = 27.0 Hz), 55.4, 72.4, 114.3, 126.4, 127.0 (q, J = 279.8 Hz), 128.5, 129.0, 130.3, 142.9, 159.6; ^{19}F NMR ($CDCl_3$): δ = −70.7 (d, J = 9.3 Hz); HR-MS: m/z = 310.1188, calcd. for $C_{17}H_{17}F_3O_2$ (M^+): 310.1181; IR (neat): ν = 3387, 2921, 1515, 1246, 1177, 1148, 1106, 1033, 1021 cm^{-1}.

4,4,4-Trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-ol (4e): *Diastereoisomer 1:* light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.81 (bs, 1H), 2.14–2.24 (m, 1H), 2.43 (ddd, 1H, J = 14.2 Hz, J = 10.9 Hz, J = 3.4 Hz), 3.83–3.98 (m, 1H), 4.28 (d, 1H, J = 10.9 Hz),7.26–7.39 (m, 5H), 7.53 (d, 2H, J = 8.1 Hz), 7.69 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 38.1 (q, J = 1.8 Hz), 46.8 (q, J = 27.4 Hz), 70.5, 124.1 (q, J = 272.9 Hz), 125.7, 125.9 (q, J = 3.8 Hz), 126.8 (q, J = 279.2 Hz), 128.3, 128.7, 129.9, 130.8 (q, J = 32.7 Hz), 138.4, 143.8; ^{19}F NMR ($CDCl_3$): δ = −63.2 (s), −69.9 (d, J = 9.4 Hz); HR-MS: m/z = 348.0957, calcd. for $C_{17}H_{14}F_6O$ (M^+): 348.0949; IR (neat): ν = 3387, 2940, 1324, 1258, 1159, 1116, 1070, 1057, 1020, 835, 700 cm^{-1}.

Diastereoisomer 2: light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.89 (bs, 1H), 2.37–2.52 (m, 2H), 3.23–3.37 (m, 1H), 4.55 (t, 1H, J = 7.2 Hz), 7.22–7.26 (m, 2H), 7.33–7.40 (m, 5H), 7.63 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 37.9 (q, J = 1.5 Hz), 46.6 (q, J = 27.2 Hz), 72.1, 124.0 (q, J = 272.2 Hz), 125.9 (q, J = 3.8 Hz), 126.3, 126.6 (q, J = 279.8 Hz, CF_3), 128.7 (C_{Ar}), 129.1 (C_{Ar}), 129.7 (C_{Ar}), 130.8 (q, J = 32.6 Hz, C_{Ar}), 138.9, 142.7; ^{19}F NMR ($CDCl_3$): δ = −63.2 (s), −69.9 (d, J = 9.2 Hz); HR-MS: m/z = 348.0952, calcd. for $C_{17}H_{14}F_6O$ (M^+): 348.0949; IR (neat): ν = 3347, 2940, 1324, 1258, 1155, 1113, 1070, 1019, 835, 755, 737, 701 cm^{-1}.

5,5,5-Trifluoro-4-phenylpentan-2-ol (4f): *Diastereoisomer 1:* colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.19 (d, 2H, J = 6.2 Hz), 1.27 (bs, 1H), 1.90–2.05 (m, 2H), 3.40–3.50 (m, 1H), 3.61–3.75 (m, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 24.6, 38.0 (q, J = 2.0 Hz), 46.8 (q, J = 26.9 Hz), 64.3, 127.3 (q, J = 279.4 Hz), 128.3, 128.9, 129.4, 134.6 (q, J = 1.9 Hz); ^{19}F NMR ($CDCl_3$): δ = −70.2 (d, J = 9.7 Hz); HR-MS: m/z = 218.0920, calcd. for $C_{11}H_{13}F_3O$ (M^+): 218.0918; IR (neat): ν = 3364, 2970, 1259, 1156, 1109, 1088, 1024, 702 cm^{-1}.

Diastereoisomer 2: colourless crystals; mp 59 °C; ^{1}H NMR ($CDCl_3$): δ = 1.19 (d, 2H, J = 6.2 Hz), 1.34 (bs, 1H), 2.02–2.18 (m, 2H), 3.37–3.52 (m, 1H), 3.75–3.85 (m, 1H), 7.30–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 23.4, 38.8 (q, J = 1.7 Hz), 47.2 (q, J = 26.8 Hz), 66.0, 127.1 (q, J = 280.3 Hz), 128.4, 129.0, 129.1, 135.2 (q, J = 2.0 Hz); ^{19}F NMR ($CDCl_3$): δ = −70.0 (d, J = 9.3 Hz); HR-MS: m/z = 218.0921, calcd. for $C_{11}H_{13}F_3O$ (M^+): 218.0918; IR (neat): ν = 3291, 2978, 1260, 1146, 1124, 1077, 1067, 756, 703 cm^{-1}.

