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Synthesis of tetrasubstituted α-fluoroenones

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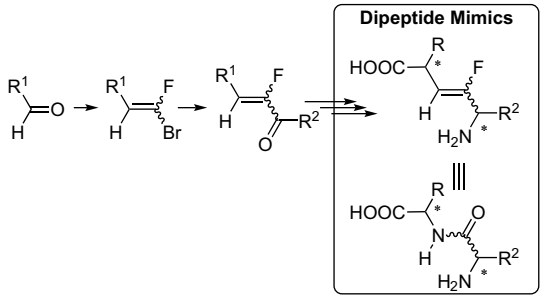
ABSTRACT

We reported the synthesis of tetrasubstituted α-fluoroenones from tetrasubstituted *gem*-bromofluoroolefins in good yields. These compounds are scarcely studied in the literature, due to difficulty of synthesis, whereas they could serve as intermediates in the synthesis of biological relevant molecules and could also be envisioned to design new constrained peptidomimetics.

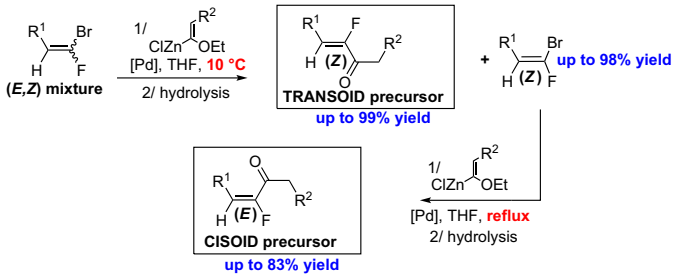
1. Introduction

The fluorine atom in organic chemistry is increasingly exploited in several fields (pharmacy, materials…) since its use usually involved new relevant properties and functionalities.[1] Indeed, the introduction of one or several fluorine atoms on a compound alters its chemical, physical and biological properties compared to non-fluorinated derivatives with often an improved therapeutic profile.[2] In our laboratory, we are developing new methodologies towards fluorinated fine chemicals and in particular for the development of new fluoropeptidomimetics bearing a fluoroolefin moiety as peptide bond mimic (Scheme 1).[3] Indeed, some computational studies showed that these moieties share geometric and electronic similarities.[4]



Scheme 1. General route envisioned to fluorinated pseudopeptides.

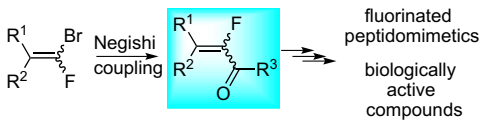
In this context, from *gem*-bromofluoroolefins,[5] we recently described new interesting synthesis of vinylic fluoride scaffolds via a Negishi coupling reaction mediated by palladium catalyst (Scheme 2).[6] The products obtained can serve as precursors for fluoropeptidomimetics synthesis.[7]



Scheme 2. Negishi reaction with trisubstituted *gem*-bromofluoroolefins.

At 10 °C, only the *E* isomer of the (*E*,*Z*) mixture of substrate reacted to give stereospecifically transoid precursor in high yields. At the same time the *Z* isomer substrate was recovered also in high yields. Then, this *Z* substrate was submitted to the Negishi reaction in refluxing condition to give cisoid precursors in good yields. This reaction is very efficient and the stereodifferentiation operating with the reaction temperature was possible whatever the nature of R^1 group (aliphatic, aromatic, with functionality such as cyano, nitro,…) and R^2 group.[6]

Here we report an extension of this method to tetrasubstituted substrates with emphasis to the synthesis of new fluorinated pseudopeptides where the native peptide bond has been replaced by a fluoroolefin moiety (Scheme 3). The tetrasubstituted fluoro-compounds can also have other relevant application as nucleosides,[8] factorXa inhibitors,[9] ….



Scheme 3. Tetrasubstituted α-fluoroenones and applications.

