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Enantioenriched quaternary α-pentafluoroethyl derivatives of alkyl 1-indanone-2-carboxylates

Albert Granados,* Anna Ballesteros and Adelina Vallribera*

Department of Chemistry and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universitat Autònoma de Barcelona, Cerdanyola del Vallès, 08193 Barcelona (Spain)

ABSTRACT: An electrophilic enantioselective catalytic method for the α-pentafluoroethylation of 3-oxoesters is described. Under the use of $La(OTf)_3$ in combination with (*S,R*)-indanyl-*pybox* ligand good results in terms of yield and enantioselectivities were achieved (up to 89% *ee*). The reaction proceeds under mild conditions leading to the formation of enantioenriched quaternary centers. This methodology uses an hypervalent iodine(III)-CF_2CF_3 reagent and mechanistic investigations are consistent with the involvement of a radical pathway.

INTRODUCTION

Over the last years, the incorporation of fluorine and fluorine containing groups into organic molecules in order to change its physical, biological and chemical properties has become a powerful tool in drug design due to its favourable effects on pharmacological profiles.[1] Among fluoroalkyl groups,[2] the pentafluoroethyl (CF_2CF_3), the bulkier analogue of CF_3 group, is nowadays one of the most attractive groups[3] in drug design. Due to its strong electron-withdrawing nature, a pentafluoroethylated drug would be less likely to be oxidized by P450 enzymes, leading to an increase of its metabolic stability.[4] Additionally, the lipophilicity of the pentafluoroethyl group is comparable to the one of the recognized lipophilic pentafluorosulfanyl ($-SF_5$) group. On the whole, the presence of a pentafluoroethyl group in drugs can improve their biological activity due to the combination of a unique steric factor with an increased electronegativity, lipophilicity and metabolic stability. In this context, Fulvestrant (estradiol containing a side chain in with CF_2CF_3 group at the end) was approved by the FDA in 2002 as a second-line theraphy for advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy (Figure 1).[5] Moreover, peptidyl pentafluoroethyl ketones have been reported to inhibit various enzymes, as for example, elastase and the hepatitis C virus N53 protease.[6] In addition, some pentafluoroethyl ketones are powerful inhibitors of Group VIA Calcium-Independent Phospholipase A2 proteases.[7] Recently, functionalisation of bicalutamide and enobosarm scaffold with pentafluorosulfanyl and pentafluoroethyl functionality lead to potent agents against prostate cancer (Figure 1).[8]

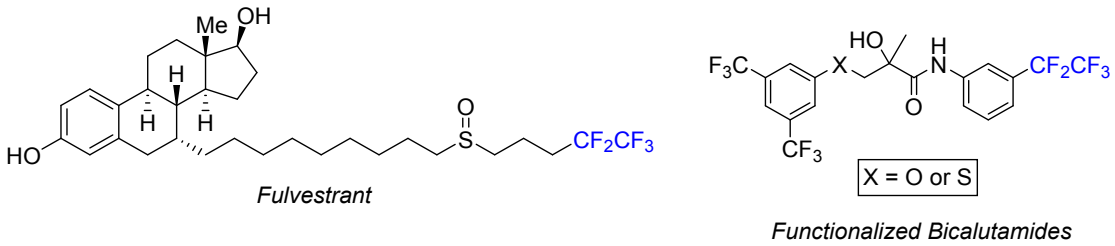


Figure 1. Pentafluoroethylated anticancer drugs

Despite the tremendous progress made in trifluoromethylation,[9] synthetic methods for the introduction of longer perfluoroalkyl chains remain underdeveloped. In contrast to trifluoromethyl, the pentafluoroethyl moiety is still poorly present in drugs in part because the methods for the incorporation of CF_2CF_3 are scarcely documented. For example, for the pentafluoroethylation of a nucleophilic carbon center alfa to carbonyl, only a few electrophilic pentafluoroethylating reagents have been described,[10] such as (pentafluoroethyl)iodonium salts developed by Yaguposkii[11] and Umemoto,[12] and the hypervalent λ^3-iodane reagents **1**[13] and **2**[14] (Scheme 1). Shen's group[15] explored the direct pentafluoroethylation of β-keto esters using reagent **1** as electrophilic CF_2CF_3 source, DBU as base in CH_3CN affording moderate to good yields (36-82%). They showed that the bulkiness of the ester group lowered the yield. Togni´s group performed the α-perfluoroethylenation of a lactam-derived ketene silyl amide using **1**, obtaining an excellent yield under $TMSNTf_2$ catalyst (only one example).[13b]

Moreover, while important catalytic enantioselective trifluoromethylation methods of the alfa carbon in carbonyl compounds have been developped,[16] to date only one isolated asymmetric pentafluoroethylation of an oxindole has been reported (using $MgBr_2.Et_2O$/*pybox* and Togni's reagent **1**) in a remarkable Katayev's work dedicated to the asymmetric trifluoromethylation of substituted oxindoles.[17] As far as we know, there are no examples regarding the enantioselective α-pentafluoroethylation of alkyl 1-indanone-2-carboxylates. In the past, our group have previously reported the asymmetric introduction of different electrophiles in β-dicarbonyl systems though lanthanide-*pybox* catalysis, from α-amination[18] to the most recent fluorination[19] and trifluoromethylation[20] reactions. Herein, we present our recent studies on the construction, for the first time, of enantioenriched pentafluoroethylated quaternary centers on alkyl 1-indanone-2-carboxylates using a combination of $La(OTf)_3$ with *pybox* type ligands.

RESULTS AND DISCUSSION

The first part of this work was dedicated to the synthesis of the reagents **1** and **2** (Figure 2). The pentafluoroethylated benziodoxole, **1**, was fully synthesized as previously described[15] in a 95% yield. On the other hand, the 1-pentafluoroethyl-1,2-benziodoxol-3-(1H)-one reagent, **2,** was prepared in three steps from 2-iodobenzoic acid in 54% overall yield.[21] We soon realized that **1** and **2** were not stable and must be kept in a vacuum desiccators' (see S76 in SI).

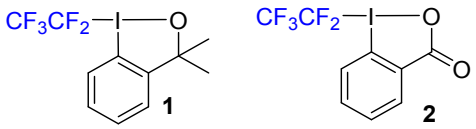
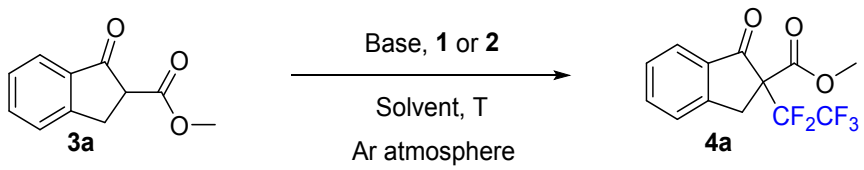


Figure 2. Pentafluoroethylating hypervalent iodine reagents

Secondly, we proceeded with the synthesis of β-keto esters **3** following the reported procedures.[18d, 20, 22] Additionally, 1,3-diketone **3n** was prepared from 1-indanone and acetic acid using a $(CF_3CO)_2O/CF_3SO_3H$ mixture (66% yield).[23] These substrates were chosen as a model for the catalytic system.

Then, we studied the pentafluoroethylation reaction of **3a** as a model (Table 1). As said before, in 2016 Shen's group[15] reported the direct pentafluoroethylation of some β-keto esters using hypervalent iodine(III)-CF_2CF_3, **1**, and the organic base DBU (2 equiv.). We wanted to study the reaction using an inorganic base that could be separated by simple filtration. Potassium carbonate in THF yielded the product **4a** in a 23% yield. Other polar solvent as CH_2Cl_2 and CH_3CN enhanced the yield (51 and 59%, Table 1, entries 2 and 3). When using Cs_2CO_3 in CH_3CN the yield was raised until 69%. Disturbing is that neither higher nor lower temperatures improve the yield of **4a**. Changing the reagent **1** by **2** did not increase the reaction yield (Table 1, entry 5). Another way of activation of β-dicarbonyl compounds is the use of Lewis acids. Thus, following the idea of Katayev and Togni,[13b] magnesium bromide ethyl etherate (10%) was used obtaining **4a** in a 68% yield. With $La(OTf)_3$ (10%) the pentafluoroethylated compound was obtained in a lower 59% yield (entry 9). On the other hand, inspired by the racemic trifluoromethylations reactions developed by Cahard[9a] using the trifluoromethylcalconium salts, we added nBu$_4$NI but without great success. Finally, although Shen's group reported[15] that using DBU **4a** was afforded in 60% yield, another organic base as DIPEA was not a good selection for this reaction.

