A Rapid Access to New Fluorinated 1,3-Dienes and Benzylic Fluorides via Metathesis on Propargylic Fluorides

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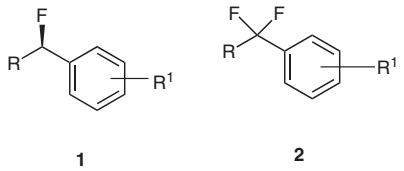
This publication is dedicated to the memory of Dr. Charles Mioskowski (1946–2007), a superb chemist and a wonderful friend.

Abstract: The cross enyne metathesis reaction of propargylic fluoride (+)-**12** with ethylene affords the enantioenriched 1,3-diene (+)-**14** having fluorine-containing side chain at 2-position in good yield. Upon Diels–Alder reaction, followed by aromatization, this diene affords the new benzylic fluorides (+)-**16** and (+)-**17** in high ee values. This new strategy has been successfully extended to the corresponding *gem*-difluoro diene **21** and benzylic fluorides **23** and **24**.

Key words: dehydroxyfluorination, enyne metathesis, Diels–Alder reaction, aromatization, benzylic fluorides

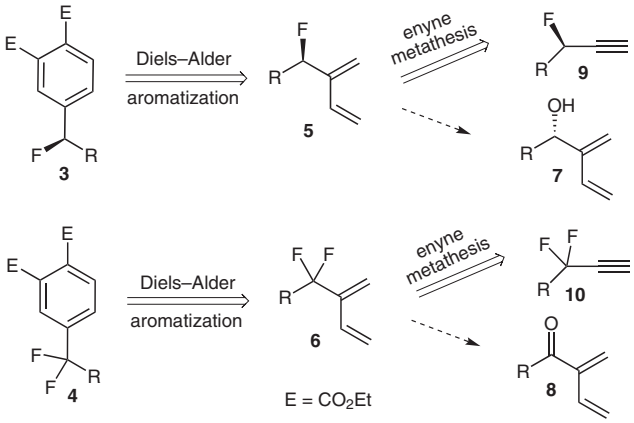
The presence of fluorine atom(s) in organic molecules is known to modify their physical, chemical and biological properties significantly.[1] Due to this, introduction of fluorine atom(s), especially by the selective replacement of C–H or C–OH bonds by C–F bonds is an important transformation practiced routinely in bioorganic and medicinal chemistry.[2] Furthermore, the stereoselective installation of fluorine is still a challenging task when optically active fluorides are required and it is worth mentioning that efforts are always on to synthesize new chiral fluorinated molecules.[3] Nevertheless, introduction of fluorine stereoselectively at positions vicinal to π-systems happens to be a tedious task,[4] and this is the case in particular for benzylic fluorides, such as shown in Figure 1, which are attractive target molecules in life and material sciences.



1 2

Figure 1 Targeted benzylic fluorides

This challenge could perhaps be circumvented if there is an efficient method to synthesize 1,3-dienes like **5** and **6** which then can undergo Diels–Alder reaction and aromatization to afford benzylic fluorides **3** and **4** (Scheme 1). Unfortunately, though it is known that the 1,3-butadien-2-ylmethanols like **7**, could be conveniently prepared in optically active form[5] their dehydroxyfluorination reaction seems to be extremely challenging, especially in terms of regio- and stereocontrol.



Scheme 1 Retrosynthetic analysis for benzylic fluorides **3** and **4** and dienes **5** and **6**

In fact, it is well established that the dehydroxyfluorination reaction of allylic alcohols occurs usually with isomerization and racemization.[6] An alternative possibility would be to use the stereodirecting effect of diene-tricarbonyl iron complexes during dehydroxyfluorination.[7] However, the iron complexes corresponding to 1,3-butadien-2-ylmethanols are available in optically active form only after tedious resolution processes.[8] On the other hand, synthesis of type **6** dienes would be also very challenging, especially if one considers the *gem*-difluorination of the corresponding 1,3-dien-2-ones.[8] First of all, such derivatives are known to be unstable, prone to dimerization processes,[9] and isolated mostly as the corresponding iron-tricarbonyl complexes.[8] Moreover the *gem*-difluorination of enones is known to be very challenging and the desired compounds are obtained only in very poor yields, except when using ultra high pressure reaction conditions.[10]

In view of the importance of the benzylic fluorides and our efforts to develop efficient synthesis of novel fluorinated key intermediates[11] which could act as useful building blocks, we became interested in designing a new