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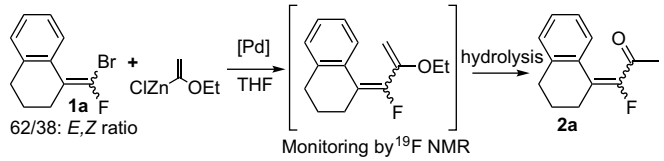
Moreover, it has to be noted that the synthesis of α-fluoroenone moiety is rare in the literature as well as its applications whereas this functionality can be easily chemically modify (asymmetric reductive amination or other specific reactions of ketone moiety) towards interesting molecules such as peptidomimetics.

2. Results and discussion

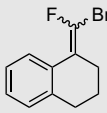
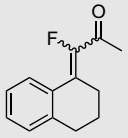
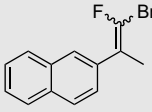
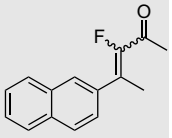
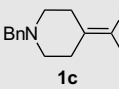
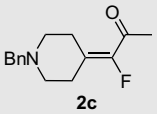
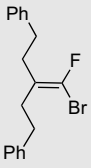
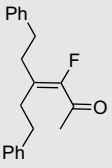
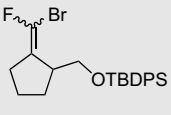
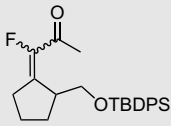
We began the study with the α-ethoxyvinylzinc chloride as organozinc derivative using the experimental conditions already described: 2 equiv of organozinc with 5% and 10% of $Pd(OAc)_2$ and PPh_3, respectively, as a catalytic system (Table 1).[6]

Table 1
Influence of the temperature on the Negishi coupling reaction of **1a**



Entry	Temperature (°C)	Reaction time (min)	Conversion (%)	*E*/*Z* ratio
1	65	15	100	30/70
2	40	15	85	26/74
		60	100	29/71
3	20	5	72	5/95
		60	100	15/85
4	5	5	80	14/86
		60	100	18/82
5	−5	15	65	15/85
		60	90	20/80
6	−20	15	30	15/85
		150	76	21/79
7	−40	150	26	23/77
8	−78	150	15	35/65

Table 2
Reactivity of tetrasubstituted bromofluoroolefins under Negishi coupling reaction conditions

Entry	Substrate (*E*/*Z* ratio)	Isolated yield (%)	Products (*E*/*Z* ratio)
1	 **1a** (62/38)	84	 **2a** (26/74)
2	 **1b** (nd)[a]	77	 **2b** (37/63)
3	 **1c**	75	 **2c**
4	 **1d**	88	 **2d**
5	 **1e** (56/44)	65	 **2e**[b] (41/59)

[a] Not determined.
[b] Reaction conducted with 3 equiv of organozinc derivative.

First, we investigated the role of the temperature on the reaction aiming at doing efficient stereodifferentiation as already observed in the case of trisubstituted *gem*-bromofluoroolefins. Whatever the temperature used in the Negishi coupling with α-ethoxyvinylzinc chloride, the kinetic control was ineffective. Actually, by monitoring the reaction by ^{19}F NMR, we can see, in all cases, that the first isomer of the *E*,*Z* mixture to react was the *E* isomer, but unfortunately, quickly followed by the *Z*-isomer, which restricted and prohibited the stereodifferentiation. By running the reaction at 40 or 65 °C (entries 1 and 2), the kinetic was better but the *E*,*Z* ratio was lower than at room temperature. On the contrary, reaction carried out at low temperature (entries 5–8) revealed to be incomplete without any gain in selectivity. The more surprising was that, starting from a 62/38 *E*,*Z* mixture of substrate, with 100% conversion, we ended up with a 15/85 *E*,*Z* mixture of enol ether (entry 3). Meaning probably that on the opposite to the observation made for trisubstituted bromofluoroolefins,[6] the tetrasubstituted fluorinated double bond isomerizes partially during the catalytic process for compound **1a**. The better compromise results/experimental procedure was for reaction conducted at room temperature. It has to be noted that we have also changed the reaction time and the number of equivalent (organozinc, substrate and catalyst) without any benefit for selectivity. So the experimental conditions used for the study were 2 equiv of organozinc with 5% and 10% of $Pd(OAc)_2$ and PPh_3, respectively, as catalytic system at room temperature. The reaction was controlled by monitoring ^{19}F NMR signal of the reaction mixture. Then, the mixture was hydrolyzed and stirred for 15 min by an aqueous solution of HCl (1 M). Table 2 showed the results obtained with different tetrasubstituted *gem*-bromofluoroolefins with α-ethoxyvinylzinc chloride.