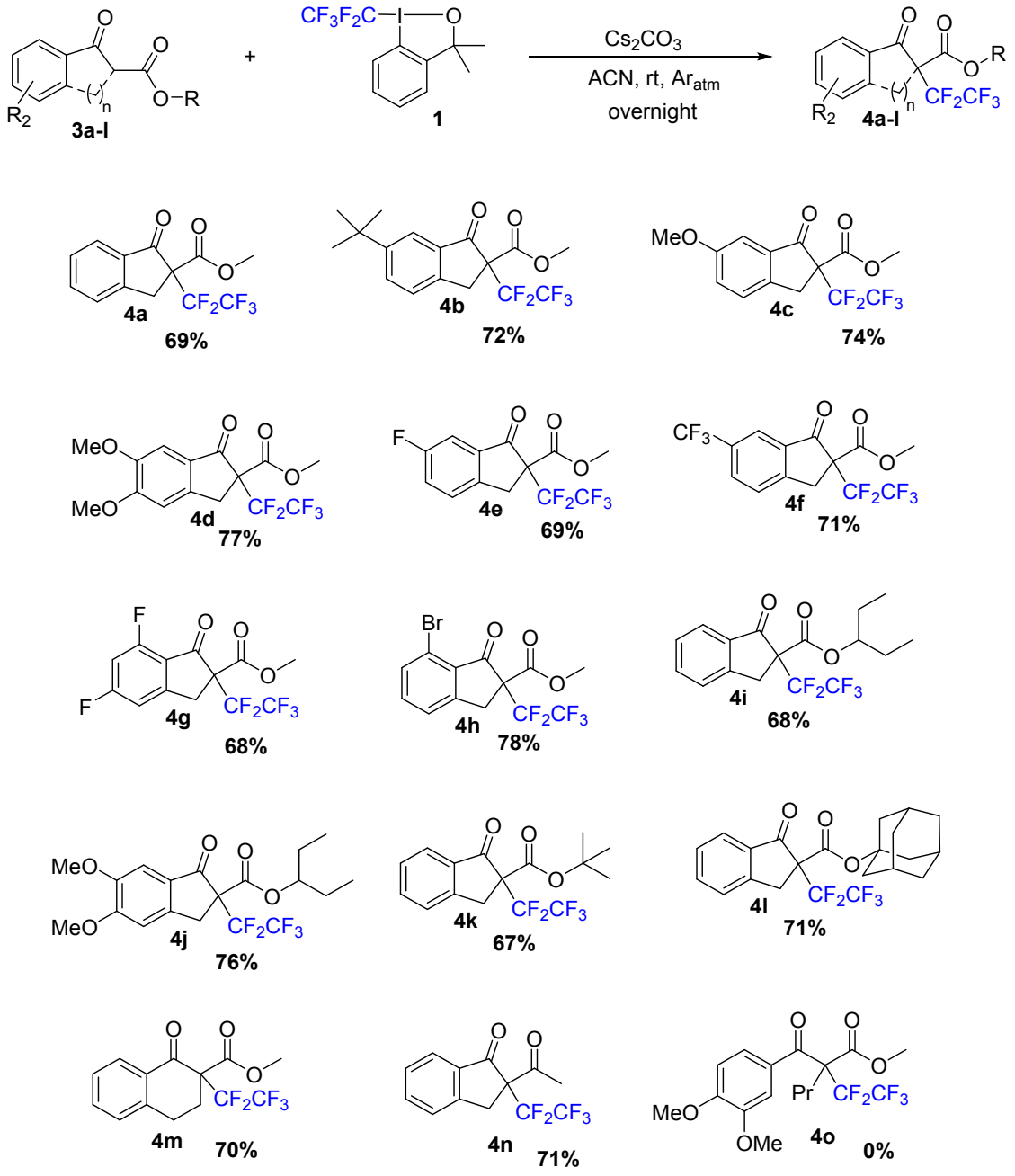
Table 1. Optimization of the α-pentafluoroethylation reaction of **3a**.



Entry	Reagent	Solvent	Base	T (°C)	Additives[a]	Yield (%)[b]
1	**1**	THF	K_2CO_3	rt	-	23
2	**1**	CH_2Cl_2	K_2CO_3	rt	-	51
3	**1**	CH_3CN	K_2CO_3	rt	-	59
4	**1**	CH_3CN	Cs_2CO_3	rt	-	69
5	**2**	CH_3CN	Cs_2CO_3	rt	-	60
6	**1**	CH_3CN	Cs_2CO_3	0	-	64
7	**1**	CH_3CN	Cs_2CO_3	50	-	57
8	**1**	CH_3CN	-	rt[c]	$MgBr_2{\cdot}Et_2O$	68
9	**1**	CH_3CN	-	rt	$La(OTf)_3$	59
10	**1**	CH_3CN	K_2CO_3	rt	$^nBu_4NI$	62
11	**1**	CH_3CN	DIPEA	rt	-	11

Reaction conditions: **3a** (1 mmol), pentafluoroethylating reagent (1.5 mmol), base (1.5 mmol), and dry solvent. [a] Added in a 10 mol%. [b] Isolated yield. [c] From -35 °C to rt.

With the optimized reaction conditions in hand, we explored the scope of the reaction for 3-oxoesters (Scheme 1). The methodology worked with a broad range of 1-indanone-2-carboxylates including primary (**3a-h**), secondary (**3i-j**) and tertiary alcohol (**3k,l**) derivatives. Moreover, β-keto esters with either electron donating (**4b-d** and **4j**) or electron-withdrawing groups (**4e-h**) at the aromatic ring provided the pentafluoroethylated quaternary carbon center compounds with good chemical yields (68-78%). To our delight, the methodology could be extended to additional six membered cyclic β-dicarbonyl compounds, such as methyl 1-tetralone-2-carboxylate (**3m**) and 2-acetyl-1-indanone (**3n**). In both cases the pentafluoroethylated compounds (**4m** and **4n**) were afforded in high 70 and 71% yields respectively. Unfortunately, this methodology could not be successfully applied to the acyclic β-keto ester **3o**.



Scheme 1. Scope of α-pentafluoroethylating reaction of β-dicarbonyl compounds

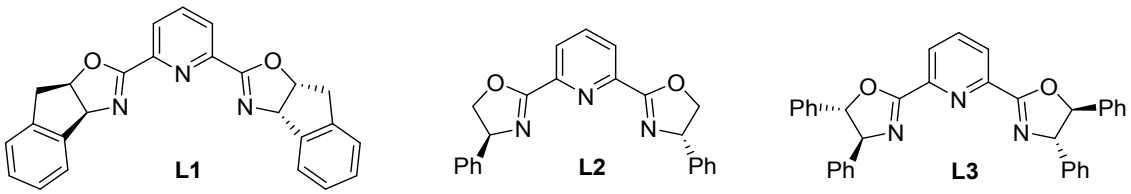
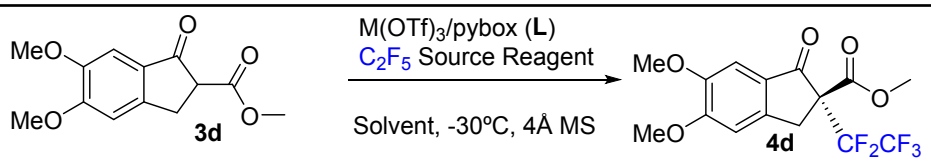


Figure 3. *Pybox* ligands used in the optimization of the electrophilic enantioselective pentafluoroethylation reaction.