4-Benzyl-5,5,5-trifluoropentan-2-ol (4g): Two diastereoisomers (A:B = 1:1.6): light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.00–1.04 (m, 4H, H_{1A+B} + OH_{A+B}), 1.33–1.49 (m, 1H, H_{3A+B}), 1.59–1.74 (m, 1H, $H_{3'A+B}$), 2.45–2.71 (m, 2H, H_{5A+B} + H_{4A+B}), 2.93–3.06 (m, 1H, $H_{5'A+B}$), 3.52–3.62 (m, 1H, H_{2B}), 3.72–3.82 (m, 1H, H_{2A}), 7.12–7.27 (m, 5H, H_{ArA+B}); ^{13}C NMR ($CDCl_3$): δ = 24.0 (C_{1B}), 24.4 (C_{1A}), 34.7 (q, J = 2.8 Hz, C_{5B}), 35.2 (q, J = 3.2 Hz, C_{5A}), 37.5–37.6 (m, C_{3A+B}), 41.2 (q, J = 24.9 Hz, C_{4A}), 42.0 (q, J = 25.2 Hz, C_{4B}), 65.1 (C_{2B}), 65.7 (C_{2A}), 126.8 (C_{ArA+B}), 128.4 (q, J = 279.9 Hz, CF_{3B}), 128.5 (q, J = 280.5 Hz, CF_{3A}), 128.7 (C_{Ar}), 129.2 (C_{Ar}), 129.3 (C_{Ar}), 138.1 (C_{ArA}), 138.5 (C_{ArB}); ^{19}F NMR ($CDCl_3$): δ = −70.9 (d, J = 9.1 Hz, A), −71.5 (d, J = 9.1 Hz, B); HR-MS: m/z = 232.1082, calcd. for $C_{12}H_{15}F_3O$ (M^+): 232.1075; IR (neat): ν = 3375, 2973, 1254, 1160, 1112, 1085, 1072, 742, 699 cm^{-1}.

5,5,5-Trifluoro-4-(2-methoxyphenyl)pentan-2-ol (4h): *Diastereoisomer 1:* colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.07 (d, 3H, J = 6.2 Hz), 1.76–1.99 (m, 2H), 2.04 (bs, 1H), 3.31–3.33 (m, 1H), 3.79 (s, 3H), 4.13–4.28 (m, 1H), 6.85–6.95 (m, 2H), 7.18–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 23.4, 37.6 (q, J = 27.6 Hz), 38.8 (q, J = 1.5 Hz), 56.2, 64.5, 111.3, 121.6, 123.2 (q, J = 1.8 Hz), 127.5 (q, J = 279.6 Hz), 128.4, 129.3, 157.7; ^{19}F NMR ($CDCl_3$): δ = −69.2 (d, J = 9.9 Hz); HR-MS: m/z = 248.1026, calcd. for $C_{12}H_{15}F_3O_2$ (M^+): 248.1024; IR (neat): ν = 3384, 2966, 2933, 1603, 1496, 1465, 1441, 1245, 1155, 1124, 1099, 1085, 1026, 753 cm^{-1}.

Diastereoisomer 2: colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.17 (d, 2H, J = 6.5 Hz), 1.40 (bs, 1H), 3.68–3.79 (m, 1H), 3.85 (s, 3H), 4.08–4.25 (m, 1H), 6.87–7.00 (m, 2H), 7.26–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 23.2, 37.7 (q, J = 26.7 Hz), 38.8 (q, J = 1.7 Hz), 55.9, 66.2, 111.1, 121.1, 123.7 (q, J = 2.0 Hz), 127.3 (q, J = 279.9 Hz), 128.6, 129.3, 157.4; ^{19}F NMR ($CDCl_3$): δ = −69.9 (d, J = 9.6 Hz); HR-MS: m/z = 248.1030, calcd. for $C_{12}H_{15}F_3O_2$ (M^+): 248.1024; IR (neat): ν = 3347, 2969, 1603, 1496, 1465, 1441, 1246, 1156, 1121, 1071, 1027, 753 cm^{-1}.

5,5,5-Trifluoro-4-(4-methoxyphenyl)pentan-2-ol (4i): *Diastereoisomer 1:* light yellow oil; ^{1}H NMR ($CDCl_3$): δ = 1.19 (d, 2H, J = 6.2 Hz), 1.23 (bs, 1H), 1.88–2.04 (m, 2H), 3.42–3.52 (m, 1H), 3.54–3.69 (m, 1H), 3.81 (s, 3H), 6.88–6.92 (m, 2H), 7.22–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 24.6, 38.0 (q, J = 2.0 Hz), 45.9 (q, J = 26.9 Hz), 55.4, 64.3, 114.3, 126.4 (q, J = 2.0 Hz), 127.4 (q, J = 279.3 Hz), 130.4, 159.5; ^{19}F NMR ($CDCl_3$): δ = −70.6 (d, J = 9.7 Hz); HR-MS: m/z = 248.1031, calcd. for $C_{12}H_{15}F_3O_2$ (M^+): 248.1024; IR (neat): ν = 3372, 2973, 1515, 1245, 1180, 1155, 1105, 1084, 1026 cm^{-1}.