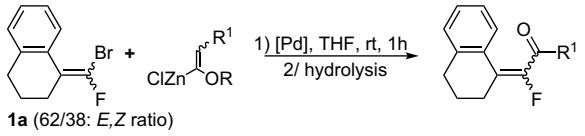
Reaction yields were good for all substrates (65–88%), i.e., aliphatic (linear or cyclic) or aromatic molecules. Despite no stereodifferentiation was possible, an interesting feature is the possible separation of the *E*/*Z* products starting from a non-separable *E*/*Z* mixture of tetrasubstituted *gem*-bromofluoroolefin. Depending on the substrate, partial isomerization occurred sometimes during the hydrolysis step, probably through a thermodynamic equilibrium of the tetrasubstituted α-fluoroenones in acidic medium.

The reaction could lead to a fluorinated proline analogue (entry 5). This molecule is very relevant and can serve as intermediate for fluorinated proline-containing peptidomimetic as well as DPPIV or DPPII inhibitor precursors.[10]

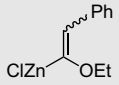
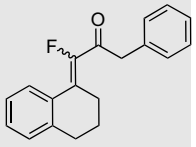
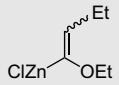
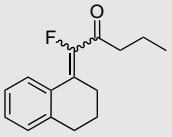
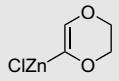
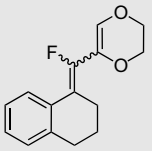
To extend the scope of the reaction, we then did the reaction with various organozinc derivatives (Table 3).

In that case, results are good with the possible separation of *E*/*Z* isomers of product **4**. Unfortunately, the *E*/*Z* products **3** and **5** proved to be unseparable at this stage. The *E*/*Z* ratio with 2-phenyl-1-ethoxyvinylzinc chloride was quite high: 4/96. This result can be explained by isomerization of the double bond under harsher hydrolysis conditions needed in that case because of the conjugation of phenyl group with the enol moiety of the intermediate (*E*/*Z* ratio of enol before hydrolysis: 36/64).

Table 3
Reactivity of **1a** under Negishi coupling reaction condition using different organozinc derivatives



1a (62/38: *E,Z* ratio)

Entry	ClZn(R^1)OR	Isolated yield	Products (*E*/*Z* ratio)
1		65	 **3** (4/96)[a]
2		62	 **4** (27/73)[a]
3		79	 **5** (29/71)

[a] Hydrolysis with HCl 6 M at 70 °C.

3. Conclusion

To resume, we extended the scope of the Negishi type reaction to tetrasubstituted *gem*-bromofluoroolefin with success in terms of yield. Unfortunately, no stereodifferentiation was possible during the coupling process but the (*E,Z*) mixture of products obtained was often separable by column chromatography. The fluorocompounds synthesized can have different relevant uses and current researches are done towards the synthesis of dipeptidic analogues containing proline derivatives.

4. Experimental section

4.1. General methods

Experiments involving organometallics were carried out under argon atmosphere. All moisture-sensitive reactants were handled under argon atmosphere. Low temperature experiments were carried out by cooling down the flasks with a acetone bathfrozen by dry-ice. The flasks were equipped with septum caps. THF was distilled before using from sodium benzophenone ketyl under nitrogen atmosphere. TLC was performed on Merck 60F-250 silica gel plates, using UV light as a visualizing agent and an ethanolic solution of phosphomolybdic acid and heat as developing agents. Flash column chromatography purifications were carried out using silica gel (70–230 mesh). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR ($CFCl_3$ as external reference) were recorded at 300.13, 75.47 and 282.40 MHz, respectively, on a Bruker DXP 300. Abbreviations used for peak multiplicity are s: singlet, b: broad singlet, d: doublet, t: triplet, q: quadriplet, m: multiplet. *J* was used to indicate coupling constant in hertz. IR spectra were recorded on a Perkin–Elmer 500 FT-IR spectrometer. Absorption bands are reported in cm^{-1}. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Bruker-Esquire mass spectrometer. Electronic impact (EI—70 eV), chemical ionization (CI—200 eV) or high-resolution MS experiments were recorded on a JEOL AX 500 mass spectrometer using a mass resolution of 5000. Elemental analyses were performed on a CE Instruments EA 110 CHNS-O instrument. Melting points were measured by Koffler bench and are uncorrected.