Next, we studied the enantioselective version of this electrophilic pentafluoroethylation reaction. In the first attempt, we selected **3d** and reagent **1** under the combination of

europium(III) triflate and (*S*,*R*)-indanyl-*pybox* (**L1**, Figure 3) as catalyst at -30 ºC (Table 2, entry 1). The enantiopure *pybox* ligand will act as a chiral ligand and base. Compound **4d** was obtained in low yield and enantioselectivity. Next, we moved to yterbium, achieving the fluorinated product in good yield (76%) and moderate enantioselectivity (45%). Then, we performed the reaction changing the metal source to lanthanum(III) triflate and we afforded **4d** in a 80% *ee* and good 72% yield (entry 3). In order to improve these results, we moved to (*R*,*R*)-Ph-*pybox* (**L2**) and (*S,R*)-diPh-*pybox* (**L3**), but the reaction was worst in both terms of yield and *ee* (entries 4 and 5). We checked CH_2Cl_2 as solvent at -78 ºC, but acetonitrile at -30 ºC gave better results (entry 3 *vs* 6). Performing the reaction at room temperature did not enhance the *ee* (entry 3 *vs* entry 7). Then, we used an automatic injector to make a slow addition of the pentafluorofluoroethylating agent **1** to the reaction mixture, affording the product with the same enantioselectivity but slightly lower yield (entry 3 *vs* 8). Next, we decided to assay $MgBr_2{\cdot}Et_2O$, a completely different Lewis acid that has been recently used by Katayev's group in combination with pybox-type ligands in the trifluoromethylation of oxindoles.[17] In our case, using **L1** as chiral ligand, we reached compound **4d** in a 74% *ee* and a 76% yield (Table 2 entry 11). Next, we studied $MgBr_2{\cdot}Et_2O$ with **L2** and **L3** *pybox* ligands (Figure 3) affording **4d** in low *ee's* in both cases (Table 2, entries 12 and 13). In order to test the role of the magnesium counter anion, we carried out the reaction using the $Mg(OTf)_2$/**L1** combination and formation of **4d** was not observed (Table 2, entry 14). In fact, Katayev's group has previously reported the dependence of the catalytic behavior, on the different magnesium salts, in the trifluoromethylation of 3-substituted oxoindoles.[13b] Finally, we assayed $Ga(OTf)_3$, a Lewis acid which has showed high efficacy for a great number of electrophilic reactions.[24] In our case, $Ga(OTf)_3$ combined with **L1** gave the pentafluoroethylated compound **4d** in a 76% yield, but poorly enantioenriched (20% *ee*).

Table 2. Optimization of the enantioselective pentafluoroethylation reaction.



Entry	Metal	Pybox	Solvent	Reagent	Yield[a]	*ee*[b] *(major R)*
1	$Eu(OTf)_3$	**L1**	MeCN	**1**	11%	50%
2	$Yb(OTf)_3$	**L1**	MeCN	**1**	76%	45%

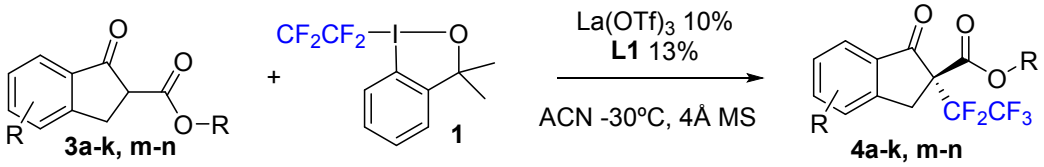
3	$La(OTf)_3$	**L1**	MeCN	**1**	72%	80%
4	$La(OTf)_3$	**L2**	MeCN	**1**	36%	10%
5	$La(OTf)_3$	**L3**	MeCN	**1**	56%	36%
6[c]	$La(OTf)_3$	**L1**	CH_2Cl_2	**1**	20%	25%
7[d]	$La(OTf)_3$	**L1**	MeCN	**1**	55%	63%
8[e]	$La(OTf)_3$	**L1**	MeCN	**1**	35%	75%
9	$La(OTf)_3$	**L1**	MeCN	**2**	60%	72%
10	$Eu(OTf)_3$	**L1**	MeCN	**2**	55%	70%
11	$MgBr_2{\cdot}Et_2O$	**L1**	MeCN	**1**	76%	74%
12	$MgBr_2{\cdot}Et_2O$	**L2**	MeCN	**1**	67%	15%
13	$MgBr_2{\cdot}Et_2O$	**L3**	MeCN	**1**	76%	40%
14	$Mg(OTf)_2$	**L1**	MeCN	**1**	<10%	*nd*
15	$Ga(OTf)_3$	**L1**	MeCN	**1**	73%	20%

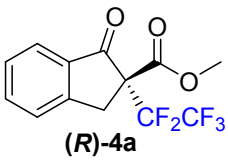
Reactions conditions: 1 equiv. of **3d**, 1.3 equiv. **1** or **2**, 0.13 equiv. *pybox* and 0.10 equiv. metal. [a] Yields of isolated pure compound **4d**. [b] Enantiomeric excesses determined by HPLC. [c] Reaction done at -78 °C. [d] Reaction done at room temperature. [e] The reagent **1** was added dropwise by an automatic injector.

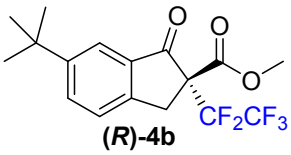
Next, we wanted to explore the scope of the reaction (Scheme 2). So, a range of cyclic 3-oxoesters were tested using the optimized pre-catalyst combination, $La(OTf)_3$, **L1** and hypervalent iodine(III)-CF_2CF_3 **1** in acetonitrile at -30 °C, under argon atmosphere and in presence of 4Å molecular sieves. The reaction was performed with a series of compounds derived from primary esters (**3a-h**). In general, the presence of electron-withdrawing groups at sixth position of the aromatic ring injures the *ee's* (**4e** and **4f,** 50-60% *ee*). In contrary, those primary β-keto esters with no substituents or with electron-donating groups (**4a,c-e**) in the same aromatic position gave around or over 80% *ee*. The presence of sterically bulky ^{t}Bu and CF_3 groups at sixth position (**4b** and **4f**) diminishes the *ee*, being lower for the electron-withdrawing CF_3. Once again, the effect of a bulkier ester is harmful for the enantiodifferentiation (**4a** *vs* **4k** and **4d** *vs* **4j**), as we have previously seen in our related previous work of trifluoromethylation.[20] The reaction of the more flexible cyclic six-membered ring **3m** gave the pentafluoroethylated product with a significant decrease of enantioselectivity (34% *ee*) compared with **3a** under the same conditions (87% *ee*). We also tested the 1,3-diketone **3n,** affording **4n** in a high yield (79%)

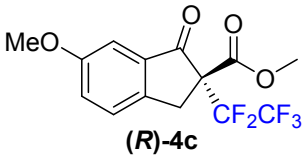
but unfortunately as a racemic mixture. Finally, due to the moderate 74% *ee* obtained for **4d** (Table 2, entry 11) using the $MgBr_2{\cdot}Et_2O$ and **L1** combination, we decided to assay this pre-catalyst with two other substrates. Compounds **3k** and **3j** were selected in order to improve their enantioselectivites, but **4k** and **4j** were obtained in 24% and 20% *ee*'s respectively.

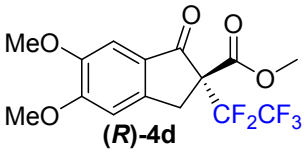
The assignment of the absolute configuration of compounds **4a-h**,**j-m** was based on the comparison of the signal of their Cotton Effect (all compounds present a negative Cotton effect, see SI), as well as their negative specific rotation values. Both properties were consistent with the ones of the previously prepared trifluoromethylated analogues.[9a,16c,20] Thus, we assigned the absolute configuration *R* to all compounds **4**.