Diastereoisomer 2: white solid; mp 67 °C; ^{1}H NMR ($CDCl_3$): δ = 1.18 (d, 2H, J = 6.2 Hz), 1.34 (bs, 1H), 1.99–2.15 (m, 2H), 3.20–3.45 (m, 1H), 3.74–3.84 (m, 1H), 3.80 (s, 1H), 6.87–6.91 (m, 2H), 7.22–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 23.3, 38.7 (q, J = 1.7 Hz), 46.4 (q, J = 26.9 Hz), 55.4, 66.1, 114.3, 127.0 (q, J = 2.2 Hz), 127.1 (q, J = 279.7 Hz), 130.1, 159.6; ^{19}F NMR ($CDCl_3$): δ = −70.5 (d, J = 9.3 Hz); HR-MS: m/z = 248.1028, calcd. for $C_{12}H_{15}F_3O_2$ (M^+): 248.1024; IR (neat): ν = 3282, 2966, 1516, 1245, 1181, 1151, 1113, 1067, 1024 cm^{-1}.

3-(4-Bromophenyl)-4,4,4-trifluoro-1-phenylbutan-1-ol (4j): The diastereomeric alcohols **4j** were obtained in mixture with debrominated alcohols **4a**. ^{1}H and ^{13}C NMR are very similar for these compounds and very difficult to assign.

1st diastereoisomer: ^{19}F NMR ($CDCl_3$): δ = −70.2 (d, J = 9.2 Hz).

2nd diastereoisomer: ^{19}F NMR ($CDCl_3$): δ = −70.3 (d, J = 10.3 Hz)

5,5,5-Trifluoro-1-phenylpentan-2-ol (4l): Colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.55 (d, 1H, J = 3.9 Hz), 1.56–1.82 (m, 2H), 2.00–2.21 (m, 1H), 2.21–2.42 (m, 1H), 2.60 (dd, 1H, J = 13.5 Hz, J = 8.5 Hz), 2.78 (dd, 1H, J = 13.5 Hz, J = 4.2 Hz), 3.78 (m, 1H), 7.13–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 29.1 (q, J = 2.8 Hz), 30.4 (q, J = 28.9 Hz), 44.3, 71.3, 127.0, 127.5 (q, J = 275.9 Hz), 128.9, 129.5, 137.7; ^{19}F NMR ($CDCl_3$): δ = −66.8 (t, J = 11.0 Hz); HR-MS: m/z = 218.0918, calcd. for $C_{11}H_{13}F_3O$ (M^+): 218.0918; IR (neat): ν = 3342, 2914, 1308, 1260, 1129, 1110, 1086 cm^{-1}.

4,4,4-Trifluoro-3-phenylbutan-1-ol (4m): Colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.51 (bs, 1H), 1.94–2.03 (m, 1H), 2.13–2.23 (m, 1H), 3.25–3.33 (m, 1H), 3.50–3.59 (m, 1H), 3.40–3.55 (m, 1H), 7.23–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 31.9 (d, J = 2.0 Hz), 46.6 (q, J = 26.8 Hz), 59.5, 127.4 (q, J = 279.6 Hz), 128.6, 129.1, 129.4, 134.6 (q, J = 1.9 Hz); ^{19}F NMR ($CDCl_3$): δ = −70.1 (d, J = 9.5 Hz); HR-MS: m/z = 204.0766, calcd. for $C_{10}H_{11}F_3O$ (M^+): 204.0762; IR (neat): ν = 3339, 2963, 1257, 1151, 1108, 1041, 1029, 700 cm^{-1}.

7-Methyl-3-(trifluoromethyl)-6-octenol (4n): Colourless oil; ^{1}H NMR ($CDCl_3$): δ = 1.13–1.31 (m, 1H), 1.38–1.50 (m, 1H), 1.61–1.73 (m, 8H), 1.82–1.93 (m, 1H), 2.04–2.09 (m, 1H), 2.17–2.29 (m, 1H), 3.72 (t, 2H, J = 7 Hz), 5.04–5.09 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 17.8, 25.4, 25.8, 28.3 (q, J = 2 Hz), 31.1 (q, J = 2 Hz), 38.8 (q, J = 25 Hz), 60.2, 123.3, 128.8 (q, J = 279 Hz), 134.3; ^{19}F NMR ($CDCl_3$): δ = −70.8 (d, J = 10 Hz); HR-MS: m/z = 210.1237, calcd. for $C_{10}H_{17}F_3O$ (M^+): 210.1231; IR (neat): ν = 3334, 3934, 1453, 1379, 1259, 1151, 1114, 1053, 1029 cm^{-1}.

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