4.2. General procedure for the preparation of fluorinated methylketones from mixtures of tetrasubstituted bromofluoroolefins (Table 2)

To a mixture of potassium *tert*-butoxide (2 equiv), ethylvinylether (2 equiv) in anhydrous THF (5 mL/mmol of *t*-BuOK) at −78 °C under argon was added dropwise *n*-BuLi in hexanes (1.6 M, 2 equiv). The mixture was stirred for 30 min at −78 °C and then a solution of dry zinc chloride (4 equiv) in THF (4 mL/mmol of $ZnCl_2$) was added dropwise. After 10 min, the cooling bath was removed and the solution was allowed to warm to room temperature for 30 min. The mixture was then added slowly to a solution of palladium diacetate (0.05 equiv), triphenylphosphine (0.1 equiv) and mixture of tetrasubstituted bromofluoroolefins (1 equiv) in anhydrous THF (10 mL/mmol of bromofluoroolefin) at room temperature under argon. The mixture was stirred for 1 h. After the reaction was completed, controlled by monitoring ^{19}F NMR signal of the reaction mixture, HCl aq (1 N) was added and the mixture was stirred for 15 min. The mixture was then extracted with Et_2O (×3), washed with brine and the combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: cyclohexane/AcOEt), affording tetrasubstituted fluorinated methylketones.

*4.2.1. (Z)- and (E)-1-Fluoro-1-(2,3-dihydronaphthalen-4(1H)-ylidene)propan-2-one: 74/26 (**2a**)*

Orange oil, R_f 0.3 (2% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.7 (0.7H, m, H_Z), 7.5–7.4 (0.3H, m, H_E), 7.2–7.1 (3H, m), 3.0–2.9 (2H, m), 2.7 (1.5H, t, $^4J_{H-F}$=6.2 Hz, H_Z), 2.6–2.5 (0.5H, m, H_E), 2.3 (2.2H, d, $^4J_{H-F}$=6.2 Hz, H_Z), 2.2 (0.8H, d, $^4J_{H-F}$=5.1 Hz, H_E), 1.7–1.5 (2H, m, H_4). ^{19}F NMR dec (282.5 MHz, $CDCl_3$) δ −117.3 (0.3F, F_E), −123.2 (0.7F, F_Z). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.2 (d, $^2J_{C-F}$= 41 Hz, C_Z), 193.1 (d, $^2J_{C-F}$=40 Hz, C_E), 150.5 (d, $^1J_{C-F}$=261 Hz, C_Z), 149.8 (d, $^1J_{C-F}$=261 Hz, C_E), 141.6 (C_Z), 141.1 (C_E), 136.2 (d, $^2J_{C-F}$= 12 Hz, C_Z), 134.9 (d, $^2J_{C-F}$=14 Hz, C_E), 130.9 (C_E), 130.6 (C_Z), 130.4–125.2, 30.4 (C_Z), 29.9 (C_E), 28.6 (C_Z), 28.4 (C_E), 26.4 (C_Z), 26.4 (C_E), 22.6 (C_E), 22.6 (C_Z). MS (EI) 204 (M^+), 199 (M^+-CH_3), 176 (M^+-CO), 161 (M^+-CH_3CO), 146, 43 (CH_3CO^+). IR (neat) 3061, 2937, 1712, 1689, 1596, 1453, 1357, 1287, 1252, 1984, 763.