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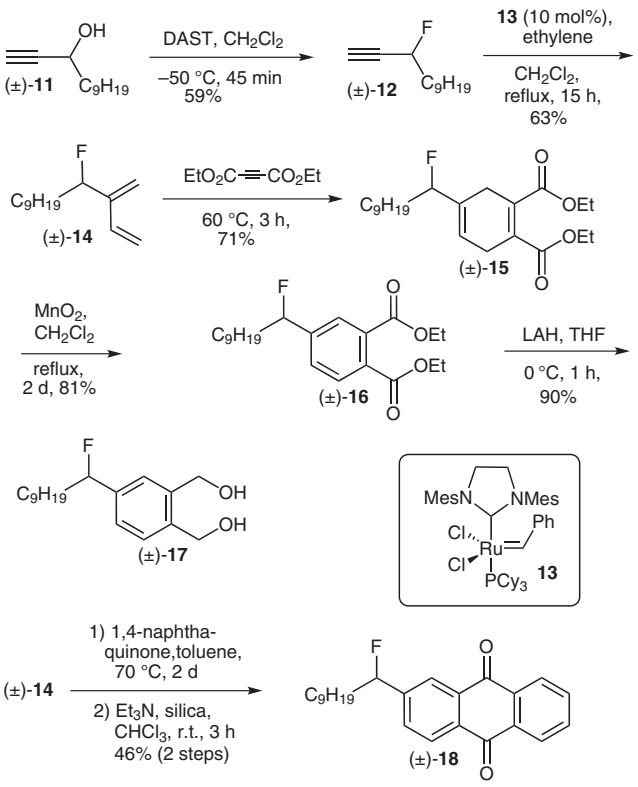
strategy for these benzylic fluorides. While various new approaches were evaluated, it occurred to us that based on our earlier work,[12] dienes of type **5** and **6** could be synthesized easily starting from alkynes **9** and **10** via cross enyne metathesis with ethylene (Scheme 1). Herein, we report a rapid access to these new 1,3-dienes with the fluorine-containing side chain at 2-position using enyne cross-metathesis reaction,[12] and then to the corresponding benzylic fluorides through a Diels–Alder-aromatization sequence. The purpose of this publication is to demonstrate that this strategy offers a short and efficient route to such monofluorinated molecules, including in optically active form, and extension to corresponding *gem*-difluorinated derivatives has been also demonstrated.

The cross enyne metathesis reaction has been found to be very fruitful for the preparation of new 1,3-dienes, of much use later on in synthesis.[13] Furthermore, this reaction was found to be compatible with heteroatoms in propargylic position including free, or protected alcohols.[12,14] However, to the best of our knowledge, except in a very recent paper and in the intramolecular mode,[15] this reaction has never been used starting from propargylic fluorides. To demonstrate our strategy the known propargylic fluoride **12** (Scheme 2) has been selected as a model compound for these studies since it is easily accessible, including in optically active form, by diethylaminosulfur trifluoride (DAST) mediated dehydroxyfluorination of the corresponding propargylic alcohol **11**.[16]

The cross-metathesis reaction of (±)-**12** with ethylene (1 atm) in the presence of 10 mol% Grubbs II catalyst **13** in refluxing dichloromethane afforded the desired diene (±)-**14** in 63% yield (Scheme 2). This compound was isolated by chromatography on SiO_2 and characterized by its spectral and analytical data. It was then subjected to a Diels–Alder reaction with diethyl acetylenedicarboxylate to obtain the cyclohexadiene (±)-**15** in 71% yield. Aromatization was performed by using a suspension of MnO_2 in refluxing dichloromethane affording the desired benzylic fluoride (±)-**16** in 81% yield [21% overall yield from alcohol (±)-**11**]. Reduction by $LiAlH_4$ was compatible with the fluoride in benzylic position affording the corresponding diol (±)-**17**. By using naphthaquinone as dienophile, a similar series of reactions (cycloaddition followed by aromatization) yielded the new benzylic fluoride (±)-**18** in 17% overall yield from alcohol (±)-**11** (Scheme 2).