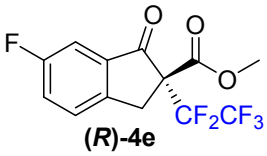


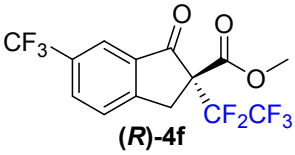

(*R*)-4a
58% yield, 87% *ee*

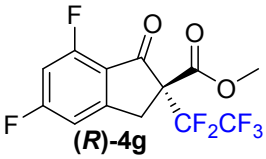

(*R*)-4b
78% yield, 63% *ee*

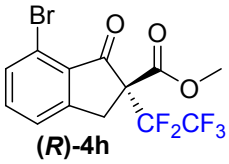

(*R*)-4c
63% yield, 89% *ee*

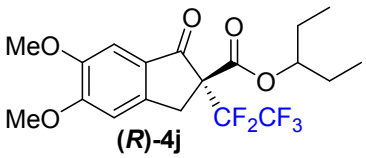

(*R*)-4d
72% yield, 80% *ee*

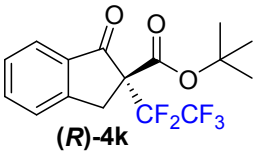

(*R*)-4e
72% yield, 60% *ee*

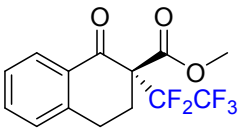

(*R*)-4f
63% yield, 50% *ee*

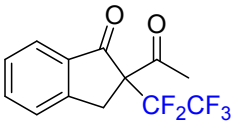

(*R*)-4g
68% yield, 75% *ee*


(*R*)-4h
71% yield, 80% *ee*


(*R*)-4j
47% yield, 30% *ee*


(*R*)-4k
32% yield, 28% *ee*


(*R*)-4m
65% yield, 34% *ee*


4n
79% yield, 0% *ee*

Scheme 2. Scope of the enantioselective α-pentafluoroethylation of cyclic β-dicarbonyl compounds.

The activation of Togni type reagents have been previously studied by ^{19}F NMR in different research groups.[16g,17,20,25] In this work, we mixed **1** with $La(OTf)_3$ (1:1) in deuterated acetonitrile. After 5 minutes, **1** was converted to a new species with a chemical shift of the CF_3 from δ = -81.7 to δ = -79.5 ppm and a chemical shift of the CF_2 from δ = -99.7 to δ = -82.6 ppm. Thus, a very significant change was observed which indicates the coordination of **1** to lanthanide. Further ^{19}F NMR-based titration furnished a Job plot indicating a 1:1 complexation of **1** with $La(OTf)_3$ (Figure 4), in agreement with some examples in the literature.[13b,20] Thus, we propose the formation of the cationic iodonium species **5** shown in Figure 4.

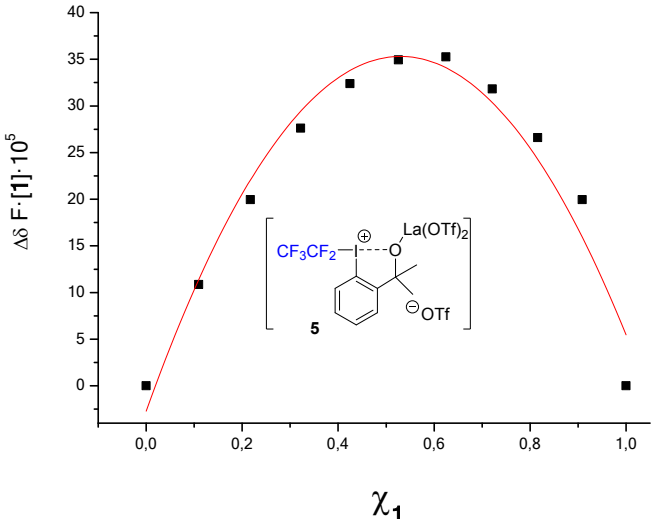
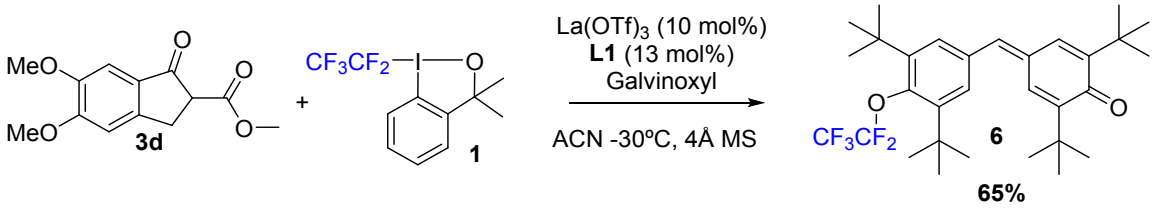
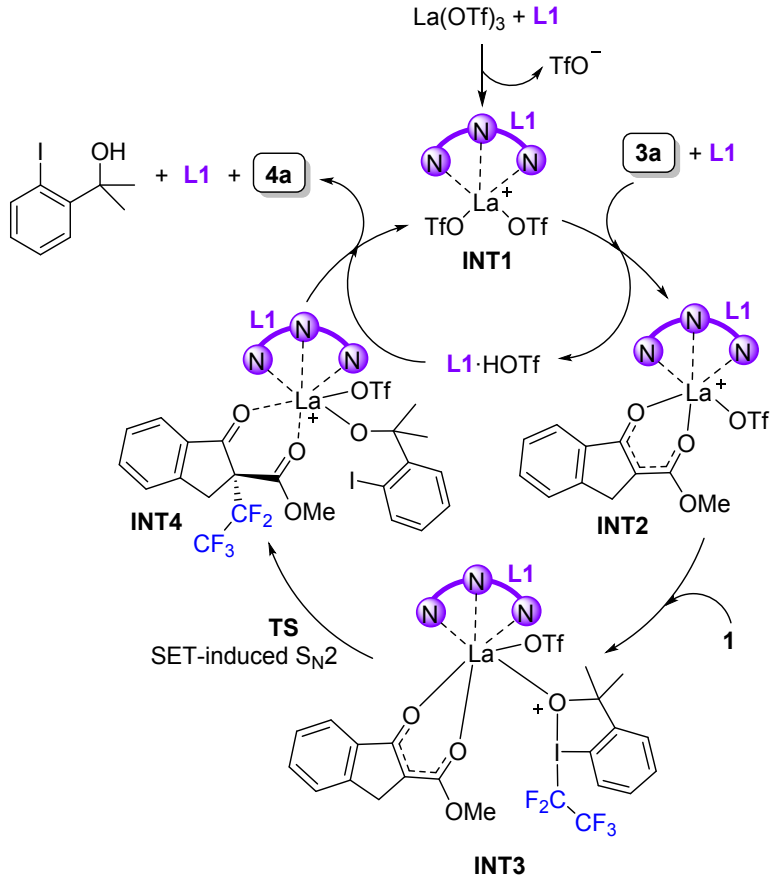


Figure 4. Job plot (**1**+$La(OTf)_3$) by ^{19}F NMR (CD_3CN, 25 °C, 400 MHz) of the CF_2 signal and the proposed cationic iodonium species, **5**, formation.

Next, the enantioselective catalytic reaction was tested in the presence of Galvinoxyl free radical, which is a classical radical scavenger. After 36 hours, the only products detected in the reaction of **3d** and **1** were the starting material and the pentafluoroethylated Galvinoxyl **6** (Scheme 3). Thus, the presence of Galvinoxyl inhibits the pentafluoroethylation reaction. This new compound **6** was isolated in a 65% yield and it was completely characterized by spectroscopic techniques, including HR-ESI-MS. The radical reaction pathway indicated by this result is in line with the known propensity of hypervalent iodine(III)-CF_3 to generate CF_3 radicals.[13b, 17, 20, 26]



Scheme 3. Pentafluoroethylation conducted in the presence of Galvinoxyl.



Scheme 4. Proposed catalytic cycle for the formation of **(*R*)-4a** from **3a** with $La(OTf)_3$, reagent **1** and the *pybox* ligand **L1**.