*4.2.2. (Z)- and (E)-3-Fluoro-4-(naphthalen-6-yl)pent-3-en-2-one: 63/37 (**2b**)*

Yellow oil, R_f 0.3 (2% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.7 (4H, m), 7.4–7.2 (3H, m), 2.4 (1.9H, d, $^4J_{H-F}$=3.8 Hz, H_Z), 2.3 (1.1H, d, $^4J_{H-F}$=5.9 Hz, H_Z), 2.1 (1.1H, d, $^4J_{H-F}$=4.6 Hz, H_E), 2.0 (1.9H, d, $^4J_{H-F}$=3.8, H_E). ^{19}F NMR dec (282.5 MHz, $CDCl_3$) δ −119.6 (0.4F, F_E), −122.4 (0.6F, F_Z). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.4 (d, $^2J_{C-F}$=41 Hz, C_Z), 192.2 (d, $^2J_{C-F}$=34 Hz, C_E), 151.7 (d, $^1J_{C-F}$=255 Hz, C_E), 150.6 (d, $^1J_{C-F}$=255 Hz, C_Z), 136.1–126.1 ($10C^{Arom}_{Z\&E}$), 131.7 (d, $^2J_{C-F}$=11 Hz, C_Z), 130.5 (d, $^2J_{C-F}$=10 Hz, C_E), 28.9 (C_E), 28.6 (C_Z), 20.1 (C_E), 18.5 (C_Z). MS (EI) 228 (M^+), 213 (M^+-CH_3), 183, 165, 43 (CH_3CO^+). IR (neat) 3057, 3017, 2924, 1697, 1613, 1422, 1358, 1254, 1120, 962, 859, 819, 748, 588, 477. Anal. Calcd for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 78.85; H, 5.61.

*4.2.3. 1-(1-Benzylpiperidin-4-ylidene)-1-fluoropropan-2-one (**2c**)*

Note: quenching with $NaHCO_3$ 5% aq instead of HCl. Brown oil, R_f 0.3 (20% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2–7.1 (5H,

m), 3.4 (2H, s), 2.9–2.8 (2H, m), 2.4–2.3 (6H, m), 2.2 (3H, d, $^4J_{H-F}$=5.6 Hz). ^{19}F NMR dec (282.5 MHz, $CDCl_3$) δ −126.7. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.0 (d, $^2J_{C-F}$=40 Hz), 149.0 (d, $^1J_{C-F}$=249 Hz), 138.5, 131.4 (d, $^2J_{C-F}$=14 Hz), 129.5, 128.7, 127.5, 63.7, 54.2, 53.6, 28.6, 27.2 (d, $^3J_{C-F}$=2 Hz). MS (EI) 247 (M^+), 227, 204 (M^+-CH_3CO), 91 ($PhCH_2^+$), 43 (CH_3CO^+). IR (neat) 3028, 2907, 2801, 2760, 1701, 1639, 1454, 1422, 1358, 1280, 1214, 1100, 970, 741, 698, 585. Anal. Calcd for $C_{15}H_{18}FNO$: C, 72.85; H, 7.34; N, 5.66. Found: C, 72.41; H, 7.19; N, 5.55.

*4.2.4. 1-(1,5-Diphenyl-3-pentylidene)-1-fluoropropan-2-one (**2d**)*

Yellow oil, R_f 0.3 (2% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.0 (10H, m), 2.8–2.5 (6H, m), 2.5–2.3 (2H, m), 2.1 (3H, d, $^4J_{H-F}$=5.6 Hz). ^{19}F NMR dec (282.5 MHz, $CDCl_3$) δ −123.5. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 194.2 (d, $^2J_{C-F}$=41 Hz), 152.2 (d, $^1J_{C-F}$=252 Hz), 141.8–141.4 (2C), 134.6 (d, $^2J_{C-F}$=12 Hz), 129.0–128.8 (4C), 126.7–126.5 (2C), 35.1 (d, $^4J_{C-F}$=4 Hz), 34.2 (d, $^4J_{C-F}$=2 Hz), 33.3 (d, $^3J_{C-F}$=8 Hz), 32.9 (d, $^3J_{C-F}$=3 Hz), 28.4 (d, $^3J_{C-F}$=2 Hz). MS (EI) 296 (M^+), 281 (M^+-CH_3), 191 ($M^+-PhCH_2CH_2$), 91 ($PhCH_2^+$), 43 (CH_3CO^+). IR (neat) 3085, 3062, 3027, 2928, 2861, 1698, 1633, 1604, 1495, 1454, 1350, 1267, 1221, 1178, 1099, 1074, 749, 699, 581, 550. Anal. Calcd for $C_{20}H_{21}FO$: C, 81.05; H, 7.14. Found: C, 80.86; H, 6.93.