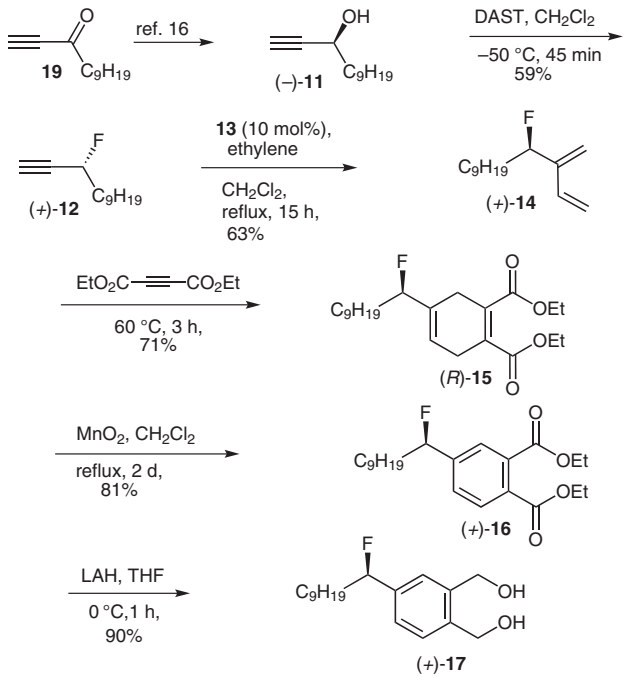


Scheme 2 Synthesis and reactions of diene (±)-**14**

It is important to note that this strategy is complementary to a previous work involving Diels–Alder reactions performed on electrophilic propargylic fluorides.[17] The substitution pattern of the groups on the aromatic ring are different in the two processes. Taking into account the challenges of preparing optically active benzylic fluorides,[17,18] the next key issue was the extension of this strategy to enantioenriched compounds. For that purpose, the (*S*)-propargylic alcohol (–)-**11** was prepared in 88% ee (determined through the NMR analysis of the corresponding Mandelic esters) by asymmetric reduction of ketone **19** using (*S*)-alpine borane (Scheme 3). The *R* fluoride (+)-**12** was obtained through the DAST-mediated dehydroxyfluorination of (–)-**11**.[16a] The corresponding diene (+)-**14** was synthesized by the enyne cross-metathesis reaction. Using the same sequence of reactions as described previously in racemic series, the cycloadduct **15** and the benzylic fluorides (+)-**16** and (+)-**17** were obtained. For the latter derivative, a 84% ee value was measured by chiral HPLC analysis.[19] Therefore, this complete sequence of reactions, starting from enantioenriched propargylic alcohol (–)-**11** up to (+)-**17**, occurs with very little loss (≤4%) of optical purity and validates this new strategy (Scheme 3).

It is worth mentioning that type **14** fluorinated dienes, easily synthesized in a few steps by this route, appear very difficult to obtain by alternative methods. The extension of this strategy to corresponding *gem*-difluorodienes was also of interest. The *gem*-difluoropropargylic derivative **20** was easily obtained in 72% yield by reaction of DAST with ketone **19** (Scheme 4).

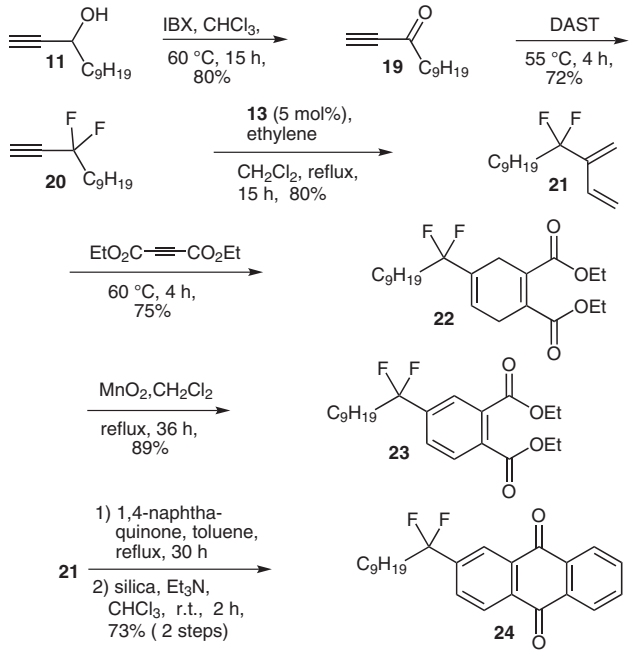
Using again Grubbs II catalyst **13** (at 5 mol%) the enyne cross-metathesis reaction afforded the desired diene **21** in 80% yield (Scheme 4). This intermediate was purified by chromatography on silica gel chromatography and characterized by the spectral and analytical data. Diels–Alder reaction of **21** with diethyl acetylenedicarboxylate gave the cyclohexadiene **22** in 75% yield. Aromatization using a suspension of MnO_2 in refluxing dichloromethane afforded the desired benzylic *gem*-difluoride **23** in 89% yield (31% overall yield from alcohol **11**). In the same way, by using naphthaquinone as dienophile, the condensed system **24** was obtained (34% overall yield from alcohol **11**). Therefore, in the case of these *gem*-difluoro-