At the present stage we assume that the pentafluoroethylation step proceeds *via* a similar mechanistic scenario (Scheme 4) as we suggested in our recent work on the enantioselective α-trifluoromethylation of cyclic β-keto esters.[20] First, **INT1** is formed by coordination of the *pybox* ligand to the metal by displacement of a OTf. *Pybox* ligand is the responsible for the abstraction of the α-H in β-keto ester. Next, coordination of **enolate-3a** and reagent **1** to metal center is produced to form **INT2**. The subsequent coordination of reagent **1** to **INT2** is based on complex **5**, which formation has been demonstrated in this work by ^{19}F NMR

experiments (Figure 4). Then, the coordination pattern of the **enolate-3a** in **INT3** reveals an efficient blockage of the prochiral *Si* face of the La(III) enolate. The hindrance of the *Si* face of this intermediate **INT3** results in an efficient S_N2-like saddle point TS, which consists of a *Re* attack of the C_α atom of the enolate moiety on the carbon atom of the CF_2CF_3 group in **1**, with concomitant departure of the iodine-aryl group. With the CF_2CF_3 transfer appearing to proceeded through a nucleophilic substitution and the experimentally demonstrated presence of CF_2CF_3 radicals we propose a single–electron transfer(SET) induced S_N2-type pathway, that can explain the control of selectivity. This mechanism has been also proposed by other authors in the asymmetric catalyzed trifluoromethylation of oxindoles.[17] In fact, hypervalent iodine(III)-CF_3 reagent has been described as a precursor of electrophilic CF_3 radical species.[26] To date however, there exist only very few examples on its use in asymmetric trifluoromethylation.[13b,17,20] This report is thereby the first example on the construction of enantioenriched pentafluoroethylated carbon centers using hypervalent iodine-based reagents proceeding through a SET pathway.

CONCLUSIONS

In summary, an efficient method for the enantioselective α-pentafluoroethylation of alkyl 1-indanone-2-carboxylates is described. Racemic conditions were optimized using Cs_2CO_3 as base in acetonitrile (15 examples). The enantioenriched pentafluoroethylated 3-oxo esters were prepared using an hypervalent iodine(III)-CF_2CF_3 reagent and a lanthanide-*pybox* pre-catalyst to achieve good chemical yields and *ee*'s (up to 89%, 11 examples). The enantioselectivity of the reaction stems from the efficient blockage of one of the prochiral faces of the La(III) enolate by one unit of the C2-symmetric ligand. We propose that the mechanism proceeds through a SET pathway involving CF_2CF_3 radicals.

EXPERIMENTAL SECTION

General information: The chemicals and solvents were purchased from Sigma-Aldrich or Fluorochem. A silicone bath has been used for reactions that require heating. Solvents were distilled and stored under argon in molecular sieves. IR spectra were determined either by transmission or by attenuated total reflectance mode (ATR). Enantiomeric excesses were determined, unless otherwise stated, by HPLC using a chiral column Daicel-AD-H. Optical rotation were measured with a Rudolph Autopol I polarimeter and they are reported as follows:

$[\alpha]_D^{rt}$ (c in g per 100 mL, solvent). ^{1}H NMR spectra were recorded operating at 250, 360, and 400 MHz. ^{13}C NMR spectra were registered at 63, 91, and 101 MHz. ^{19}F NMR spectra were recorded decoupled to protons. Circular Dicroism were recorded in a spectropolarimeter J-715, JASCO, equipped with Peltier thermostat module. HRMS were recorded by a Bruker micrOTOF-QII mass spectrometer (fly time analyzer) through positive electrospray ionization. Compounds **3** (**3a,**[20] **3b**,[20] **3c**,[20] **3d**,[15] **3e**,[20] **3f,**[20] **3g**,[20] **3h**[20], **3m**[20]) were prepared as previously reported in our group. Compounds **3i**,[19] **3k**,[19] and **3l**[19] were synthesized by a transesterification reaction from the corresponding methyl ester following a methodology adapted from a previously reported method of our group.[22] Compound **3n**[23] was prepared following a reported procedure.

Pentan-3-yl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**3j**): The methodology of preparation was adapted from a reported procedure:[22] In a round-bottomed flask 0.50 g of **3d** (1 eq.), ZnO (0.2 eq.) and pentan-3-ol (10 equivalents) were dissolved in toluene. The reaction mixture was heated up to 140 ^{o}C, under a distillation setup, until total conversion was observed by TLC. Then, the reaction mixture was filtered through Celite® and the solvent was removed under reduced pressure. The product obtained was purified by column chromatography on silica-gel (hexane:ethyl acetate (10:1)) obtaining 0.51 g (1.67 mmol) of **3j** (84% yield). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 0.84 (m, 6H), 1.53 (m, 4H), 3.23 (dd, $^3J_{(H,H)}$ = 7.2 Hz, $^2J_{(H,H)}$ = 18.0 Hz, 1H), 3.39 (dd, $^3J_{(H,H)}$ = 3.6, $^2J_{(H,H)}$ =18.0 Hz, 1H), 3.65 (dd, $^3J_{(H,H)}$ = 3.6 Hz, $^3J_{(H,H)}$ = 7.2 Hz, 1H), 3.84 (s, 3H), 3.92 (s, 3H), 4.85 (quint, $^3J_{(H,H)}$ = 7.2 Hz, 1H), 6.87 (s, 1H), 7.11 ppm (s, 1H). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 9.5, 9.6, 26.5, 26.5, 30.1, 53.8, 56.0, 56.3, 78.2, 104.7, 107.2, 127.9, 149.2, 149.6, 155.9, 169.3, 198.2 ppm. IR (ATR): 2967, 1731, 1591, 1313, 1194, 1021 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{22}O_5Na$ 349.0270; found 349.0264.

Methyl 2-(3,4-dimethoxybenzoyl)pentanoate (**3o**)**:** In a 250 mL round-bottom flask 2 equiv of sodium hydride and 2 equiv of dimethyl carbonate were added in 25 mL of THF. Then a solution of 3,4-dimethoxyacetophenone (1g, 5.55 mmol, 1 equiv) in THF (15 mL) is added dropwise. When the reaction was finished, it was neutralized with 1 M HCl; and then extractions with dichloromethane were carried out. The organics were dried, and solvent was removed under high vacuum. The crude reaction mixture was purified by column chromatography on silica-gel using hexane:AcOEt (8:2) as eluent, obtaining methyl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate in a 95% yield (1.25 g). In a 10 mL round-bottom flask provided with a reflux condenser 1.25 mmol of β-keto ester were dissolved in 3 mL of dry acetone. Then, 1.38 mmol of K_2CO_3 and 1.82 mmol of propyl iodide were added. The system was maintained at 40 °C with stirring up to 24 h. Then, the solution was filtered, the crude was extracted with CH_2Cl_2 and washed with 1 M HCl. The organic phase was dried and evaporated. The crude was purified by

column chromatography on silica-gel using mixtures of hexane:AcOEt (7:3) as eluent yielding **3o** in 90% yield (0.31 g). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 0.95 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 3H), 1.36 (m, 2H), 1.97 (m, 2H), 3.69 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.32 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 6.92 (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.57 (bs, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.66 ppm (d, $^{4}J_{(H,H)}$ = 1.1 Hz, 1H). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 14.3, 21.3, 31.7, 52.8, 53.8, 56.3, 56.5, 110.5, 111.0, 123.7, 129.8, 149.6, 154.1, 171.2, 194.1 ppm. IR (ATR): 2968, 1710, 1607, 1207, 1091, 988 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{20}O_5Na$ 303.1208; found 303.1209.

General procedure for the enantioselective electrophilic α-pentafluoroethylation of 3-oxoesters: In a 10 ml dried Schlenk flask in presence of 4Å molecular sieves, $La(OTf)_3$ (0.10 equiv.) and (*S,R*)-indanyl-*pybox* (0.13 equiv.) were dissolved in dry acetonitrile (3 mL). The colourless reaction mixture was left stirring at room temperature under inert atmosphere overnight. Next, the corresponding β-keto ester (80 mg; 1 equiv.) was added to the reaction mixture and it was left stirring at room temperature for 30 minutes. Then, the reaction mixture was cooled down until -35 ^{o}C and, once at this temperature, the pentafluoroethylating agent (1.3 equiv.) was added to the mixture in one portion. The reaction mixture was left at this temperature under argon atmosphere until complete conversion observed by TLC. Afterwards, the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel.