*4.2.5. (Z)- and (E)-1-[2-(tert-Butyldiphenylsilyloxymethyl)-cyclopentylidene]-1-fluoropropan-2-one: 59/41 (**2e**)*

Yellow oil, R_f 0.4 (2% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6–7.5 (4H, m), 7.3–7.2 (6H, m), 3.7–3.4 (2.6H, br m), 3.1–3.0 (0.6H, m, H_Z), 2.6 (1H, m, H_Z), 2.4 (1H, m, H_E), 2.1 (3H, d, $^4J_{H-F}$=5.3 Hz, H_{15}), 1.9–1.6 (4H, br m), 1.0 (9H, s). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −119.2 (0.4F, m, F_E), −123.6 (0.6F, m, F_Z). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 192.2 (d, $^2J_{C-F}$=41 Hz, C_Z), 191.7 (d, $^2J_{C-F}$=40 Hz, C_E), 148.6 (d, $^1J_{C-F}$=251 Hz, C_Z), 148.5 (d, $^1J_{C-F}$=251 Hz, C_E), 139.3 (d, $^2J_{C-F}$=14 Hz, C_E), 138.5 (d, $^2J_{C-F}$=13 Hz, C_Z), 134.6 (2C), 132.6, 128.6–128.5 (2C), 126.6–126.5 (2C), 63.3 (C_E), 62.8 (C_Z), 44.8 (C_Z), 43.3 (C_E), 30.3 (C_Z), 29.3 (C_E), 28.7 (C_E), 27.5 (C_Z), 26.3, 25.8, 23.8 (C_Z), 21.7 (C_E), 18.2. MS (EI) 353 (M^+-t-Bu), 201, 199 (M^+−TBDPS), 181, 135, 91, 77 (Ph^+), 57 (t-Bu^+). IR (neat) 3072, 2968, 2930, 1702, 1638, 1477, 1428, 1382, 1277, 1089, 1049, 881, 703, 505. Anal. Calcd for $C_{25}H_{31}FO_2Si$: C, 73.13; H, 7.61. Found: C, 73.48; H, 7.25.

4.3. Preparation of fluorinated benzylketone 3 (Table 3)

To a mixture of potassium *tert*-butoxide (4 equiv), 1-(2-ethoxyvinyl)benzene (4 equiv) in anhydrous THF (5 mL/mmol of *t*-BuOK) at −78 °C under argon was added dropwise *n*-BuLi in hexanes (1.6 M, 4 equiv). The mixture was stirred for 30 min at −78 °C and then a solution of dry zinc chloride (8 equiv) in THF (4 mL/mmol of $ZnCl_2$) was added dropwise. After 10 min, the cooling bath was removed and the solution was allowed to warm to room temperature for 30 min. The mixture was then added slowly to a solution of palladium diacetate (0.05 equiv), triphenylphosphine (0.1 equiv) and mixture of tetrasubstituted bromofluoroolefin (1 equiv) in anhydrous THF (10 mL/mmol of bromofluoroolefin) at room temperature under argon. The mixture was stirred for 1 h. After the coupling reaction was completed, controlled by monitoring ^{19}F NMR signal of the reaction mixture, HCl aq (6 N) was added and the mixture was stirred at 70 °C for another hour. After cooling to room temperature, the mixture was then extracted with Et_2O (×3), washed with brine and the combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: 2% AcOEt in cyclohexane), affording the mixture of fluorinated benzylketones.