Scheme 3 Synthesis and reactions of diene (+)-**14**

dienes, the route through the propargylic fluorides is again highly advantageous (Scheme 4).

In conclusion, we have demonstrated that the enyne cross-metathesis reaction is compatible with propargylic monofluorides, affording directly and efficiently the desired 1,3-dienes including in optically active form.[20–23] Such dienes are excellent starting material for the preparation of new enantioenriched benzylic fluorides through a Diels–Alder aromatization sequence. This route was successfully extended to synthesize the corresponding *gem*-difluorinated dienes and their benzylic derivatives using the same Diels–Alder aromatization sequence.



Scheme 4 Synthesis and reactions of diene **21**

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References and Notes

(1) (a) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Gordon and Breach Science Publishers: Tokyo, **1998**. (b) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II: A Critical Review, ACS Monograph 187*; American Chemical Society: Washington DC, **1995**. (c) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum: New York, **1994**, Chap. 3, 57–88; and references therein.

(2) (a) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers in Fluorine Chemistry, ACS Symposium Series 639*; American Chemical Society: Washington DC, **1996**. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley Interscience: New York, **1991**. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; and references therein.

(3) For recent examples, see: (a) Thibaudeau, S.; Fuller, R.; Gouverneur, V. *Org. Biomol. Chem.* **2004**, *2*, 1110. (b) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422. (c) Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7887.

(4) See for instance: Prakesch, M.; Grée, D.; Grée, R. In *Fluorine-Containing Synthons, ACS Symposium Series 911*; Soloshonok, V. A., Ed.; American Chemical Society: Washington DC, **2005**, 173; and references therein.

(5) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100.

(6) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) De Jonghe, S.; Van Overmeire, I.; Poulton, S.; Hendrix, C.; Busson, R.; Van Calenbergh, S.; De Keukeleire, D.; Spiegel, S.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3175.

(7) Grée, D. M.; Kermarrec, C. J. M.; Martelli, J. T.; Grée, R. L.; Lellouche, J. P.; Toupet, L. J. *J. Org. Chem.* **1996**, *61*, 1918.

(8) Franck-Neumann, M.; Martina, D.; Heitz, M. P. *J. Organomet. Chem.* **1986**, *301*, 61.

(9) Hoffmann, H. M. R.; Eggert, U.; Poly, W. *Angew. Chem. Int. Ed.* **1987**, *26*, 1015.

(10) (a) McClinton, M. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2149. (b) Box, J. M.; Harwood, L. M.; Whitehead, R. C. *Synlett* **1997**, 571. (c) Ohba, T.; Ikeda, E.; Takei, H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1875; and references therein.

(11) See, for example: (a) Prakesch, M.; Grée, D.; Grée, R. *Acc. Chem. Res.* **2002**, *35*, 175. (b) Prakesch, M.; Kerouredan, E.; Grée, D.; Grée, R.; De Chancie, J.; Houk, K. N. *J. Fluorine Chem.* **2004**, *125*, 537. (c) Manthati, V.; Grée, D.; Grée, R. *Eur. J. Org. Chem.* **2005**, 3825. (d) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Tetrahedron Lett.* **2007**, *48*, 5305. (e) Blayo, A.-L.; Le Meur, S.; Grée, D.; Grée, R. *Adv. Synth. Catal.* **2008**, *350*, 471.

(12) (a) Kaliappan, K. P.; Ravikumar, V. *Org. Biomol. Chem.* **2005**, *3*, 848. (b) Kaliappan, K. P.; Ravikumar, V.; Pujari, S. A. *Tetrahedron Lett.* **2006**, *47*, 981. (c) Kaliappan, K. P.; Subrahmanyam, A. V. *Org. Lett.* **2007**, *9*, 1121. (d) Kaliappan, K. P.; Ravikumar, V. *Synlett* **2007**, 977.