Methyl (R)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4a**):[15] According to the general procedure, 375 mg (1.22 mmol) of **4a** were prepared from 400 mg of starting material **3a** (58% yield) as a colourless oil, after purification by column chromatography on silica-gel (hexane:ethyl acetate (2:1)). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 3.62 (d, $^{2}J_{(H,H)}$ = 17.7 Hz, 1H), 3.82 (s, 3H), 3.93 (d, $^{2}J_{(H,H)}$ = 17.7 Hz, 1H), 7.47 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.55 (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.71 (td, $^{3}J_{(H,H)}$ = 7.5 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.85 ppm (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ = -79.6 (s, 3F), -115.0 (d, $^{2}J_{(F,F)}$ = 278.0 Hz, 1F), -116.8 ppm (d, $^{2}J_{(F,F)}$ = 278.0 Hz, 1F); $[\alpha]_D^{20}$ = -21.9 (c = 0.0032 in MeCN), 87% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 11.14 min and t_r(*S*) = 18.34 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-(tert-butyl)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4b**): According to the general procedure, 86 mg (0.24 mmol) of **4b** were synthesized from 75 mg of starting material **3b** (78% yield) as colourless oil, after purification by column chromatography on silica gel (hexane:dichloromethane (2:1)). ^{1}H NMR (360 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 1.36 (s, 9H), 3.57 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.83 (s, 3H), 3.87 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 7.47 (d, $^{3}J_{(H,H)}$ = 7.8

Hz, 1H), 7.57 (d, $^{3}J_{(H,H)}$ = 7.8 Hz, 1H), 7.82 ppm (bs, 1H); ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C, TMS): δ =-79.5 (s, 3F), -114.9 (d, $^{2}J_{(F,F)}$ = 278.1 Hz, 1F), -116.6 ppm (d, $^{2}J_{(F,F)}$ = 278.1 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 31.2, 33.0 (bs), 53.8, 62.7 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.2 Hz), 77.2, 115.5 (m), 120.0 (m), 121.7, 125.7, 133.9, 134.4, 149.0, 152.2, 165.0 (d, $^{3}J_{(C,F)}$ = 6.8 Hz), 192.4 ppm. IR (ATR): 2961, 1785, 1730, 1435, 1191, 1072 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}F_5O_3Na$ 387.0990; found 387.0986. $[\alpha]_D^{20}$ = -12.6 (c = 0.0039 in MeCN), 63% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 6.37 min and t_r(*S*) = 6.93 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-methoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4c**): According to the general procedure, 96 mg (0.28 mmol) of **4c** were synthesized from 100 mg of starting material **3c** (63% yield) as colourless oil, after purification by column chromatography on silica gel (hexane:ethyl acetate (2:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 3.53 (d, $^{2}J_{(H,H)}$ = 18.0 Hz, 1H), 3.81 (m, 7H), 7.23 (d, $^{4}J_{(H,H)}$ = 2.3 Hz, 1H), 7.27 (dd, $^{3}J_{(H,H)}$ = 8.4 Hz, $^{4}J_{(H,H)}$ = 2.3 Hz, 1H), 7.41 ppm (d, $^{3}J_{(H,H)}$ = 8.4 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C, TMS): δ =-79.5 (s, 3F), -114.9 (d, $^{2}J_{(F,F)}$ = 278.8 Hz, 1F), -116.5 ppm (d, $^{2}J_{(F,F)}$ = 278.8 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 32.8 (bs), 53.9, 55.7, 62.9 (dd, $^{2}J_{(C,F)}$ = 22.3 Hz, $^{2}J_{(C,F)}$ = 18.2 Hz), 106.2, 112.8 (m), 127.7 (m), 126.1, 126.9, 135.2, 144.5, 160.1, 165.0 (d, $^{3}J_{(C,F)}$ = 6.7 Hz), 192.2 ppm. IR (ATR): 2924, 1725, 1495, 1434, 1194, 1026 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{11}F_5O_4Na$ 361.0470; found 361.0467; $[\alpha]_D^{20}$ = -10.0 (c = 0.0027 in MeCN), 89% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 8.59 min and t_r(*S*) = 10.58 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-5,6-dimethoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4d**):[15] According to the general procedure, 84 mg (0.23 mmol) of **4d** were synthesized from 80 mg of starting material (72% yield) as colourless solid after purification by column chromatography on silica gel (hexane:ethyl acetate (2:1)). M.p.: 51-53 °C. ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 3.51 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 3.82 (m, 4H), 3.94 (s, 3H), 4.02 (s, 3H), 6.93 (s, 1H), 7.21 ppm (s, 1H), ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -79.5 (s, 3F), -114.9 (d, $^{2}J_{(F,F)}$ = 279.7 Hz, 1F), -117.5 ppm (d, $^{2}J_{(F,F)}$ = 279.7 Hz, 1F); $[\alpha]_D^{20}$ = -14.0 (c = 0.0032 in MeCN), 80% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 44.36 min and t_r(*S*) = 54.47 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99:1) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-fluoro-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4e**): According to the general procedure, 90 mg (0.28 mmol) of **4e** were synthesized from 80 mg of

starting material **3e** (72% yield) as colourless oil, after purification by column chromatography on silica gel (hexane:dichloromethane (7:3)). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 3.59 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.82 (s, 3H), 3.89 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 7.45 (m, 2H), 7.53 ppm (dd, $^{3}J_{(H,F)}$ = 8.3 Hz, $^{4}J_{(H,H)}$ = 2.1 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ =-78.6 (s, 3F), -112.9 (s, 1F), -114.8 (d, $^{2}J_{(F,F)}$ = 278.5 Hz, 1F), -116.6 ppm (d, $^{2}J_{(F,F)}$ = 278.5 Hz, 1F). ^{13}C[^{1}H] NMR (91 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 32.9 (d, $^{3}J_{(C,F)}$ = 3.2 Hz), 54.0, 63.1 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.2 Hz), 111.2 (d, $^{2}J_{(C,F)}$ = 22.5 Hz), 112.2 (m), 117.6 (m), 124.2 (d, $^{2}J_{(C,F)}$ = 24.0 Hz), 127.7 (d, $^{3}J_{(C,F)}$ = 8.1 Hz), 135.7 (d, $^{3}J_{(C,F)}$ = 8.1 Hz), 146.9 (d, $^{4}J_{(C,F)}$ = 2.2 Hz), 161.5, 164.0, 164.5 (d, $^{3}J_{(C,F)}$ = 7.1 Hz), 191.2 ppm. IR (ATR): 2921, 1751, 1721, 1614, 1296, 1149 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^{+}$ Calcd for $C_{13}H_8F_6O_3Na$ 349.0270; found 349.0264. $[\alpha]_D^{20}$ = -19.7 (c = 0.0036 in MeCN), 60% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 7.34 min and t_r(*S*) = 8.01 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99:1) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-6-(trifluoromethyl)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4f**): According to the general procedure, 71 mg (0.16 mmol) of **4f** were synthesized from 80 mg of starting material **3f** (63% yield) as colourless oil after purification by column chromatography on silica gel (hexane: dichloromethane (9:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 3.68 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.83 (s, 3H), 4.01 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 7.70 (d, $^{3}J_{(H,H)}$ = 8.1 Hz, 1H), 7.95 (dd, $^{3}J_{(H,H)}$ = 8.1 Hz, $^{4}J_{(H,H)}$ = 1.7 Hz, 1H), 8.11 ppm (d, $^{4}J_{(H,H)}$ = 1.7 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ =-63.2 (s, 3F), -79.6 (s, 3F), -114.7 (d, $^{2}J_{(F,F)}$ = 278.7 Hz, 1F), -116.7 ppm (d, $^{2}J_{(F,F)}$ = 278.7 Hz, 1F). ^{13}C[^{1}H] NMR (91 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 33.5 (m), 54.2, 62.6 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.8 Hz), 112.2 (m), 117.6 (m), 122.7 (q, $^{3}J_{(C,F)}$ = 3.9 Hz), 123.3 (q, $^{1}J_{(C,F)}$ = 273.1 Hz), 127.1, 131.5 (q, $^{2}J_{(C,F)}$ = 32.7 Hz), 132.7 (d, $^{3}J_{(C,F)}$ = 3.9 Hz), 134.3, 154.5, 164.2 (d, $^{3}J_{(C,F)}$ = 7.1 Hz), 191.0 ppm. IR (ATR): 2922, 1751, 1722, 1614, 1257, 1150. cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^{+}$ Calcd for $C_{14}H_8F_8O_3Na$ 399.0238; found 399.0229. $[\alpha]_D^{20}$ = -8.6 (c = 0.0022 in MeCN), 50% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 6.04 min and t_r(*S*) = 6.82 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-5,7-difluoro-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4g**): According to the general procedure, 73 mg (0.21 mmol) of **4g** were synthesized from 70 mg of starting material 3g (68% yield) as a colourless oil, after purification by column chromatography on silica gel (hexane: dichloromethane (1:1)). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 3.59 (d, $^{2}J_{(H,H)}$ = 18.1 Hz, 1H), 3.85 (s, 3H), 3.94 (dd, $^{2}J_{(H,H)}$ = 18.1 Hz, 1H), 6.85 (td, $^{3}J_{(H,F)}$ = 9.0 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.04 ppm (d, $^{3}J_{(H,F)}$ = 7.6 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ = -79.6 (s, 3F), -95.1 (d, $^{4}J_{(F,F)}$ = 14.8 Hz, 1F), -107.1 (d, $^{4}J_{(F,F)}$ = 14.8 Hz, 1F), -114.9 (d, $^{2}J_{(F,F)}$