*4.3.1. (Z) and (E) 1-Fluoro-1-(2,3-dihydronaphthalen-4(1H)-ylidene)-3-phenylpropan-2-one: 88/12 (**3**)*

Yellow oil, R_f 0.5 (5% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (0.9H, m, H_Z), 7.4–7.0 (8.1H, m), 3.9 (1.8H, d, $^4J_{H-F}$=4.9 Hz, H_Z), 3.8 (0.2H, d, $^4J_{H-F}$=4.1 Hz, H_E), 3.0–2.9 (1.8H, m, H_Z), 2.8 (0.2H, m, H_E), 2.7–2.5 (2H, m), 1.8–1.5 (2H,m). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −118.6 (0.1F, m, F_E), −125.2 (0.9F, m, F_Z). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 194.8 (d, $^2J_{C-F}$=32 Hz), 157.0 (d, $^1J_{C-F}$=278 Hz), 141.9, 134.2, 131.2, 130.9–125.6 (8C), 113.9 (d, $^2J_{C-F}$=11 Hz), 47.6 (C_E), 47.4 (C_Z), 30.6 (C_Z), 30.2 (C_E), 26.8 (C_Z), 26.3 (C_E), 23.0 (C_E), 22.8 (C_Z). MS (EI) 280 (M^+), 189 (M^+-CH_2Ph), 146, 91 ($PhCH_2^+$). IR (neat) 3062, 3029, 2936, 2869, 1727, 1694, 1582, 1495, 1454, 1308, 1289, 1184, 1101, 1029, 764, 743, 697. Anal. Calcd for $C_{19}H_{17}FO$: C, 81.40; H, 6.11. Found: C, 81.49; H, 6.28.

4.4. Preparation of fluorinated propylketone 4 (Table 3)

To a mixture of potassium *tert*-butoxide (4 equiv), butenylethylether (4 equiv) in anhydrous THF (5 mL/mmol of *t*-BuOK) at −78 °C under argon was added dropwise *n*-BuLi in hexanes (1.6 M, 4 equiv). The mixture was stirred for 30 min at −78 °C and then a solution of dry zinc chloride (8 equiv) in THF (4 mL/mmol of $ZnCl_2$) was added dropwise. After 10 min, the cooling bath was removed and the solution was allowed to warm to room temperature for 30 min. The mixture was then added slowly to a solution of palladium diacetate (0.05 equiv), triphenylphosphine (0.1 equiv) and mixture of tetrasubstituted bromofluoroolefin (1 equiv) in anhydrous THF (10 mL/mmol of bromofluoroolefin) at room temperature under argon. The mixture was stirred for 1 h. After the reaction was completed, controlled by monitoring ^{19}F NMR signal of the reaction mixture, HCl aq (1 N) was added and the mixture was stirred for 15 min. The mixture was then extracted with Et_2O (×3), washed with brine and the combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: cyclohexane/AcOEt), affording the mixture of fluorinated propylketones.

*4.4.1. (Z) and (E) 1-Fluoro-1-(2,3-dihydronaphthalen-4(1H)-ylidene)pentan-2-one: 73/27 (**4**)*

Yellow oil, R_f 0.5 (5% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.7 (0.7H, m, H_Z), 7.4–7.3 (0.3H, m, H_E), 7.2–7.0 (3H, m), 3.0 (1.4H, td, $^3J_{H-H}$=6.7 Hz, $^4J_{H-F}$=2.7 Hz, H_Z), 2.7–2.5 (4.6H, m), 1.8–1.7 (2H, m), 1.7–1.5 (2H, m), 0.9–0.8 (3H, m). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −119.4 (0.3F, m, F_E), −125.8 (0.7F, m, F_Z). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.7 (d, $^2J_{C-F}$=39 Hz, C_Z), 195.4 (d, $^2J_{C-F}$=37 Hz, C_E), 150.6 (d, $^1J_{C-F}$=253 Hz, C_E), 149.8 (d, $^1J_{C-F}$=261 Hz, C_Z), 141.5 (C_Z), 140.8 (d, J=4 Hz, C_E), 131.1, 130.4 (d, J=18 Hz, C_Z), 130.1 (C_E), 129.4 (C_E), 129.2 (C_Z), 128.7 (C_Z), 127.7 (C_E), 127.6 (d, $^2J_{C-F}$=4 Hz), 126.0 (C_Z), 125.2 (C_E), 42.4(C_E), 42.2 (C_Z), 30.4 (C_Z), 29.9 (C_E), 26.3 (C_Z), 25.4 (d, $^3J_{C-F}$=9 Hz, C_E), 22.6 (C_Z), 21.2 (C_E), 17.2 (C_E), 17.1 (C_Z), 13.9. MS (EI) 232 (M^+), 203 ($M^+-CH_3CH_2$), 189 ($M^+-CH_3CH_2CH_2$), 146, 141, 133. IR (neat) 3063, 3021, 2961, 2874, 1692, 1608, 1585, 1482, 1454, 1308, 1196, 1101, 1023, 764, 744. Anal. Calcd for $C_{15}H_{17}FO$: C, 77.56; H, 7.38. Found: C, 77.96; H, 7.46.