(13) For enyne cross-metathesis reactions with ethylene, see: (a) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788. (b) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271. (c) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235. (d) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793.

(14) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271.

(15) Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656.

(16) (a) Madiot, V.; Lesot, P.; Grée, D.; Courtieu, J.; Grée, R. *Chem. Commun.* **2000**, 169. (b) Filmon, J.; Grée, D.; Grée, R. *J. Fluorine Chem.* **2001**, *107*, 271.

(17) Grée, D.; Grée, R. *Tetrahedron Lett.* **2007**, *48*, 5435; and references therein.

(18) Sai Krishna Murthy, A.; Tardivel, R.; Grée, R. In *Science of Synthesis*, Vol. 34; Percy, J. M., Ed.; Thieme: Stuttgart, **2006**, 295–317.

(19) All our attempts to measure the ee values of the intermediates (+)-**14** and (+)-**15** by NMR in the presence of chiral shift reagents or by chiral HPLC have been unsuccessful so far. This is a well known problem for such chiral monofluorinated molecules, see for instance ref 16a.

(20) **General Procedure for Cross Enyne Metathesis**: A solution of propargyl fluoride (1 mmol) in degassed CH_2Cl_2 (10 mL) was purged with ethylene and treated with the Grubbs II catalyst **13** (5 or 10 mol%). The reaction mixture was refluxed for 15 h under ethylene atmosphere. After being cooled to r.t., the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to afford the fluorodiene. Spectral data for diene (+)-**14**: R_f 0.71 (pentane); $[\alpha]_D^{20}$ 8.0 (c = 0.2, $CHCl_3$). IR (neat): 2927, 1966, 1650, 1456, 1216, 1023, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.28–6.38 (m, 1 H, H2), 5.05–5.31 (m, 5 H, 2 × =CH_2, CHF), 1.28–1.52 (m, 14 H, 7 × CH_2), 1.72–1.83 (m, 2 H, CH_2), 0.90 (t, J = 6.6 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1 (d, J = 17.5 Hz, C3), 135.3 (d, J = 3.9 Hz, C2), 115.0 (d, J = 10.5 Hz, C14), 114.7 (C1), 92.1 (d, J = 171.5 Hz, C4), 34.7 (d, J = 22.6 Hz, CH_2CHF), 31.9, 29.5, 29.4, 29.3, 25.1(d, J = 3.5 Hz), 22.7 (6 × d, J = 3.5 Hz, 6 × CH_2), 14.1 (Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –181.9 (dt, J_{H-F} = 48.7, 23.6 Hz). HRMS: m/z $[M]^+$ calcd for $C_{14}H_{25}F$: 212.1940; found: 212.1933. Spectral data for diene **21**: R_f 0.91 (pentane). IR (neat): 2955, 2927, 2855, 1682, 1596, 1467, 1174, 1087, 1004 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.27 (dd, J = 17.7, 11.3 Hz, 1 H, H2), 5.53 (dd, J = 17.7, 1.3 Hz, 1 H, H1), 5.44 (d, J = 5.5 Hz, 2 H, H14), 5.23 (d, J = 11.3 Hz, 1 H, H1), 1.91–2.07 (m, 2 H, CH_2), 1.22–1.45 (m, 14 H, 7 × CH_2), 0.91 (t, J = 6.8 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5 (t, J = 24.2 Hz, C3), 132.6 (t, J = 2.8 Hz, C2), 122.4 (t, J = 242.4 Hz, C4), 117.3 (t, J = 1.4 Hz, C1), 116.3 (t, J = 9.5 Hz, C14), 36.5 (t, J = 26.1 Hz, CH_2CF_2), 31.8, 29.4, 29.3, 29.27, 29.23, 22.6, 22.3 (t, J = 4.3 Hz), 14.1 (Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –97.44 (t, J_{H-F} = 16.6 Hz). HRMS: m/z $[M]^+$ calcd for $C_{14}H_{24}F_2$: 230.1846; found: 230.1846.

(21) **General Procedure for Diels–Alder Reaction with Diethyl Acetylenedicarboxylate Followed by Aromatization**: A mixture of diene (1 mmol) and diethyl acetylenedicarboxylate (1.2 mmol) was heated at 60 °C in an oil bath for 3 h. After bringing the mixture to r.t., the crude material was purified by silica gel column chromatography to give the cycloadduct. To a solution of the above cycloadduct (1 mmol) in CH_2Cl_2 (40 mL) was added MnO_2 (10 mmol) and the mixture was refluxed for 2 d. After being cooled to r.t., the reaction mixture was passed through a small pad of celite and the filtrate was concentrated and purified by flash column chromatography on silica gel to afford the corresponding aromatized product.