= 279.5 Hz, 1F), -117.0 ppm (d, $^{2}J_{(F,F)}$ = 279.5 Hz, 1F). $^{13}C[^{1}H]$ NMR (91 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 33.3, 54.2, 62.9 (dd, $^{2}J_{(C,F)}$ = 22.0 Hz, $^{2}J_{(C,F)}$ = 18.5 Hz), 104.9 (dd, $^{3}J_{(C,F)}$ = 27.0 Hz, $^{3}J_{(C,F)}$ = 23.1 Hz), 109.5 (dd, $^{3}J_{(C,F)}$ = 23.1 Hz, $^{3}J_{(C,F)}$ = 4.3 Hz), 113.4 (m), 116.8 (m), 125.3 (m), 143.3, 155.1 (dd, $^{3}J_{(C,F)}$ = 12.3 Hz, $^{4}J_{(C,F)}$ = 3.1 Hz), 160.5 (dd, $^{1}J_{(C,F)}$ = 270.4 Hz, $^{3}J_{(C,F)}$ = 14.2 Hz), 164.2 (d, $^{3}J_{(C,F)}$ = 11.1 Hz), 168.8 (dd, $^{1}J_{(C,F)}$ = 270.4 Hz, $^{3}J_{(C,F)}$ = 14.2 Hz), 186.5 ppm. IR (ATR): 2968, 1751, 1721, 1622, 1495, 1258 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_7F_7O_3Na$ 367.0176; found 367.0176. $[\alpha]_D^{20}$ = -16.3 (c = 0.0032 in MeCN), 75% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 9.96 min and t_r(*S*) = 13.48 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Methyl (R)-7-bromo-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4h**): According to the general procedure, 81 mg (0.21 mmol) of **4h** were synthesized from 80 mg of starting material **3h** (71% yield) as a colourless oil, after purification by column chromatography on silica gel (hexane:dichloromethane (6:4)). ^{1}H NMR (400 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 3.56 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 3.83 (s, 3H), 3.89 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 7.50 (m, 2H), 7.84 ppm (dd, $^{3}J_{(H,F)}$ = 7.1 Hz, $^{4}J_{(H,H)}$ = 1.3 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C, TMS): δ = -79.1 (s, 3F), -1145 (d, $^{2}J_{(F,F)}$ = 279.1 Hz, 1F), -116.4 ppm (d, $^{2}J_{(F,F)}$ = 279.1 Hz, 1F). $^{13}C[^{1}H]$ NMR (101 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 32.4 (bs), 54.1, 63.9 (dd, $^{2}J_{(C,F)}$ = 22.0 Hz, $^{2}J_{(C,F)}$ = 18.5 Hz), 112.5 (m), 117.5 (m), 125.1, 131.5, 133.7, 136.5, 154.1, 164.5 (d, $^{3}J_{(C,F)}$ = 7.3 Hz), 189.2 ppm. IR (ATR): 2961, 1758, 1722, 1618, 1284 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_8BrF_5O_3Na$ 408.9469; found 408.9463. $[\alpha]_D^{20}$ = -14.3 (c = 0.0031 in MeCN), 80% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 13.58 min and t_r(*S*) = 19.80 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Pentan-3-yl 1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4i**): According to the general procedure, 99 mg (0.28 mmol) of **4i** were synthesized from 100 mg of starting material **3i** (68% yield) as a colourless oil, after purification by column chromatography on silica gel (hexane:dichloromethane (9:1)). ^{1}H NMR (360 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 0.83 (m, 6H), 1.58 (m, 4H), 3.61 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 3.88 (d, $^{2}J_{(H,H)}$ = 17.5 Hz, 1H), 4.83 (quint, $^{3}J_{(H,H)}$ = 7.2 Hz, 1H), 7.46 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.54 (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.69 (td, $^{3}J_{(H,H)}$ = 7.5 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.83 ppm (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C, TMS): δ =-78.8 (s, 3F), -114.0 (d, $^{2}J_{(F,F)}$ = 279.4 Hz, 1F), -115.0 ppm (d, $^{2}J_{(F,F)}$ = 279.4 Hz, 1F). $^{13}C[^{1}H]$ NMR (400 MHz, [D]$CDCl_3$, 25 °C, TMS): δ = 9.1, 26.0, 33.6 (d, $^{3}J_{(C,F)}$ = 2.6 Hz), 62.7 (dd, $^{2}J_{(C,F)}$ = 22.5 Hz, $^{2}J_{(C,F)}$ = 18.6 Hz), 80.5, 113.0 (m), 118.1 (m), 125.3, 126.1, 128.4, 134.2, 136.1, 151.4, 164.2 (d, $^{3}J_{(C,F)}$ = 11.1 Hz), 192.5 ppm. IR (ATR): 2924 1721, 1607, 1464, 1274, 1185. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}F_5O_3Na$ 387.0990; found 387.0994.

Pentan-3-yl (R)-5,6-dimethoxy-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4j**): According to the general procedure, 45 mg (0.11 mmol) of **4j** were synthesized from 70 mg of starting material **3j** (47% yield) as colourless oil, after purification by column chromatography on silica gel (hexane:dichloromethane (9:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 0.87 (m, 6H), 1.61 (m, 4H), 3.50 (d, $^{2}J_{(H,H)}$ = 17.3 Hz, 1H), 3.78 (d, $^{2}J_{(H,H)}$ = 17.3 Hz, 1H), 3.94 (s, 3H), 4.02 (s, 3H), 4.85 (quint, $^{3}J_{(H,H)}$ = 6.9 Hz, 1H), 6.93 (s, 1H), 7.21 ppm (s, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ =-78.6 (s, 3F), -114.2 (d, $^{2}J_{(F,F)}$ = 278.9 Hz, 1F), -115.4 ppm (d, $^{2}J_{(F,F)}$ = 278.9 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 9.3, 26.0, 33.2 (m), 56.2, 56.4, 62.9 (dd, $^{2}J_{(C,F)}$ = 22.0 Hz, $^{2}J_{(C,F)}$ = 18.5 Hz), 80.3, 105.3, 106.9, 112.0 (m), 117.5 (m), 127.0, 143.3, 147.3, 150.2, 164.6 (d, $^{3}J_{(C,F)}$ = 7.0 Hz), 190.9 ppm. IR (ATR): 2971, 1762, 1714, 1592, 1504, 1201 cm^{-1}. HR-MS (ESI) m/z: [M+Na]$^{+}$ Calcd for $C_{19}H_{21}F_5O_5Na$ 447.1201; found 447.1198. $[\alpha]_D^{20}$ = -6.1 (c = 0.0040 in MeCN), 30% *ee* (absolute configuration *R*). HPLC: t_r(*S*) = 7.19 min and t_r(*R*) = 7.81 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