4.5. Preparation of fluorinated dihydrodioxines 5 (Table 3)

To 1,4-diox-2-ene (4 equiv) in anhydrous THF (5 mL/mmol of enol ether) at −30 °C under argon was added dropwise *t*-BuLi in hexanes (1.6 M, 4 equiv). The mixture was stirred for 1 h at −20 °C and then a solution of dry zinc chloride (8 equiv) in THF (4 mL/mmol of $ZnCl_2$) was added dropwise at −20 °C. After 10 min, the cooling bath was removed and the solution was allowed to warm to room temperature for 30 min. The mixture was then added slowly to a solution of palladium diacetate (0.05 equiv), triphenylphosphine (0.1 equiv) and mixture of tetrasubstituted bromofluoroolefin (1 equiv) in anhydrous THF (10 mL/mmol of bromofluoroolefin) at room temperature under argon. The mixture was stirred for 1 h. After the coupling reaction was completed, controlled by monitoring ^{19}F NMR signal of the reaction mixture, NH_4Cl aq (satd) was added and the mixture was stirred for 5 min. The mixture was then extracted with Et_2O (×3), washed with

brine and the combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on basic alumina (eluent: cyclohexane), affording the mixture of fluorinated dihydrodioxines.

*4.5.1. (Z) and (E) 5-(Fluoro(2,3-dihydronaphthalen-4(1H)-ylidene)methyl)–2,3–dihydro-1,4-dioxene: 69/31 (**5**)*

Yellow oil, R_f 0.3 (cyclohexane, *aluminium oxide neutral*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.7 (0.7H, m, H_Z), 7.3 (0.3H, m, H_E), 7.2–7.0 (3H, m), 6.3 (0.7H, d, $^4J_{H-F}$=1.0 Hz, H_Z), 6.2 (0.3H, d, $^4J_{H-F}$=2.6 Hz, H_E), 4.1–4.0 (4H, m), 2.7 (1.4H, m, H_Z), 2.6 (0.6H, m, H_E), 2.5 (2H, m), 1.8–1.6 (2H, m). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −108.3 (0.3F, m, F_E), −117.7 (0.7F, m, F_Z). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.1 (d, $^1J_{C-F}$= 241 Hz, C_E), 150.7 (d, $^1J_{C-F}$=248 Hz, C_Z), 139.5 (d, J=6 Hz, C_Z), 138.6 (C_E), 133.0 (d, J=6 Hz, C_E), 132.8 (C_Z), 131.6 (d, $^2J_{C-F}$=34 Hz, C_E), 131.4 (d, $^2J_{C-F}$=34 Hz, C_Z), 130.5–130.3 (2C), 130.0 (d, J=16 Hz, C_Z), 129.2, 128.6 (d, J=32 Hz, C_E), 127.6 (C_Z), 127.4 (C_E), 126.0 (C_Z), 125.4 (C_E), 119.7 (d, $^2J_{C-F}$=24 Hz, C_E), 117.0 (d, $^2J_{C-F}$=9 Hz, C_Z), 64.6, 64.5, 64.4, 64.2, 30.5, 27.4 (C_Z), 24.6 (d, $^3J_{C-F}$=6 Hz, C_E), 24.0 (C_Z), 22.8 (C_E). MS (EI) 246 (M^+), 187, 159, 146, 141, 133. IR (neat) 3098, 3062, 2933, 2874, 1727, 1651, 1484, 1454, 1314, 1263, 1159, 1097, 1050, 919, 764. Anal. Calcd for $C_{15}H_{15}FO_2$: C, 73.15; H, 6.14. Found: C, 72.27; H, 5.75.

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