(22) **General Procedure for One-Pot Diels–Alder Reaction with 1,4-Naphthaquinone and Aromatization**: A solution of diene (1 mmol) in anhyd toluene (15 mL) was treated with 1,4-naphthaquinone (1.2 mmol) and the resulting mixture was heated at 70 °C for 2 d. The solvent was removed and the crude product was dissolved in $CHCl_3$ (4 mL). To this solution silica gel purged in Et_3N (2 g) was added and the mixture was stirred for another 3 h at r.t. The reaction mixture was concentrated and the crude material was purified by column chromatography to afford the corresponding aromatized adducts.

(23) Spectral data for selected compounds: Compound (+)-**16**: R_f 0.30 (pentane–Et_2O, 9:1); $[\alpha]_D^{20}$ 14.8 (c = 0.2, $CHCl_3$). IR (neat): 3020, 1966, 1731, 1650, 1216, 1045, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.0 Hz, 1 H, H6), 7.65 (s, 1 H, H3), 7.49 (dd, J = 8.0, 1.6 Hz, 1 H, H5), 5.55 (ddd, J = 47.7, 8.0, 4.7 Hz, 1 H, CHF), 4.35–4.43 (m, 4 H, 2 × CH_2), 1.87–1.91 (m, 2 H, CH_2), 1.19–1.44 (m, 20 H, 7 × CH_2, 2 × Me), 0.89 (t, J = 6.4 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5 ($COOCH_2$), 167.2 ($COOCH_2$), 144.1 (d, J = 20.6 Hz, C4), 132.6, 131.6 (d, J = 1.4 Hz), 129.2, 127.6 (d, J = 7.4 Hz, C_{Ar}), 125.7 (d, J = 7.6 Hz, C_{Ar}), 92.9 (d, J = 173.2 Hz, CHF), 61.7 (OEt), 61.6 (OEt), 37.2 (d, J = 22.9 Hz, CH_2CHF), 31.8, 29.5, 29.4, 29.3, 29.2, 24.8 (d, J = 3.9 Hz), 22.7 (7 × d, J = 3.9 Hz, 7 × CH_2), 14.2, 14.1 (2 × Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.9 (ddd, J_{H-F} = 47.5, 28.9, 18.8 Hz). HRMS: m/z $[M]^+$ calcd for $C_{22}H_{33}O_4F$: 380.2362; found: 380.2381. Compound **17**: R_f 0.28 (pentane–Et_2O, 7:3); mp 65–67 °C; $[\alpha]_D^{20}$ 3.0 (c = 0.2, $CHCl_3$). IR (KBr): 3430, 3019, 1653, 1215, 1045 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.38 (m, 3 H, H_{Ar}), 5.43 (ddd, J = 47.8, 8.0, 4.9 Hz, 1 H, CHF), 4.74 (s, 2 H, CH_2OH), 4.73 (s, 2 H, CH_2OH), 3.67 (br s, 2 H, OH), 1.37–1.97 (m, 2 H, CH_2), 1.09–1.22 (m, 14 H, 7 × CH_2), 0.89 (t, J = 6.9 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9 (d, J = 19.9 Hz, C4), 139.6, 139.2 (d, J = 2.0 Hz), 129.7, 126.7 (d, J = 6.6 Hz, C_{Ar}), 125.5 (d, J = 6.8 Hz, C_{Ar}), 94.4 (d, J = 170.3 Hz, CHF), 63.8 (CH_2OH), 63.6 (CH_2OH), 37.2 (d, J = 23.4 Hz, CH_2CHF), 31.8, 29.5, 29.4, 29.3, 29.2, 25.1, 22.7 (d, J = 4.2 Hz), 14.1 (Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –174.64 (ddd, J_{H-F} = 46.7, 29.6, 17.9 Hz). HRMS: m/z $[M - F]^+$ calcd for $C_{18}H_{29}O_2$: 277.2167; found: 277.2178. Chiral HPLC analysis: column Chiralpack AD, eluent: hexane–EtOH, 98:2; flow rate: 1 mL/min; UV detection at λ = 225 nm; t_R(**17**) = 16.8 min; t_R (*ent*-**17**) = 19 min. Compound **18**: R_f 0.70 (pentane–Et_2O, 9:1); mp 99–101 °C. IR (KBr): 2919, 2849, 1676, 1593, 1351, 1290, 1156, 1021 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.30–8.35 (m, 2 H, H_{Ar}), 8.24 (s, 1 H, H_{Ar}), 7.28–7.85 (m, 4 H, H_{Ar}), 5.62 (ddd, J = 47.7, 7.9, 4.8 Hz, 1 H, CHF), 1.89–2.02 (m, 2 H, CH_2), 1.22–1.52 (m, 14 H, 7 × CH_2), 0.88 (t, J = 7.0 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9 ($COOCH_2$), 182.7 ($COOCH_2$), 147.3 (d, J = 20.5 Hz, C_{Ar}), 134.2, 134.1, 133.6, 133.5, 133.1 (d, J = 1.4 Hz), 130.7 (d, J = 7.6 Hz, C_{Ar}), 127.7, 127.3, 127.2, 124.0 (4 × d, J = 7.5 Hz, C_{Ar}), 92.6 (d, J = 173.9 Hz, CHF), 37.2 (d, J = 22.7 Hz, CH_2CHF), 31.8, 29.5, 29.4, 29.3, 29.2, 24.8, 22.6 (d, J = 3.9 Hz), 14.1 (Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –179.9 (ddd, J_{H-F} = 47.7, 28.7, 19.1 Hz). HRMS: m/z $[M]^+$ calcd for $C_{24}H_{27}O_2F$: 366.1995; found: 366.1999. Compound **23**: R_f 0.34 (pentane–Et_2O, 9:1). IR (neat): 2956, 2928, 2856, 1731, 1615, 1466, 1287, 1131, 1070, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 1.2 Hz, 1 H, H3), 7.75 (d, J = 8.0 Hz, 1 H, H6), 7.63 (dd, J = 8.0, 1.2 Hz, 1 H, H5), 4.39 (q, J = 7.1 Hz, 2 H, OEt), 4.38 (q, J = 7.1 Hz, 2 H, OEt), 2.01–2.19 (m, 2 H, CH_2), 1.25–