Tert-butyl (R)-1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4k**):[15] According to the general procedure, 28 mg (0.12 mmol) of **4k** were synthesized from 60 mg of starting material **3k** (32% yield) as colourless oil, after purification by column chromatography on silica gel (hexane:ethyl acetate (9:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 1.45 (s, 9H), 3.56 (d, $^{2}J_{(H,H)}$ = 17.7 Hz, 1H), 3.85 (d, $^{2}J_{(H,H)}$ = 17.7 Hz, 1H), 7.45 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.53 (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.68 (td, $^{3}J_{(H,H)}$ = 7.5 Hz, $^{4}J_{(H,H)}$ = 1.2 Hz, 1H), 7.83 ppm (d, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ =-78.6 (s, 3F), -113.6 (d, $^{2}J_{(F,F)}$ = 278.3 Hz, 1F), -115.6 ppm (d, $^{2}J_{(F,F)}$ = 278.3 Hz, 1F). $[\alpha]_D^{20}$ = -6.8 (c = 0.0033 in MeCN), 28% *ee* (absolute configuration *R*).

Adamantyl 1-oxo-2-(perfluoroethyl)-2,3-dihydro-1H-indene-2-carboxylate (**4l**): According to the general procedure, 107 mg (0.25 mmol) of **4l** were synthesized from 110 mg of starting material **3l** (71% yield) as a colourless oil, after purification by column chromatography on silica gel (hexane:ethyl acetate (9:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 1.64 (bs, 6H), 2.08 (bs, 6H), 2.16 (bs, 3H), 3.55 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 3.84 (d, $^{2}J_{(H,H)}$ = 17.6 Hz, 1H), 7.48 (m, 2H), 7.68 (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H), 7.83 ppm (t, $^{3}J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ = -78.5 (s, 3F), -113.6 (d, $^{2}J_{(F,F)}$ = 279.9 Hz, 1F), -115.6 ppm (d, $^{2}J_{(F,F)}$ = 279.9 Hz, 1F). ^{13}C[^{1}H] NMR (101 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 30.9, 33.6 (bs), 35.9, 40.8, 63.2 (dd, $^{2}J_{(C,F)}$ = 22.2 Hz, $^{2}J_{(C,F)}$ = 18.3 Hz), 84.7, 112.7 (m), 118.6 (m), 125.3, 126.1, 128.3, 134.2, 136.0, 151.6, 162.6 (d, $^{3}J_{(C,F)}$ = 10.9 Hz), 192.8 ppm. IR (ATR): 2914, 2853, 1752, 1725, 1607, 1457, 1204 cm^{-1}. HR-MS (ESI) m/z: [M+Na]$^{+}$ Calcd for $C_{22}H_{21}F_5O_3Na$ 451.1303; found 451.1296.

Methyl 1-oxo-2-(perfluoroethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**4m**):[15] According to the general procedure, 154 mg (0.47 mmol) of **4l** were prepared from 150 mg of starting material **3l** (65% yield) as a colourless oil, after purification by column chromatography on silica gel (hexane:Et_2O (2:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 2.52 (ddd, $^2J_{(H,H)}$ = 13.6 Hz, $^3J_{(H,H)}$ = 9.9 Hz, $^3J_{(H,H)}$ = 7.3 Hz, 1H), 2.89 (dt, $^2J_{(H,H)}$ = 13.6 Hz, $^3J_{(H,H)}$ = 3.7 Hz, 1H), 3.05 (m, 2H), 3.77 (s, 3H), 7.25 (d, $^3J_{(H,H)}$ = 7.5 Hz, 1H), 7.38 (t, $^3J_{(H,H)}$ = 7.5 Hz, 1H), 7.55 (td, $^3J_{(H,H)}$ = 7.5 Hz, $^4J_{(H,H)}$ = 1.3 Hz, 1H), 8.12 ppm (d, $^3J_{(H,H)}$ = 7.5 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ = -76.9 (s, 3F), -111.5 (d, $^2J_{(F,F)}$ = 279.9 Hz, 1F), -113.2 ppm (d, $^2J_{(F,F)}$ = 279.9 Hz, 1F). $[\alpha]_D^{20}$ = -2.1 (c = 0.0038 in MeCN), 34% *ee* (absolute configuration *R*). HPLC: t_r(*R*) = 14.51 min and t_r(*S*) = 16.21 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.5:0.5) as non-stationary phase and 1.0 mL·min^{-1}.

2-Acetyl-2-(perfluoroethyl)-2,3-dihydro-1H-inden-1-one (**4n**): According to the general procedure, 118 mg (0.47 mmol) of **4n** were synthesized from 120 mg of starting material **3n** (79% yield) as a yellow liquid after purification by column chromatography on silica gel (hexane:Et_2O (2:1)). ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 3.53 (s, 3H), 3.39 (d, $^2J_{(H,H)}$ = 17.6 Hz, 1H), 4.12 (d, $^2J_{(H,H)}$ = 17.6 Hz, 1H), 7.43 (td, $^3J_{(H,H)}$ = 7.6 Hz, $^4J_{(H,H)}$ = 1.1 Hz, 1H), 7.54 (dd, $^3J_{(H,H)}$ = 7.6 Hz, $^4J_{(H,H)}$ = 1.1 Hz, 1H), 7.69 (td, $^3J_{(H,H)}$ = 7.5 Hz, $^4J_{(H,H)}$ = 1.1 Hz, 1H), 7.79 ppm (d, $^3J_{(H,H)}$ = 7.6 Hz, 1H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ = -82.5 (s, 3F), -114.0 (d, $^2J_{(F,F)}$ = 281.2 Hz, 1F), -116.3 ppm (d, $^2J_{(F,F)}$ = 281.2 Hz, 1F). ^{13}C[^{1}H] NMR (63 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 27.9, 31.0 (bs), 70.4 (m), 125.6, 126.0 (m), 126.7, 127.9 (m), 128.6, 136.8, 143.8, 152.8, 193.9 (bs), 195.3 ppm (bs). IR (ATR): 2928, 1718, 1204, 1096 cm^{-1}. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_9F_5O_2Na$ 315.0415; found 315.0415. HPLC: t_r(*1*) = 14.14 min and t_r(*2*) = 16.84 min, Daicel Chiralpack AD-H column (0.46 cm ϕ x 25 cm) with hexane:^{i}PrOH (99.8:0.2) as non-stationary phase and 0.5 mL·min^{-1}.

2,6-Di-tert-butyl-4-(3,5-di-tert-butyl-4-(pentafluoroethoxy)benzylidene)cyclohexa-2,5-dien-1-one (**6**): Yellowish oil, ^{1}H NMR (250 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 1.30 (bs, 36H), 6.59 (bs, 3H), 6.84 ppm (bs, 2H). ^{19}F NMR (235 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ = -77.8 (s, 3F), -117.1 ppm (s, 2F). ^{13}C[^{1}H] NMR (63 MHz, [D]$CDCl_3$, 25 ^{o}C, TMS): δ = 29.3, 29.6, 35.0, 35.6, 115.2 (m), 121.2 (m), 124.3, 133.5, 134.8, 135.5, 150.5, 186.3 ppm. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $C_{31}H_{41}F_5O_2$ 563.2919; found 563.2911.

ASSOCIATED CONTENT

The Supporting Information includes the preparation of **1** and **2**, as well as ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra and ESI and HPLC chromatograms.

AUTHOR INFORMATION

* E-mail: albert.granados@uab.es

* Email: adelina.vallribera@uab.es

ORCID

Albert Granados: 0000-0002-5362-5966

Adelina Vallribera: 0000-0002-6452-4589

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