1.41 (m, 20 H, 7 × CH_2, 2 × Me), 0.87 (t, J = 6.4 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 ($COOCH_2$), 166.8 ($COOCH_2$), 140.3 (t, J = 27.8 Hz, C4), 133.5 (t, J = 1.3 Hz), 132.3, 129.1, 127.6 (t, J = 6.1 Hz), 125.7 (t, J = 6.3 Hz, C_{Ar}), 122.3 (t, J = 243.0 Hz, CF_2), 61.9 (OEt), 61.8 (OEt), 38.9 (t, J = 26.7 Hz, CH_2CF_2), 31.8, 29.4, 29.3, 29.2, 29.1, 22.6, 22.3 (t, J = 4.0 Hz), 14.1 (3 × Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –96.25 (t, J_{H-F} = 16.4 Hz). HRMS: m/z $[M]^+$ calcd for $C_{22}H_{32}O_4F_2$: 398.2268; found: 398.2261.

Compound **24**: R_f 0.71 (pentane–Et_2O, 9:1); mp 88–90 °C. IR (KBr): 2920, 2851, 1673, 1594, 1340, 1163, 1129, 1031, 707 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.41 (m, 4 H, H_{Ar}), 7.80–7.91 (m, 3 H, H_{Ar}), 2.11–2.27 (m, 2 H, CH_2), 1.25–1.50 (m, 14 H, 7 × CH_2), 0.86 (t, J = 6.4 Hz, 3 H, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.5 (2 × $COOCH_2$), 143.3 (t, J = 27.6 Hz, C_{Ar}), 134.3, 134.1 (t, J = 1.3 Hz), 130.5 (t, J = 6.0 Hz), 127.7, 127.4, 127.3, 124.1 (t, J = 6.1 Hz), 122.3 (t, J = 243.3 Hz, CF_2), 38.8 (t, J = 26.6 Hz, CH_2CF_2), 31.8, 29.4, 29.3, 29.2, 29.1, 22.3 (t, J = 3.9 Hz), 14.1 (Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –96.46 (t, J_{H-F} = 16.4 Hz). HRMS: m/z $[M]^+$ calcd for $C_{24}H_{26}O_2F_2$: 384.1900; found: 384.1915.